



eunethta
EUROPEAN NETWORK FOR HEALTH TECHNOLOGY ASSESSMENT

EUnetHTA Joint Action 3 WP4

“Rolling Collaborative Review” of Covid-19 treatments

MAVRILIMUMAB FOR THE TREATMENT OF COVID-19

Project ID: RCR21
Monitoring Report

Version 2.0, March 2021

Template version February 2021



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

DOCUMENT HISTORY AND CONTRIBUTORS

Version	Date	Description of changes
V 1.0	18/01/2021	First version
V 1.1	10/03/2021	Literature searches, Literature screening
V 1.2	11/03/2021	Data extraction and analysis complete
V 1.3	12/03/2021	Check of data extraction and analysis
V 2.0	15/03/2021	Second version

Major changes from previous version

Chapter, page no.	Major changes from version 1.0
Chapter 4.3 (page 11) Tables 4.2 and 4.3 (pages 13-14)	One ongoing RCT was terminated according to a press release by the pharmaceutical company. Two ongoing RCTs registered changes in study status, recruitment status, study design, eligibility, or outcome measures.

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 \(https://eunetha.eu/doi\)](https://eunetha.eu/doi).

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How to cite this assessment

Please cite this assessment as follows:

EUnetHTA Rolling Collaborative Review (RCR21) Authoring Team. Mavrilimumab for the treatment of COVID-19. Diemen (The Netherlands): EUnetHTA; 2021. [date of citation]. 23 pages. Report No.: RCR21, v2.0. Available from: [https //www.eunetha.eu](https://www.eunetha.eu).

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LIST OF ABBREVIATIONS

AE	Adverse Event
CI	Confidence Interval
DOI	Declaration of interest
EUnetHTA	European Network of Health Technology Assessment
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
HR	Hazard Ratio
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

1 OBJECTIVE

The aim of this EUnetHTA Rolling Collaborative Review is

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

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

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

2 METHODS

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

2.1 Scope

Table 2-1 Scope of the RCR

Description	Project Scope
Population	<p>Disease</p> <ul style="list-style-type: none"> • 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. <p>ICD-Codes (https://www.who.int/classifications/icd/covid19/en)</p> <ul style="list-style-type: none"> • 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. <p>MeSH-terms</p> <ul style="list-style-type: none"> • COVID-19, Coronavirus Disease 2019 <p>Target population (https://www.covid19treatmentguidelines.nih.gov/overview/management-of-covid-19/)</p>

	<ul style="list-style-type: none"> 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	Mavrilimumab, human monoclonal antibody that inhibits the human granulocyte macrophage colony-stimulating factor (GM-CSF) receptor
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	<p><u>Main outcome:</u></p> <ul style="list-style-type: none"> All-cause Mortality (Survival) <p><u>Additional Outcomes:</u></p> <p><u>Efficacy:</u></p> <ul style="list-style-type: none"> 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. <p><u>Safety:</u></p> <ul style="list-style-type: none"> Adverse events (AE), Severe adverse events (SAE), Withdrawals due to AEs, Most frequent AEs, Most frequent SAEs. <p>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.</p>
Study design	<p>Efficacy: randomised controlled trials (RCT)</p> <p>Safety: observational studies (comparative or single-arm prospective studies and registries)</p>

2.2 Sources of information

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

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

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

The literature search is conducted in the following databases:

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

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

- <https://www.fhi.no/en/gk/systematic-reviews-hta/map/>

Search methods are described in more detail in Appendix Table 6-2.

Population	See project Scope
Intervention	Mavrilimumab, human monoclonal antibody that inhibits the human granulocyte macrophage colony-stimulating factor (GM-CSF) receptor
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).

