



# eunethta

EUROPEAN NETWORK FOR HEALTH TECHNOLOGY ASSESSMENT

EUnetHTA Joint Action 3 WP4

**“Rolling Collaborative Review” of Covid-19 treatments**

## **SOLNATIDE FOR THE TREATMENT OF COVID-19**

**Project ID: RCR06**  
Monitoring Report

**Version 4.0, December 2020**

Template version November 2020



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

## DOCUMENT HISTORY AND CONTRIBUTORS

Version	Date	Description of changes
V 1.0	14/08/2020	First version
V 2.0	15/09/2020	Second version
V 3.0	15/10/2020	Third version
V 3.1 and V 3.2	December 2020	Literature searches, Literature screening, Clinical Trials Registries search
V 3.3	14/12/2020	Check of report
V 4.0	15/12/2020	Fourth version

### Major changes from previous version

Chapter, page no.	Major changes from version 3.0
	<ul style="list-style-type: none"><li>No major changes</li></ul>
	<b>From October 2020, the update of the literature search is being done on a bi-monthly basis. In case new evidence is identified in the bi-monthly literature search, this RCR will be updated and may be put back into the monthly process.</b>

### 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.

### Rolling Collaborative Review team

Author(s)	Austrian Institute for Health Technology Assessment (AIHTA), Austria
Co-Author(s)	Department of Epidemiology Lazio Regional Health Service (DEPLazio), Italy

## Further contributors

Project Management	
Zorginstituut Nederland (ZIN), Netherlands	Coordination between involved parties throughout the assessment
Austrian Institute for Health Technology Assessment (AIHTA), Austria	Coordination of RCR

## 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>).

## Copyright

EUnetHTA assessments are published under a “CC/BY/NC” [Creative Commons Licence](#).



## How to cite this assessment

Please cite this assessment as follows:

EUnetHTA Rolling Collaborative Review (RCR06) Authoring Team. Solnatide for the treatment of COVID-19. Diemen (The Netherlands): EUnetHTA; 2020. [date of citation]. 22 pages. Report No.: RCR06. Version 4.0, December 2020. Available from: <https://www.eunethta.eu>

Contact the EUnetHTA Secretariat [EUnetHTA@zinl.nl](mailto:EUnetHTA@zinl.nl) with inquiries about this assessment.

## TABLE OF CONTENTS

<b>DOCUMENT HISTORY AND CONTRIBUTORS.....</b>	<b>2</b>
<b>TABLE OF CONTENTS.....</b>	<b>4</b>
<b>LIST OF TABLES AND FIGURES.....</b>	<b>4</b>
<b>1 OBJECTIVE .....</b>	<b>6</b>
<b>2 METHODS.....</b>	<b>6</b>
2.1 SCOPE.....	6
2.2 SOURCES OF INFORMATION.....	8
<b>3 ABOUT THE TREATMENT .....</b>	<b>11</b>
3.1 MODE OF ACTION.....	11
3.2 REGULATORY STATUS .....	11
3.3 LEVEL OF EVIDENCE .....	11
<b>4 SUMMARY .....</b>	<b>12</b>
<b>5 REFERENCES.....</b>	<b>14</b>
<b>6 APPENDIX .....</b>	<b>15</b>
6.1 SEARCH STRATEGY TO IDENTIFY RANDOMISED CONTROLLED TRIALS.....	15
6.2 SEARCH STRATEGY TO IDENTIFY OBSERVATIONAL STUDIES .....	18
6.3 SEARCH STRATEGY TO IDENTIFY ONGOING STUDIES.....	20
6.4 FLOW DIAGRAMS .....	21

## LIST OF TABLES AND FIGURES

Table 2-1 Scope of the RCR .....	6
Table 4-1 Ongoing trials of single agent solnatide .....	13
Table 6-1 Search strategy to identify randomised controlled studies.....	16
Table 6-2 Search strategy to identify observational studies.....	18
Table 6-3 Search strategy to identify ongoing studies .....	20
Appendix Figure 6-1. Flow diagram depicting the selection process of RCTs.....	21
Appendix Figure 6-2. Flow diagram depicting the selection process of observational studies .....	22

