EUnetHTA Joint Action 3 WP4

“Rolling Collaborative Review” of Covid-19 treatments

ANAKINRA FOR THE TREATMENT OF COVID-19

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Monitoring Report

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V 6.0	**20/01/2021**	Sixth version
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V 7.1	**March 2021**	Literature searches, Literature screening, Clinical Trials Registries search, Data extraction
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Major changes from previous version

Chapter, page no.	Major changes from version 7.0
Chapter 4	1 new ongoing RCT added (RECOVERY)

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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
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/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	Anakinra (Kineret®): immunosuppressive medicine, a copy of a natural human protein - 'human interleukin 1 receptor antagonist' (r-metHuIL-1ra, produced in Escherichia coli cells by recombinant DNA technology); it neutralises the biologic activity of interleukin-1α (IL-1α) and interleukin-1β (IL-1β) by competitively inhibiting their binding to interleukin-1 type I receptor (IL-1RI). Interleukin-1 (IL-1) is a pivotal pro-inflammatory cytokine mediating many cellular responses including those important in synovial inflammation.
Comparison	Any active treatment, placebo, or standard of care. **Rationale**: Since there is no gold standard treatment any comparator is acceptable as well as the above listed interventions.
Outcomes	<u>Main outcome:</u> • All-cause Mortality (Survival) <u>Additional Outcomes:</u> Efficacy: • Length of hospital stay, • Viral burden (2019-nCoV RT-PCR negativity), • Clinical progression (WHO Clinical Progression Scale measured daily over the course of the study), • Rates of hospitalization and of patients entering ICU, • Duration of mechanical ventilation, • Quality of life. Safety: • Adverse events (AE), • Severe adverse events (SAE), • Withdrawals due to AEs, • Most frequent AEs, • Most frequent SAEs. **Rationale:** We will give priority according to the Core Outcome Set for Clinical Trials on Coronavirus Disease 2019 (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7102592/pdf/main.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 Table 6-2.

Population	See project Scope
Intervention	Anakinra (Kineret®): immunosuppressive medicine, a copy of a natural human protein - 'human interleukin 1 receptor antagonist' (r-metHuIL-1ra, produced in Escherichia coli cells by recombinant DNA technology); it neutralises the biologic activity of interleukin-1α (IL-1α) and interleukin-1β (IL-1β) by competitively inhibiting their binding to interleukin-1 type I receptor (IL-1RI). Interleukin-1 (IL-1) is a pivotal pro-inflammatory cytokine mediating many cellular responses including those important in synovial inflammation.
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 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 Table 6-3.

Data are presented in tabular form.

3 ABOUT THE TREATMENT

3.1 Mode of Action

Anakinra (Kineret®) is an immunosuppressive medicine, a copy of a natural human protein - 'human interleukin 1 receptor antagonist' (r-metHuIL-1ra, produced in Escherichia coli cells by recombinant DNA technology). Anakinra neutralises the biologic activity of interleukin-1α (IL-1α) and interleukin-1β (IL-1β) by competitively inhibiting their binding to interleukin-1 type I receptor (IL-1RI). Interleukin-1 (IL-1) is a pivotal pro-inflammatory cytokine mediating many cellular responses including those important in synovial inflammation [4]. Boehringer Ingelheim RCV GmbH & Co KG, Austria and Pfizer Health AB, Sweden, are listed as manufacturers of the biological active substance, and Swedish Orphan Biovitrum AB, Sweden, as Marketing Authorisation Holder, responsible for batch release.

3.2 Regulatory Status

Anakinra is authorised in the EU for Rheumatoid Arthritis (RA), Cryopyrin-Associated Periodic Syndromes (CAPS), Familial Mediterranean Fever (FMF) and Still's Disease [4, 5]. Kineret® received a marketing authorisation valid throughout the European Union on 8 March 2002; Anakinra received the FDA approval in November 2001. It is available as a solution for injection under the skin.

Anakinra is not authorised in Covid-19 patients (EMA, FDA) [5].

3.3 Level of Evidence

Currently, one publication related to an RCT of anakinra treatment in COVID-19 patients was found.

The CORIMUNO-19 Collaborative group published results from a multicentre, open-label, Bayesian randomised clinical trial (**CORIMUNO-ANA-1, NCT04341584**), nested within the CORIMUNO-19 cohort in France, with mild-to-moderate COVID-19 pneumonia, severe acute respiratory syndrome coronavirus 2 infection confirmed by real-time RT-PCR, requiring at least 3 L/min of oxygen by mask or nasal cannula but without ventilation assistance, a score of 5 on the WHO Clinical Progression Scale (WHO-CPS), and a C-reactive protein serum concentration of more than 25 mg/L not requiring admission to the intensive care unit at admission to hospital [6]. Eligible patients were randomly assigned (1:1), stratified by centre and blocked with varying block sizes (randomly of size two or four), to either usual care plus anakinra (200 mg twice a day on days 1–3, 100 mg twice on day 4, 100 mg once on day 5) or usual care alone. Usual care was provided at the discretion of the site clinicians. The two co-primary outcomes were the proportion of patients who had died or needed non-invasive or mechanical ventilation by day 4 (i.e., a score of >5 on the WHO-CPS) and survival without need for mechanical or non-invasive ventilation (including high-flow oxygen) at day 14. Details can be found in Table 4-1.