Two researchers of SESCO/FIISC extract the data and assess 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 SESCO/FIISC 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*

Most of the lung damage caused by COVID-19/SARS-CoV-2 infection is driven by a surge in inflammatory cytokines [interleukin-6, interferon- γ , and granulocyte-macrophage colony-stimulating factor (GM-CSF)]. Blunting this hyperinflammation with immunomodulation may lead to clinical improvement [4,5]. GM-CSF is a cytokine that activates macrophages and neutrophils to release proinflammatory cytokines, including TNF, IL-1, IL-6, IL-23, and IL-12. It stimulates the JAK2 signal with consequent cytokine outbreak [6].

Mavrilimumab is a monoclonal antibody (human isoform IgG4) that binds to GM-CSF receptor alpha and disrupts downstream signalling [4,7]. Before COVID-19, Mavrilimumab was already in study as a potential treatment for giant cell arteritis, a chronic inflammatory disease of medium-large arteries [4–6].

3.2 *Regulatory Status*

MedImmune LLC developed Mavrilimumab (CAM-3001) and conducted several trials with this drug for the treatment of rheumatoid arthritis (RA) between 2008 and 2014 [<https://clinicaltrials.gov>]. In 2017, Kiniksa Pharmaceuticals, Ltd. acquired the rights to Mavrilimumab (now KPL-301) and in 2018 started a trial to evaluate this drug for the treatment of giant cell arteritis [8]. On September 9, 2020, the U.S. Food and Drug Administration (FDA) granted Orphan Drug designation for Mavrilimumab for giant cell arteritis [9].

Kiniksa Pharmaceuticals has received advice from the European Medicines Agency (EMA) during the clinical phase development of Mavrilimumab as a potential immunomodulator for COVID-19 [10].

Mavrilimumab has not received approval by the EMA or the FDA for Covid-19 or for any other indication.

3.3 *Level of Evidence*

No results from RCTs have been published so far. There are 5 ongoing RCTs evaluating the efficacy of Mavrilimumab against placebo in COVID-19 patients according to clinicaltrials.gov, although the enrollment in one of them was closed early according to a press release by the pharmaceutical company [11].

One observational prospective study included patients with COVID-19 pneumonia and systemic hyperinflammation admitted in a centre in Italy. The study compared 13 patients who were treated with a single intravenous dose (6 mg/kg) of Mavrilimumab added to standard care and 26 contemporaneous control patients who were admitted in the same center and who received standard care. The risk of bias of this study is high.

More evidence is needed in order to evaluate the safety and effect of Mavrilimumab in the treatment of COVID-19.

4 SUMMARY

4.1 *Effectiveness and Safety evidence from RCTs*

No published results from RCTs investigating the safety and efficacy of Mavrilimumab for the treatment of COVID-19 were identified.

4.2 Safety evidence from observational studies

One single-centre prospective cohort study compared hospitalized patients receiving a single intravenous dose (6 mg/kg) of Mavrilimumab (n=13) with a control group (n=26) that received the standard care given in San Raffaele Hospital (Milan, Italy) between March 17 and April 15, 2020 [4]. Patients in both groups were non-mechanically ventilated, and diagnosed with COVID-19 pneumonia and systemic hyperinflammation. The adverse events were monitored by daily clinical examination, that is, vitals and blood tests, blood, sputum, and urine cultures.

The authors reported no drug-related serious adverse events except for one unclear event in one patient in the Mavrilimumab group. To be precise, the authors reported that “Mavrilimumab treatment was well tolerated in all patients, without infusion reactions. We did not observe any cases of neutropenia. An increase in CRP, white blood cells, and serum procalcitonin was observed in one patient treated with mavrilimumab, and this patient was admitted to the ICU 3 days after infusion. Empirical antibiotic treatment was started; however, microbiological cultures of blood and urine obtained before antibiotic treatment remained negative. Three (12%) patients in the control group developed infectious complications” (See Table 4-1).

The risk of bias in this study was considered high mainly due to the short follow-up (28 days), the fact that the outcomes were assessed by assessors aware of the interventions received by study participants, the small sample size in both groups, and some unbalanced characteristics at baseline, such as sex (92% of Mavrilimumab group was male) and duration of fever (p=.0038 for differences between groups) [12].