## LIST OF ABBREVIATIONS

AE	Adverse Event
ARR	Absolute Risk Reduction
ATC	Anatomical Therapeutic Chemical [Classification System]
ATMP	Advanced therapy medicinal product
CI	Confidence Interval
DOI	Declaration of interest
EUnetHTA	European Network of Health Technology Assessment
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
HR	Hazard Ratio
HRQOL	Health-related Quality of Life
ICD	International Classification of Diseases
ITT	Intention-to-treat
MD	Mean Difference
MeSH	Medical Subject Headings
NA	Not applicable
NR	Not reported
OR	Odds Ratio
PP	Per Protocol
RCT	Randomized Controlled Trial
RCR	Rolling Collaborative Review
REA	Relative Effectiveness Assessment
RR	Relative Risk
SAE	Serious Adverse Event
SD	Standard Deviation
SMD	Standardized Mean Difference
SmPC	Summary of product characteristics
SOP	Standard Operating Procedure
WP4	Work Package 4

## 1 OBJECTIVE

The aim of this EUnetHTA Rolling Collaborative Review is

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

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

The scope of the Rolling Collaborative Review is of descriptive nature. These **EUnetHTA Rolling Collaborative Reviews are not meant to substitute a joint Relative Effectiveness Assessment (REA)** adhering to the agreed procedures 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 15<sup>th</sup> of the month.

### 2.1 Scope

Table 2-1 Scope of the RCR

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

	<ul style="list-style-type: none"> <li>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.</li> <li>Moderate Illness: Individuals who have evidence of lower respiratory disease by clinical assessment or imaging and a saturation of oxygen (<math>\text{SpO}_2</math>) <math>\geq 94\%</math> on room air at sea level.</li> <li>Severe Illness: Individuals who have respiratory frequency <math>&gt;30</math> breaths per minute, <math>\text{SpO}_2 &lt; 94\%</math> on room air at sea level, ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (<math>\text{PaO}_2/\text{FiO}_2</math>) <math>&lt; 300 \text{ mmHg}</math>, or lung infiltrates <math>&gt;50\%</math>.</li> <li>Critical Illness: Individuals who have respiratory failure, septic shock, and/or multiple organ dysfunction.</li> </ul>
<b>Intervention</b>	Solnatide, a synthetic peptide of less than 20 amino acids; reported to activate epithelial sodium channels (ENaC), promoting lung alveolar fluid clearance through a novel mechanism of ENaC activation.
<b>Comparison</b>	<p>Any active treatment, placebo, or standard of care.</p> <p><b>Rationale:</b> Since there is no gold standard treatment any comparator is acceptable as well as the above listed interventions.</p>
<b>Outcomes</b>	<p><b>Main outcome:</b></p> <ul style="list-style-type: none"> <li>All-cause Mortality (Survival)</li> </ul> <p><b>Additional Outcomes:</b></p> <p><b>Efficacy:</b></p> <ul style="list-style-type: none"> <li>Length of hospital stay,</li> <li>Viral burden (2019-nCoV RT-PCR negativity),</li> <li>Clinical progression (WHO Clinical Progression Scale measured daily over the course of the study),</li> <li>Rates of hospitalization and of patients entering ICU,</li> <li>Duration of mechanical ventilation,</li> <li>Quality of life.</li> </ul> <p><b>Safety:</b></p> <ul style="list-style-type: none"> <li>Adverse events (AE),</li> <li>Severe adverse events (SAE),</li> <li>Withdrawals due to AEs,</li> <li>Most frequent AEs,</li> <li>Most frequent SAEs.</li> </ul> <p><b>Rationale:</b> We will give priority according to the Core Outcome Set for Clinical Trials on Coronavirus Disease 2019 (<a href="https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7102592/pdf/main.pdfc">https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7102592/pdf/main.pdfc</a>) 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>
<b>Study design</b>	<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

<b>Population</b>	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.
<b>Intervention</b>	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.
<b>Comparison</b>	Any active treatment, placebo, or standard of care.
<b>Outcomes</b>	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.
<b>Study design</b>	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 6-1Table 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/qk/systematic-reviews-hta/map/>

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

<b>Population</b>	See project Scope
<b>Intervention</b>	Solnatide, a synthetic peptide of less than 20 amino acids; reported to activate epithelial sodium channels (ENaC), promoting lung alveolar fluid clearance through a novel mechanism of ENaC activation.
<b>Comparison</b>	Any active treatment, placebo, or standard of care.
<b>Outcomes</b>	See project Scope
<b>Study design</b>	Inclusion criteria: Prospective non-randomised controlled trials, prospective case series, 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 AIHTA 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 AIHTA 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 Appendix Table 6-3.