The study was **stopped early,** following the recommendation of the data and safety monitoring board, after the recruitment of 116 patients: 59 were assigned to the anakinra group and 57 were assigned to the usual care group. Two patients in the usual care group withdrew consent and were not analysed. In the analysable population, the median age was 66 years (IQR 59 to 76) and 80 (70%) participants were men. In the anakinra group, 21 (36%) of 59 patients had a WHO-CPS score of more than 5 at day 4 versus 21 (38%) of 55 in the usual care group (median posterior absolute risk difference –2·5%, 90% credible interval [CrI] –17.1 to 12.0), with a posterior probability of ARD of less than 0 (i.e., anakinra better than usual care) of 61.2%. At day 14, 28 (47%; 95% CI 33 to 59) patients in the anakinra group and 28 (51%; 95% CI 36 to 62) in the usual care group needed ventilation or died, with a posterior probability of any efficacy of anakinra (hazard ratio [HR] being less than 1) of 54.5% (median posterior HR 0.97; 90% CrI 0.62 to 1.52). At day 90, 16 (27%) patients in the anakinra group and 15 (27%) in the usual care group had died. Serious adverse events occurred in 27 (46%) patients in the anakinra group and 21 (38%) in the usual care group (p=0.45).

Related to safety evidence from prospective observational studies, four prospective cohort studies were found: one is the Ana-COVID study with 52 consecutive severe Covid-19 patients who received subcutaneous anakinra at a dose of 100 mg twice daily for 72 h, followed by 100 mg daily for 7 days, in addition to the standard treatment and supportive care (with a historical comparison group, n=44

patients, who received standard care), published by Huet et al. 2020 [7]. Safety outcomes measured were an increase in liver aminotransferase enzymes (more than three times the upper limit of normal), thromboembolic events (confirmed by a CT pulmonary angiogram for pulmonary embolism and by a venous doppler for deep vein thrombosis of the lower limbs), bacteraemia (confirmed when the patient had a recognised pathogen cultured from one or more blood cultures), and premature discontinuation of treatment. Authors reported an increase in liver aminotransferases occurred in seven (13%) patients in the anakinra group and four (9%) patients in the historical group. Ten (19%) patients in the anakinra group and five (11%) in the historical group developed a thromboembolic event during the hospital stay. Among the anakinra group, seven (13%) had a pulmonary embolism, three (6%) had deep vein thrombosis of the lower limbs, and one (2%) had arterial thrombosis. None of the patients in the anakinra group had a documented bacterial infection during the hospital stay [7].

The 2nd, published by Bozzi et al. [8], is related to a prospective observational cohort study at a tertiary health care facility in Italy, including a total of 120 COVID-19 patients with hyperinflammation (32.5% on mechanical ventilation). Of these, 65 were treated with a combination of anakinra and methylprednisolone, and 55 were untreated historical controls. Grade 3 or greater gamma-glutamyl transferase increase (27.7%), anemia (24.6%), alanine transaminase increase (6.2%), and granulocytopenia (1.5%) were observed in treated patients; a comparable proportion of these adverse events was observed within controls. Nine bloodstream infections (13.8%) were observed in the anakinra + methylprednisolone group and four (7.3%) in controls (p=0.23). No significant differences in bloodstream infections or laboratory alterations were registered.

The 3rd publication by Borie et al. 2020 [9] relates to a prospective observational cohort study in France, including 108 consecutive hospitalised patients with severe COVID-19 (70 received methylprednisolone alone, and 38 methylprednisolone plus anakinra), compared with a historical control (received standard of care, n=63). Pre-existing type 2 diabetes exacerbations were noted in 29 of 108 patients (26.9%), with oral anti-diabetic drugs alone required in 10 patients (34.5%), and insulin therapy in 19 patients (65.5%). Only three patients with steroid-induced diabetes exacerbation died, all from respiratory distress, while diabetes was correctly controlled with insulin. Pseudomonas aeruginosa pneumonia and invasive aspergillosis occurred simultaneously in one patient following ICU admission. A case of abdominal varicella-zoster occurred in one patient, with favourable evolution upon valaciclovir.

The 4th publication by Kooistra et al. 2020 [10] relates to a prospective observational cohort study in the Netherlands, including mechanically ventilated COVID-19 patients admitted to the intensive care unit (ICU) (21 received anakinra and 39 received standard care). A total of seven patients (33%) of the anakinra group developed a secondary infection during the first 28 days after alignment day versus nine patients (23%) of the control group (p=0.54).