4.3 Ongoing studies

Six hits were retrieved from the search on the trials registries. After deduplication, 5 ongoing RCTs evaluating Mavrilimumab against placebo were identified: 4 phase II trials and one phase II/III trial (see Table 4-2 and Table 4-3). Two of the clinical trials, including the phase II/III study, have registered important changes in February/March 2021 in clinicaltrials.gov. The completion date for 3 trials is due before July 2021. The largest trial has postponed the completion date to February 2022. According to a press release by the pharmaceutical company [11], one of the trials was terminated earlier (NCT04399980), showing “early signal of efficacy, with trends toward clinical improvement as well as lower mortality and shorter duration of mechanical ventilation in patients treated with mavrilimumab on top of corticosteroids”. The press release reported 40 patients enrolled (instead of the 60 patients originally estimated) and non-significant differences for any outcome.

4.4 Scientific conclusion about status of evidence generation

More evidence is needed to be able to draw conclusions on the clinical effect and safety of Mavrilimumab in COVID-19 patients. Four clinical trials are underway.

Table 4-1 Summary of safety from observational studies (AE and SAE) of Mavrilimumab

Author, year	De Luca, 2020
Country	Italy
Sponsor/ lead institution	IRCCS San Raffaele Scientific Institute
Intervention/Product (drug name)	Mavrilimumab (added to standard care)
Dosage	a single intravenous dose (6 mg/kg)
Comparator	standard care given by the hospital at the time
Study design	single-centre prospective cohort study
Setting	hospital
Number of pts	13 in Mavrilimumab group; 26 in control group
Inclusion criteria	non-mechanically ventilated patients, aged 18 years or older, diagnosed with COVID-19 pneumonia, acute lung injury, no clinical evidence of left atrial hypertension, hyperinflammation
Exclusion criteria	management (including mechanical ventilation) in the intensive care unit, evidence of bacterial infection, concomitant administration of other immunosuppressive biological agents or corticosteroids
Age of patients (yrs)	Mavrilimumab group: 57 years (median); 52–58 (interquartile range) Control group: 60 (median); 53–67 (interquartile range)
Disease severity	severe: COVID-19 pneumonia and systemic hyperinflammation
Follow-up (days)	28 days
Loss to follow-up, n (%)	No reported
RoB	high
Safety – Outcomes*	
Overall AEs, n (%)	No AEs except for one patient in the Mavrilimumab group
Serious AE (SAE), n (%)	No drug-related SAEs reported
Most frequent AEs n (%)	n.a.
Most frequent SAEs, n (%)	n.a.
AEs of special interest, n (%)	No reported
Death as SAE, n (%)	0 deaths in Mavrilimumab group
Withdrawals due AEs, n (%)	n.a.

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

Table 4-2 Ongoing trials of single agent Mavrilimumab

Trial Identifier/registry ID(s)/contact	NCT04492514	NCT04463004	NCT04399980
	Contact: Kristin Hudock, hudockkn@ucmail.uc.edu Autumn Cresie, studeran@ucmail.uc.edu	Contact: Antonio Abbate, antonio.abbate@vcuhealth.org	Contact: Paul C Cremer, The Cleveland Clinic
Study design, study phase	RCT, phase 2	RCT, phase 2	RCT, phase 2
Recruitment status	Recruiting (update 2020 July 30)	Active, not recruiting (update 2021 Feb 17)	Active, not recruiting (update 2020 Oct 6) **
Number of Patients (estimated enrollment), Disease severity*	60 participants Documented COVID19 pneumonia, hypoxia, increased serum inflammatory marker, and severity of disease warrants inpatient hospitalization	60 participants Documented COVID19 pneumonia, hypoxia, increased serum inflammatory marker, and severity of disease warrants inpatient hospitalization	60 participants*** Documented COVID19 pneumonia, hypoxia, increased serum inflammatory marker, and severity of disease warrants inpatient hospitalization
Setting (hospital, ambulatory,..)	hospital	hospital	Hospital
Intervention (generic drug name and dosage)	Mavrilimumab, treatment infusion	Mavrilimumab, treatment infusion	Mavrilimumab, treatment infusion
Comparator (standard care or generic drug name and dosage)	Placebo infusion	Placebo infusion	Placebo infusion
Primary Outcome(s)	Proportion of subjects alive and off oxygen at day 14	Proportion of subjects alive and off of oxygen at day 14	Proportion of subjects alive and off of oxygen at day 14
Sponsor/ lead institution, country (also country of recruitment if different)	Kristin Hudock, University of Cincinnati, USA	Virginia Commonwealth University, USA	The Cleveland Clinic, USA