Data are presented in tabular form.

### 3 ABOUT THE TREATMENT

#### 3.1 Mode of Action

The therapeutic molecule solnatide (INN) has been designed by APEPTICO (a privately-held biotechnology company from Vienna/Austria) for the therapeutic treatment of patients with Acute Respiratory Distress Syndrome (ARDS) and various forms of life-threatening Pulmonary Oedema (PPO). Solnatide is a synthetic peptide of less than 20 amino acids; it has been reported to activate epithelial sodium channels (ENaC), promoting lung alveolar fluid clearance through a novel mechanism of ENaC activation. This peptide directly binds to intracellular carboxy-terminal of the  $\alpha$ -subunit of ENaC, which increases the likelihood of the channel being open and thus enhances  $\text{Na}^+$  absorption [4, 5]. In 2013, APEPTICO successfully completed a phase I clinical study in healthy subjects, proving the safety of solnatide (AP301), as well as two phase II clinical studies (a randomized, double-blinded placebo-controlled trial using inhaled solnatide in mechanically-ventilated ARDS patients with lung oedema, NCT01627613, EudraCT 2012-001863-64 [5]; a randomized, placebo-controlled pilot study in patients suffering from primary graft dysfunction (PGD) following lung transplantation, EudraCT 2013-000716-21, [6]. Krenn et al. 2017 published results from a randomized, double-blind, placebo-controlled trial for proof of concept, which included 40 adult mechanically ventilated patients with ARDS. Patients were treated with inhaled AP301 ( $n = 20$ ) or placebo (0.9% NaCl;  $n = 20$ ) twice daily for 7 days. There was no difference in the  $\text{PaO}_2/\text{FiO}_2$  ratio, ventilation pressures, Murray lung injury score, or 28-day mortality between the treatment groups. An exploratory subgroup analysis according to severity of illness showed reductions in EVLWI ( $p = 0.04$ ) and ventilation pressures ( $p < 0.05$ ) over 7 days in patients with initial sequential organ failure assessment (SOFA) scores  $\geq 11$  inhaling AP301 versus placebo, but not in patients with SOFA scores  $\leq 10$  [5]. Aigner et al. 2017 conducted and published a proof-of-concept randomized, placebo-controlled, single-centre pilot-study; 20 patients with Primary graft dysfunction (PGD) after lung transplantation (LTx) were randomized 1:1 to AP301 (Group 1) or placebo (Group 2). As authors concluded, the study demonstrated relevant clinical effects of inhaled AP301 on patients with PGD after primary LTx. The improved gas exchange led to a significantly shorter duration of mechanical ventilation and a trend towards a shorter ICU stay [6]. Currently, solnatide is investigated in a phase IIB randomised, placebo-controlled, double-blind trial (EudraCT 2017-003855-47) for the treatment of pulmonary permeability oedema in patients with ARDS. The phase IIB clinical trial has been approved by the German and the Austrian Competent Authorities, as well by Ethic Committees of leading Medical University Hospitals in Germany as well Austria. Main objective of the trial is to assess the local and systemic safety of 7 days orally inhaled sequential multiple ascending doses of solnatide in 80 patients with pulmonary permeability oedema and moderate-to-severe ARDS [7].

#### 3.2 Regulatory Status

Solnatide is not approved by the European Medicines Agency (EMA) or the American Food and Drug Administration (FDA) for COVID-19 patients. In April 2020, solnatide has been approved for Compassionate Use by the Austrian Federal Office for Safety in Health Care (BASG) for the treatment of patients infected by the novel coronavirus SARS-CoV-2 and subsequently developing severe pulmonary dysfunction (severe COVID-19), as well as by the Italian Medicines Agency and the Ethics Committee of the National Institute for Infectious Diseases (Lazzaro Spallanzani-Rome), within the compassionate use program of drugs undergoing clinical trials for the treatment of COVID-19 patients suffering from pulmonary oedema and acute respiratory distress syndrome [7].