*Mixed COVID-19, Mild, Moderate, Severe, Critical COVID-19

**Study closed early according to a press release by the pharmaceutical company; not updated in clinicaltrials.gov at present.

***40 patients enrolled in the end according to a press release by the pharmaceutical company.

Table 4-3 Ongoing trials of single agent Mavrilimumab, continued

Trial Identifier/registry ID(s)/contact	NCT04397497 EudraCT Number: 2020-001795-15 Contact: Lorenzo Dagna, dagna.lorenzo@univr.it Giacomo De Luca, deluca.giacomo@hsr.it	NCT04447469 Contact: Kiniksa Clinical Research Team, clinicaltrials@kiniksa.com
Study design, study phase	RCT, phase 2	RCT, phase 2/3
Recruitment status	Not yet recruiting (update 2020 May 26)	Recruiting (update 2021 March 9)
Number of Patients (estimated enrollment), Disease severity*	50 participants Clinically diagnosed with SARS-CoV-2 virus; hospitalized with COVID-19-induced pneumonia; requiring oxygen supplementation and having a PAO ₂ /FIO ₂ ratio ≤ 300 mmHg; lactate dehydrogenase > normal range and at least one of the following: fever > 38.0 °C; increased levels of C-reactive Protein (CRP) ≥ 10x UNL mg/L (≥ 60 mg/l); or increased levels of ferritin ≥ 2.5x UNL (≥ 1000 µg/L)	588 participants Positive SARS-CoV-2 test within 14 days prior to randomization; hospitalized for SARS-CoV-2; bilateral pneumonia; and clinical laboratory results indicative of hyper-inflammation; and: Cohort 1 - Non-mechanically ventilated participants: Receiving any form of oxygenation or non-invasive ventilation to maintain SpO ₂ ≥ 92% and not-intubated Cohort 2 - Mechanically ventilated participants: Recently ventilated with mechanical ventilation prior to randomization
Setting (hospital, ambulatory,..)	hospital	hospital
Intervention (generic drug name and dosage)	Single dose of IV Mavrilimumab	Two interventions in both cohorts: -10 mg/kg as a single IV infusion - 6 mg/kg as a single IV infusion
Comparator (standard care or generic drug name and dosage)	Single dose of matching IV placebo	Placebo as a single IV infusion
Primary Outcome(s)	Reduction in the dependency on oxygen supplementation (within day 14 of treatment)	Cohort 1: Proportion of participants alive and free of mechanical ventilation at day 29 Cohort 2: Mortality rate at day 29
Sponsor/ lead institution, country (also country of recruitment if different)	Ospedale San Raffaele, Italy	Kiniksa Pharmaceuticals, Ltd., USA Recruitment: USA, Brazil, Chile, Peru, South Africa

*Mixed COVID-19, Mild, Moderate, Severe, Critical COVID-19

Abbreviations: FIO₂=fraction of inspired oxygen; PAO₂=partial pressure of oxygen; SpO₂=blood oxygen saturation.