#### 3.3 Level of Evidence

APEPTICO Forschung und Entwicklung GmbH has signed, together with the “solnatide consortium”, the Grant Agreement ID: 101003595 with the European Commission to accelerate the process of making the proprietary investigational medicinal product (IMP) solnatide available for medical treatment of patients severely affected by the novel coronavirus 2019 (SARS-CoV-2) disease, COVID-19. The Grant Agreement was made available via the Horizon2020 programme “Advancing knowledge for the clinical and public health response to the 2019-nCoV epidemic” ([https://ec.europa.eu/commission/presscorner/detail/en/ip\\_20\\_386](https://ec.europa.eu/commission/presscorner/detail/en/ip_20_386)). The project started on 1 April 2020 and will end on 31 December 2021 [7].

One ongoing randomised, double-blind, placebo controlled, parallel assignment trial with aim to assess efficacy and safety of 7 days orally inhaled 100 mg solnatide to treat pulmonary permeability oedema of 40 SARS-CoV-2 positive patients with moderate-to-severe ARDS is registered in EUdraCT register (EudraCT number 2020-001244-26), <https://www.clinicaltrialsregister.eu/ctr-search/trial/2020-001244-26/AT>. Details can be found in Table 4-1.

As of December 13, 2020, no completed, withdrawn, suspended or terminated studies related to solnatide in COVID-19 patients were found in ClinicalTrials.gov, ISRCTN and EUdraCT registers. No publications related to RCTs or prospective observational studies of solnatide in COVID-19 patients were found either.

## 4 SUMMARY

Currently, no publications related to RCTs of solnatide in COVID-19 patients were found. The same is true for prospective observational studies in COVID-19 patients.

At the moment, effectiveness and safety of solnatide in COVID-19 patients could not be assessed. Results from one ongoing randomised, double-blind, placebo controlled, parallel assignment trial with the aim to assess efficacy and safety of 7 days orally inhaled 100 mg solnatide to treat pulmonary permeability oedema in 40 SARS-CoV-2 positive patients with moderate-to-severe ARDS are expected.

**Table 4-1 Ongoing trials of single agent solnatide**

<b>Trial Identifier/registry ID(s)/contact</b>	EUDraCT 2020-001244-26
<b>Study design, study phase</b>	RCT, phase 2
<b>Recruitment status</b>	Ongoing
<b>Number of Patients, Disease severity*</b>	40, Critical
<b>Setting (hospital, ambulatory...)</b>	Hospital
<b>Intervention (generic drug name and dosage)</b>	Solnatide 100 mg, inhalation use
<b>Comparator (standard care or generic drug name and dosage)</b>	Placebo, inhalation use
<b>Primary Outcome(s)</b>	Days free of mechanical ventilation (ventilator free days, VFD) within 28 days; Drug-related adverse events (through day 14); All adverse events through day 28; All-cause deaths through day 28; Vital signs daily through day 14 (heart rate, systolic and diastolic blood pressure, and body temperature); ECG parameters including heart rate PQ, QRS, QT and QTc intervals through day 7; Clinical laboratory assessments (haematology, clinical chemistry, blood gases and urine analysis) daily through day 14; 24-hour fluid balance through day 7; Hemodynamic parameters: mean arterial pressure, pulmonary blood volume (PBV), cardiac index and cardiac output assessed at screening and daily until end of treatment; Need for vasoactive drugs assessed at screening and daily until end of treatment
<b>Sponsor/ lead institution, country (also, country of recruitment if different)</b>	Department of Clinical Pharmacology, Medical University of Vienna, Vienna Austria, Austria