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12. Khan AR, Soneja M, Tirlangi PK, Wig N. Mavrilimumab for severe COVID-19. *Lancet Rheumatol* [Internet]. 2020;2:e661–e662. Available from: <https://linkinghub.elsevier.com/retrieve/pii/S2665991320303064>
13. Live map of COVID-19 evidence [Internet]. Oslo: Norwegian Institute of Public Health; 2021 [cited 2021 Feb 9]. Available from: <https://www.fhi.no/en/qk/systematic-reviews-hta/map/>
14. COVID-19: a living systematic map of the evidence [Internet]. London: EPPI Centre, University College London; 2021 [cited 2021 Feb 9]. Available from: <http://eppi.ioe.ac.uk/cms/Projects/DepartmentofHealthandSocialCare/Publishedreviews/COVID-19Livingssystematicmapofthevidence/tabid/3765/Default.aspx>

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 (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/ictcp/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	<p>1. ((((((("Coronavirus"[Mesh]) OR (coronavirus*[Title/Abstract] OR coronavirus*[Title/Abstract] OR coronavirus*[Title/Abstract] OR coronavirus*[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 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 [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 (2019/10/01:2020[dp]))</p>	28/02/2020

Database	URL	Search line / Search terms	Date of search
Ovid MEDLINE(R) ALL)	ovidsp.dc2.ovid.com	<ol style="list-style-type: none"> 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	<ol style="list-style-type: none"> 1. exp Coronavirinae/ or exp Coronavirus/ 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 Academic Graph (MAG). We supplemented these studies with a weekly search in Scopus (Elsevier). Detailed descriptions of the EPPI and NIPHNO searches are given at their websites [13,14]. 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		Lines 1 and 2 are copies of Ovid's Expert searches for covid-19 in MEDLINE and Embase	From 4/2/2021 until 26/2/2021
Ovid MEDLINE(R) ALL 1946 to 2021		<p>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]</p> <p>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]</p> <p>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/</p>	

		<p>or exp Interferons/ or 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]</p> <p>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 oomezd [Emtree-terms for drugs in Embase]</p> <p>5 ((convalescent adj (plasma or sera or serum)) or serotherap* or ((atoxin or hyperimmunoglobulin or hyperimmune globulin or hyperimmune gammaglobulin) adj therap*) or passive immunization or (tocilizumab or atilizumab 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 (favipiravir 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]</p> <p>6 (202009* or 202010* or 202011 or 202012* or 202101* or 202102*).dt. use medall [time limits in MEDLINE]</p> <p>7 (202009* or 202010* or 202011 or 202012* or 202101* or 202102*).dc. use oomezd [time limits in Embase]</p> <p>8 (1 and (3 or 5) and 6) use medall</p> <p>9 (2 and (4 or 5) and 7) use oomezd</p>	
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6.3 Search strategy to identify ongoing studies

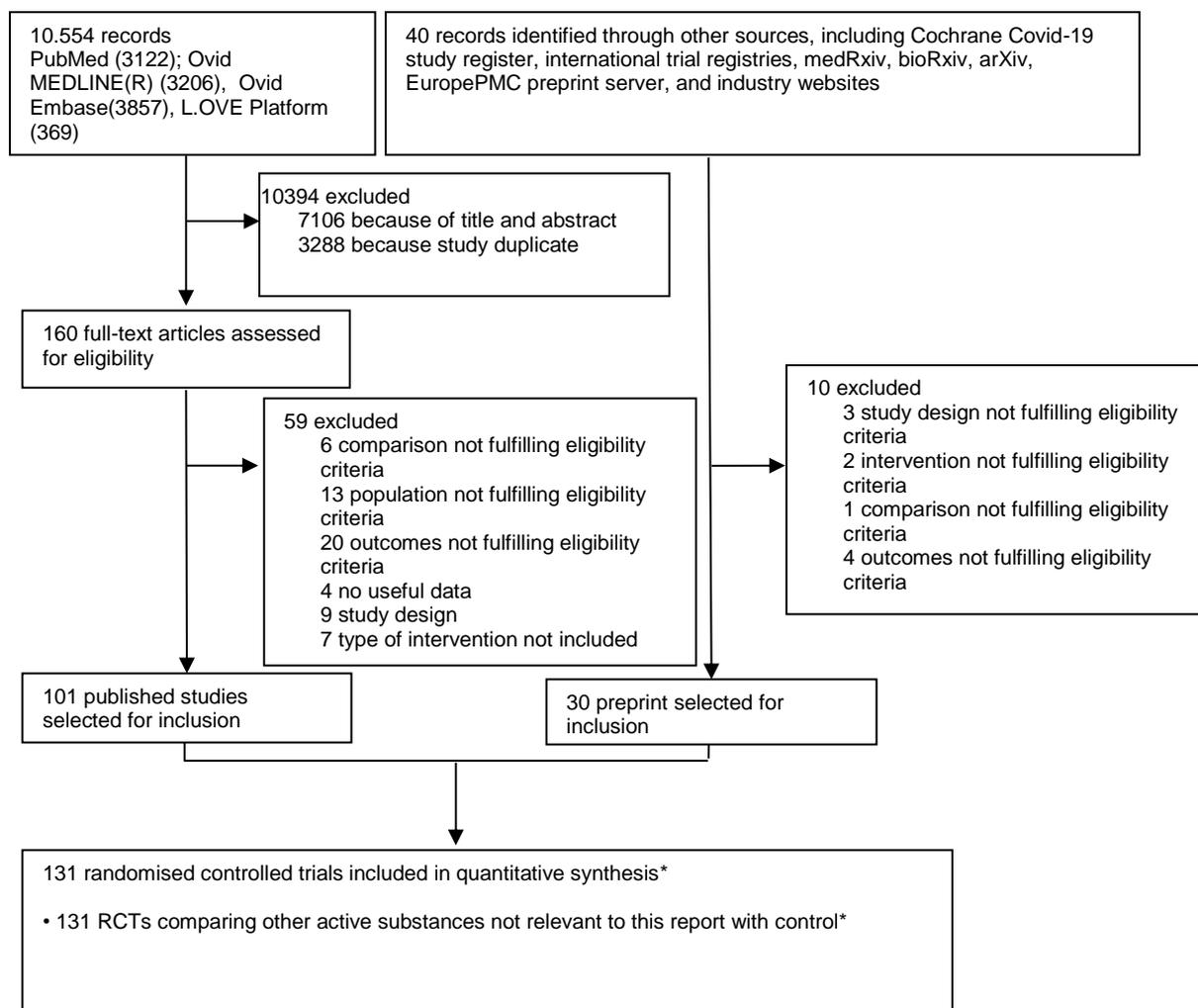
SESCS/FIISC is responsible for searching in trial registries to identify ongoing and unpublished studies. The combination of search terms related to COVID-19 and Mavrilimumab are described in Appendix Table 6-3.

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: <ul style="list-style-type: none"> • covid-19 • SARS-CoV-2 • Coronavirus Terms used at "other terms": <ul style="list-style-type: none"> • Mavrilimumab • KPL-301 • CAM-3001 	10/03/2021	5 0 new
ISRCTN	https://www.isrctn.com/	Basic search mode Search terms: <ol style="list-style-type: none"> 1. covid-19 and Mavrilimumab 2. covid-19 and KPL-301 3. covid-19 and CAM-3001 4. SARS-CoV-2 and Mavrilimumab 5. SARS-CoV-2 and KPL-301 6. SARS-CoV-2 and CAM-3001 	10/03/2021	0 0 new
European Clinical Trials Registry	https://www.clinicaltrialsregister.eu/	Basic search mode Search terms: <ol style="list-style-type: none"> 1. covid-19 and Mavrilimumab 2. covid-19 and KPL-301 3. covid-19 and CAM-3001 4. SARS-CoV-2 and Mavrilimumab 5. SARS-CoV-2 and KPL-301 6. SARS-CoV-2 and CAM-3001 	10/03/2021	1 0 new