## 5 REFERENCES

- [1] Higgins JP.T, Thomas J., Chandler J., Cumpston M., Li T., Page MJ., et al. Cochrane Handbook for Systematic Reviews of Interventions version 6.0 (updated July 2019) 2019 [Available from: <http://www.training.cochrane.org/handbook>].
- [2] Der Simonian R., Laird N. Meta-analysis in clinical trials. Controlled Clinical Trials. 1986;7:177-88.
- [3] Balshem H., Helfand M., Schünemann HJ., Oxman AD., Kunz R., Brozek J., et al. GRADE guidelines: 3. Rating the quality of evidence. Journal of Clinical Epidemiology. 2011;64:401-6.
- [4] Artigas A., Camprubí-Rimblas M., Tantinyà N., Bringué J., Guillamat-Prats R., MA. M. Inhalation therapies in acute respiratory distress syndrome. Ann Transl Med. 2017;5(14):293.
- [5] Krenn K., Lucas R., Croizé A., Boehme S., Klein KU., Hermann R., et al. Inhaled AP301 for treatment of pulmonary edema in mechanically ventilated patients with acute respiratory distress syndrome: a phase IIa randomized placebo-controlled trial. Crit Care. 2017;21(1).
- [6] Aigner C., Slama A., Barta M., Mitterbauer A., Lang G., Taghavi S., et al. Treatment of primary graft dysfunction after lung transplantation with orally inhaled AP301: A prospective, randomized pilot study. J Heart Lung Transplant. 2017;S1053-2498(17):32036-3.
- [7] HTA Austria – Austrian Institute for Health Technology Assessment GmbH. AIHTA Policy Brief Nr.: 002\_V4 2020: Covid-19, HSS/ Horizon Scanning, Living Document November 2020, Part 1. Wien; 2020.

## 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](http://www.clinicaltrials.gov)) and World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) ([www.who.int/ictrp/en](http://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	<pre> ((((("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 [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]) </pre>	10/12/2020

Database	URL	Search line / Search terms	Date of search
Ovid MEDLINE(R) ALL)	ovidsp.dc2.ovid.com	<p>exp coronavirus/</p> <p>((corona* or corono*) adj1 (virus* or viral* or virinae*).ti,ab,kw.</p> <p>(coronavirus* or coronavirus* or coronavirinae* or Coronaviru* or Coronovirus* or Wuhan* or Hubel* 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 NcovHubel* or NcovChina* or NcovChinese*).ti,ab,kw.</p> <p>((respiratory* adj2 (symptom* or disease* or illness* or condition*)) or "seafood market*" or "food market*") adj10 (Wuhan* or Hubel* or China* or Chinese* or Huanan*).ti,ab,kw.</p> <p>((outbreak* or wildlife* or pandemic* or epidemic*) adj1 (China* or Chinese* or Huanan*).ti,ab,kw.</p> <p>"severe acute respiratory syndrome*".ti,ab,kw.</p> <p>or/1-6</p> <p>randomized controlled trial.pt.</p> <p>controlled clinical trial.pt.</p> <p>random*.ab.</p> <p>placebo.ab.</p> <p>clinical trials as topic.sh.</p> <p>random allocation.sh.</p> <p>trial.ti.</p> <p>or/8-14</p> <p>exp animals/ not humans.sh.</p> <p>15 not 16</p> <p>7 and 17</p> <p>limit 18 to yr="2019 -Current"</p>	10/12/2020
OVID EMBASE	ovidsp.dc2.ovid.com	<p>exp Coronavirinae/ or exp Coronavirus/</p> <p>exp Coronavirus infection/</p> <p>((("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.</p> <p>or/1-3</p> <p>Clinical-Trial/ or Randomized-Controlled-Trial/ or Randomization/ or Single-Blind-Procedure/ or Double-Blind-Procedure/ or Crossover-Procedure/ or Prospective-Study/ or Placebo/</p> <p>((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,</p> <p>5 or 6</p> <p>4 and 7</p> <p>limit 8 to yr="2019 -Current"</p>	10/12/2020

## 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. We receive studies that [EPPI Centre](#) has screened after searching weekly in Medline and Embase. We supplement these studies with a weekly search in Scopus. The retrieved hits were imported into an Endnote database and combined with generic names of the 15 included COVID-19 drugs.

**Table 6-2 Search strategy to identify observational studies**

Database	URL	Search terms / Search modality	Date of search
OVID Medline	Imported from EPPI Centre	<p>1 exp Coronavirus/      2 exp Coronavirus Infections/      3 (coronavirus* or corona virus* or OC43 or NL63 or 229E or HKU1 or HCoV* or ncov* or covid* or sarscov* or sarscov* or Sars-coronavirus* or Severe Acute Respiratory Syndrome Coronavirus*.mp.      4 (or/1-3) and ((20191* or 202*).dp. or 20190101:20301231.(ep.))      5 4 not (SARS or SARS-CoV or MERS or MERS-CoV or Middle East respiratory syndrome or camel* or dromedar* or equine or coronary or coronal or cvidence* or covidien or influenza virus or HIV or bovine or calves or TGEV or feline or porcine or BCoV or PED or PEDV or PDCoV or FIPV or FCoV or SADS-CoV or canine or CCov or zoonotic or avian influenza or H1N1 or H5N1 or H5N6 or IBV or murine corona*).mp.      6 ((pneumonia or covid* or coronavirus* or corona virus* or ncov* or 2019-ncov or sars*).mp. or exp pneumonia/ and Wuhan.mp.      7 (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 on 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.      8 COVID-19.rx,px,ox. or severe acute respiratory syndrome coronavirus 2.os.      9 ("32240632" or "32236488" or "32268021" or "32267941" or "32169616" or "32267649" or "32267499" or "32267344" or "32248853" or "32246156" or "32243118" or "32240583" or "32237674" or "32234725" or "32173381" or "32227595" or "32185863" or "32221979" or "32213260" or "32205350" or "32202721" or "32197097" or "32196032" or "32188729" or "32176889" or "32088947" or "32277065" or "32273472" or "32273444" or "32145185" or "31917786" or "32267384" or "32265186" or "32253187" or "32265567" or "32231286" or "32105468" or "32179788" or "32152361" or "32152148" or "32140676" or "32053580" or "32029604" or "32127714" or "32047315" or "32020111" or "32267950" or "32249952" or "32172715").ui.      10 or/6-9      11 5 or 10</p>	26/10/2020 until 30/11/2020  And from 1/09/2020 until 30/11/2020 for the new compounds Regeneron, Bamlanivimab, Baricitinib, Molnupiravir
OVID EMBASE		<p>1 exp Coronavirus Infections/      2 exp coronavirinae/      3 (coronavirus* or corona virus* or OC43 or NL63 or 229E or HKU1 or HCoV* or ncov* or covid* or sarscov* or sarscov* or Sars-coronavirus* or Severe Acute Respiratory Syndrome Coronavirus*.mp.      4 or/1-3      5 4 not (SARS or SARS-CoV or MERS or MERS-CoV or Middle East respiratory syndrome or camel*</p>	26/10/2020 until 30/11/2020

		<p>or dromedar* or equine or coronary or coronal or covidience* or covidien or influenza virus or HIV or bovine or calves or TGEV or feline or porcine or BCoV or PED or PEDV or PDCoV or FIPV or FCoV or SADS-CoV or canine or CCov or zoonotic or avian influenza or H1N1 or H5N1 or H5N6 or IBV or murine corona*).mp.</p> <p>6 ((pneumonia or covid* or coronavirus* or corona virus* or ncov* or 2019-ncov or sars*).mp. or exp pneumonia) and Wuhan.mp.</p> <p>7 (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 Pandem*2)) or ((covid or covid19 or covid-19) and pandemic*2) or (coronavirus* and pneumonia)).mp.</p> <p>8 6 or 7</p> <p>9 5 or 8</p>	<p>And from 1/09/2020 until 30/11/2020 for the new compounds Regeneron, Bamlanivimab, Baricitinib, Molnupiravir</p>
Scopus		<p>TITLE-ABS-KEY(((pneumonia OR covid* OR coronavirus* OR "corona virus*" OR ncov* OR 2019-ncov OR sars*) AND Wuhan) OR 2019-ncov OR ncov19 OR ncov-19 OR "2019-novel CoV" OR sarscov2 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) W/1 (CoV OR nCoV OR covid OR coronavirus* OR "corona virus*" OR pandem*)) OR ((covid OR covid19 OR covid-19) AND pandemic*) OR ((coronavirus* OR "corona virus*") AND pneumonia)) AND ORIG-LOAD-DATE &gt; 20200920[date changes from week to week] AND ORIG-LOAD-DATE &lt; 20200928 [date changes from week to week] AND NOT INDEX(medline)</p>	<p>26/10/2020 until 30/11/2020</p> <p>And from 1/09/2020 until 30/11/2020 for the new compounds Regeneron, Bamlanivimab, Baricitinib, Molnupiravir</p>