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

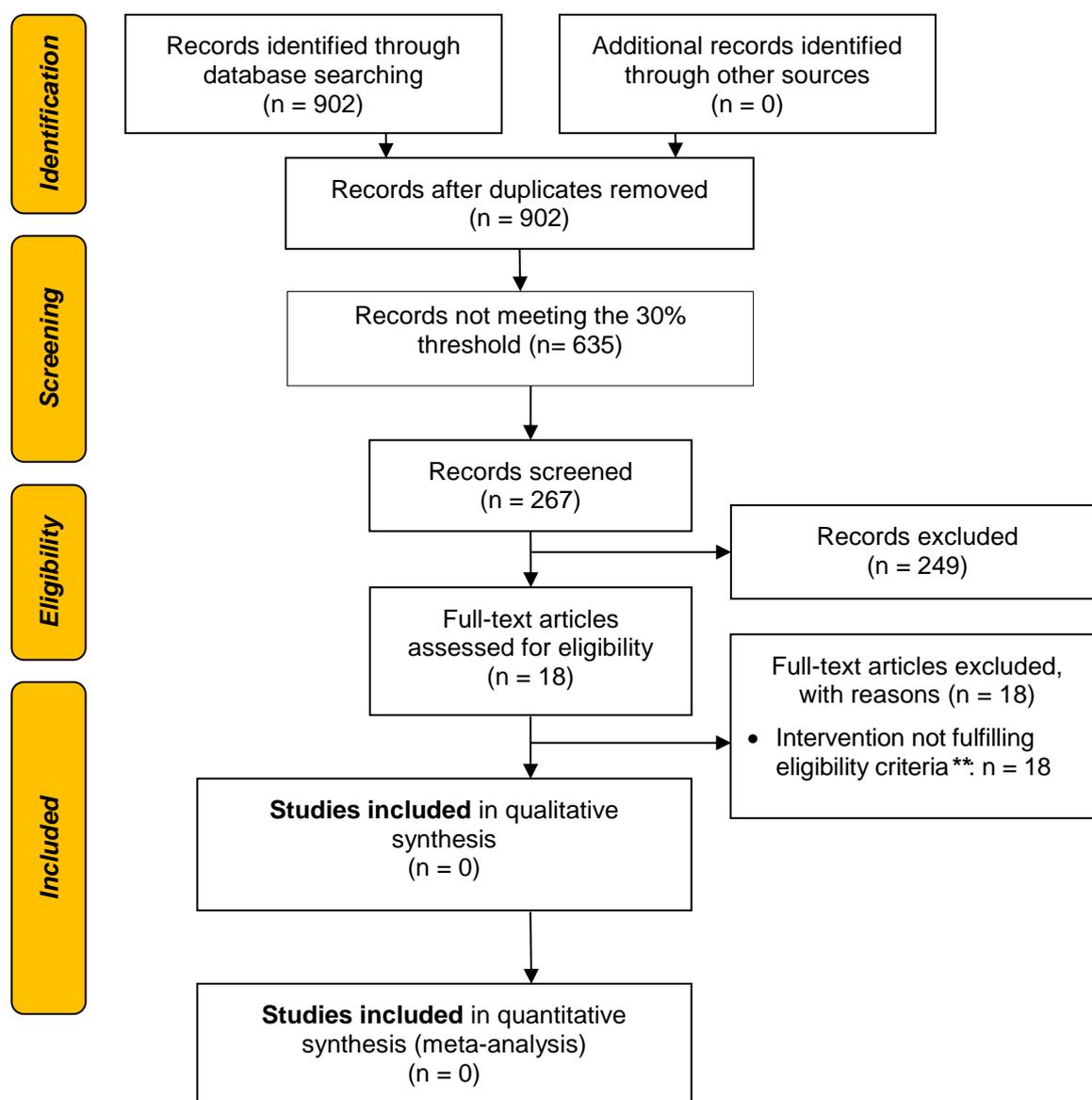
6.4 Flow diagrams



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

RCT = randomised controlled trial;

* The selection process was part of an external project, see <https://www.deplazio.net/farmacicovid> and Prospero ID CRD42020176914.



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

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