### 6.3 Search strategy to identify ongoing studies

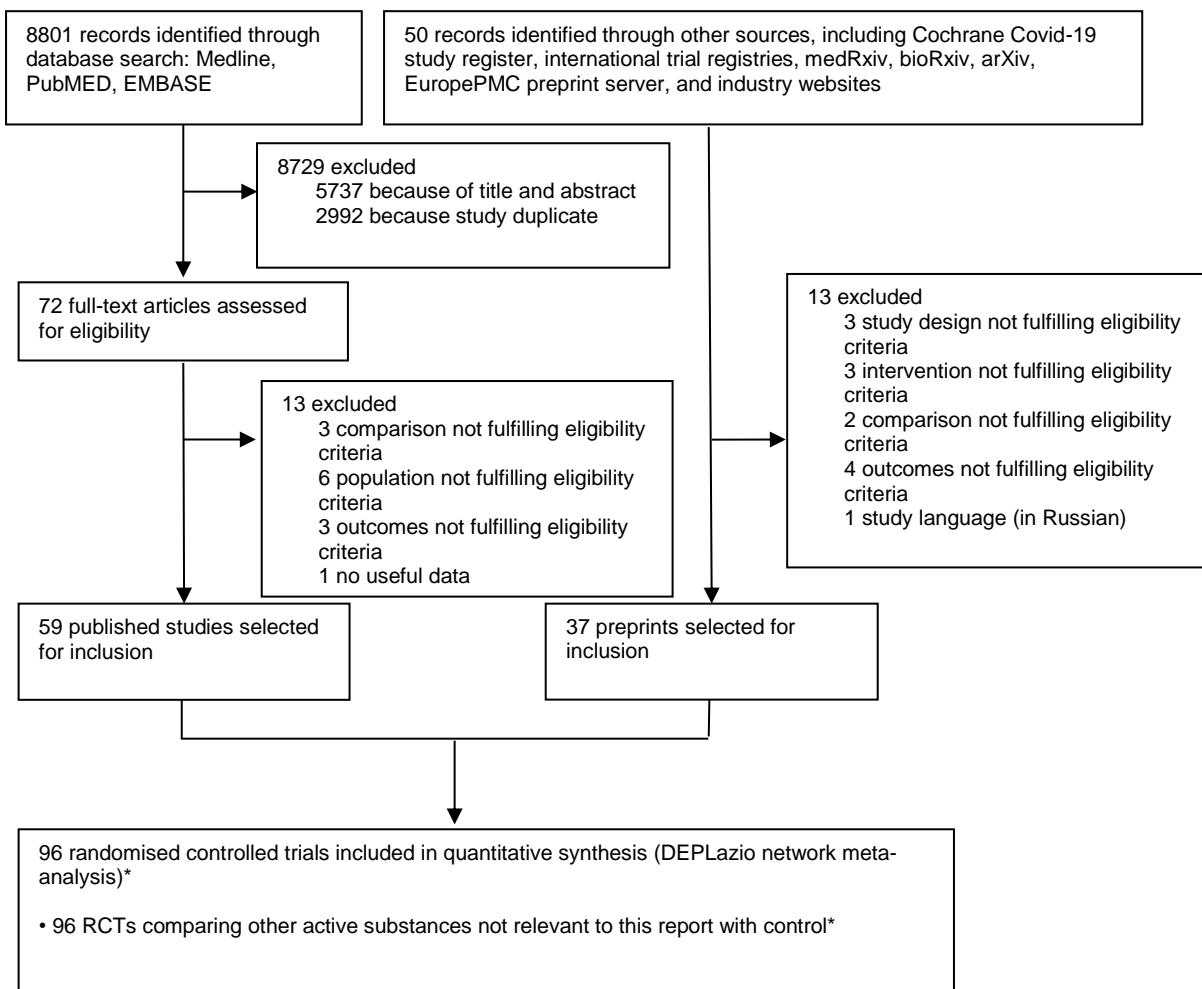
AIHTA is responsible for searching in trial registries to identify ongoing and unpublished studies. The combination of search terms related to COVID-19 and solnatide are described in Appendix Table 6-3.

**Table 6-3 Search strategy to identify ongoing studies**

Database	URL	Search line / search terms	Date of search	Hits retrieved
ClinicalTrials.gov	<a href="https://clinicaltrials.gov/">https://clinicaltrials.gov/</a>	"Basic search mode" Terms used at Condition or disease: covid-19 Terms used at "other terms": Solnatide	12/12/2020	0 0 new
ISRCTN	<a href="https://www.isrctn.com/">https://www.isrctn.com/</a>	Basic search mode Search terms: covid-19 and Solnatide SARS-CoV-2 and Solnatide	12/12/2020	0 0 new
European Clinical Trials Registry	<a href="https://www.clinicaltrialsregister.eu/">https://www.clinicaltrialsregister.eu/</a>	Basic search mode Search terms: covid-19 and Solnatide SARS-CoV-2 and Solnatide	12/12/2020	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".

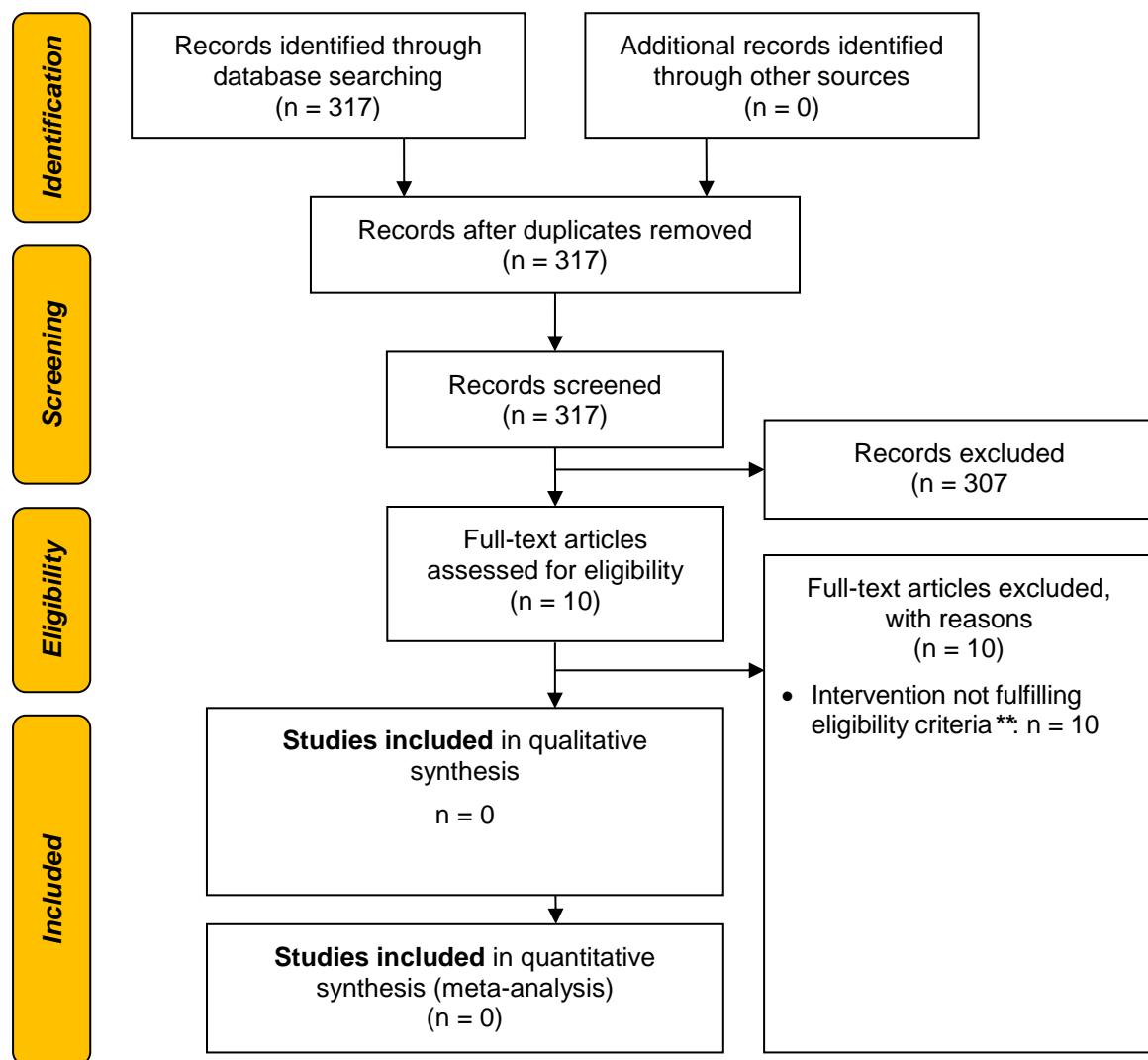
## 6.4 Flow diagrams



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

**Abbreviation:** 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