A summary of safety evidence can be found in Table 4-3. Several ongoing RCTs and one interventional nRCT are registered in EudraCT, ISRCTN and ClinicalTrials.gov registers, including 30 to 600 COVID-19 patients per study. Eight RCTs evaluate anakinra alone, as well as one interventional nRCT (completed); one RCT evaluates anakinra alone and in combination with ruxolitinib, and one RCT evaluates anakinra alone and in combination with siltuximab or tocilizumab. Details can be found in Table 4-4,Table 4-5,Table 4-6 and Table 4-7. One RCT is the RECOVERY (Randomised Evaluation of COVid-19 thERapY) trial, led by the University of Oxford, in which anakinra is investigated as a third option in the second randomisation for children >1 year old with hyperinflammatory syndrome associated with COVID-19 in children (PIMS-TS) [11].

One RCT was found in ClinicalTrials.gov and EUdraCT registers – ANACONDA (NCT04364009) – which was terminated due to efficiency and safety reasons after enrolment of 71 hospitalized COVID-19 patients in France. The intermediate review of data from this clinical trial showed early excess mortality in the group of patients treated with anakinra combined with standard optimized care, compared to the group of patients treated with standard optimized care alone. A deleterious effect of anakinra (Kineret®) cannot be ruled out, as the information available at this stage does not explain this difference between the two treatment arms. In this context, the CHRU de Tours, sponsor of this clinical trial, suspended inclusions in the ANACONDA-COVID-19 trial.
On October 29, 2020, the French National Agency for Medicines and Health Products Safety (ANSM) announced that inclusions in clinical trials evaluating anakinra (Kineret®) in the treatment of COVID-19 are suspended due to safety information regarding the ANACONDA-COVID-19 clinical trial,

https://ansm.sante.fr/S-informer/Actualite/Suspension-des-inclusions-en-France-dans-les-essais-clinique-evaluant-l-anakinra-dans-la-prise-en-charge-de-la-COVID-19-Point-d-information.

In December 2020, ANSM lifted the suspension of trials with anakinra because after further analysis in France and the EU, the risk was not confirmed.

Two others terminated RCTs were found: NCT04366232 (JAKINCOV), due to an investigator decision in France, on anakinra alone and in combination with ruxolitinib, and NCT04324021/EudraCT 2020-001167-93 (in Italy and US) due to recruitment issues.

The US COVID-19 Treatment Guidelines Panel stated that there are insufficient data to recommend either for or against anakinra therapy in patients with COVID-19 disease [12].

4 SUMMARY

4.1 Effectiveness and Safety evidence from RCTs

Low certainty evidence from one recently published RCT (stopped early) showed that anakinra, compared to standard care, does not reduce all-cause mortality (RR 0.93, 95% CI 0.47 to 1.83; 17 fewer per 1.000, 95% CI from 125 fewer to 196 more), and doesn't increase the number of patients discharged (RR 0.93, 95% CI 0.69 to 1.26; 43 fewer per 1.000, 95% CI from 192 fewer to 161 more), as well as the number of patients with any adverse events (RR 1.18, 95% CI 0.78 to 1.76; 75 more per 1.000, 95% CI from 92 fewer to 4 318 more) and the number of patients with serious adverse events (RR 1.20, 95% CI 0.77 to 1.85; 76 more per 1.000, 95% CI from 88 fewer to 325 more) (Table 4-1).

4.2 Safety evidence from observational studies

In two prospective cohort studies with high risk of bias, an increase in liver aminotransferases and secondary infections occurred in similar frequency in both groups. More patients in the anakinra group developed a thromboembolic event (pulmonary embolism, deep vein thrombosis of the lower limbs, and arterial thrombosis). In two prospective cohort studies with high risk of bias related to the combination therapy of anakinra plus methylprednisolone, an increase in liver aminotransferases, anemia and granulocytopenia occurred in similar frequency in both groups. The same was true for bloodstream infections. Pre-existing type 2 diabetes exacerbations were noted in 26.9% patients treated with methylprednisolone alone or with combination therapy of anakinra plus methylprednisolone.

4.3 Ongoing studies

Several RCTs related to anakinra alone or in combination therapy are currently ongoing. One RCT–ANACONDA (NCT04364009) – was terminated due to efficiency and safety reasons after enrolment of 71 hospitalized COVID-19 patients. On October 29, 2020, the French National Agency for Medicines and Health Products Safety (ANSM) announced that inclusions in clinical trials evaluating anakinra (Kineret®) in the treatment of COVID-19 in France are suspended due to safety information regarding the ANACONDA-COVID-19 clinical trial. In December, ANSM lifted the suspension of trials with anakinra because after further analysis in France and the EU, the risk was not confirmed. Two further RCTs were terminated: NCT04366232 (JAKINCOV), due to an investigator decision in France, on anakinra alone and in combination with ruxolitinib, and NCT04324021/EudraCT 2020-001167-93 (in Italy and US) due to recruitment issues.

4.4 Scientific conclusion about status of evidence generation

According to one stopped-early RCT in COVID-19 patients, anakinra, compared to standard care, does not reduce all-cause mortality and doesn't increase the number of patients discharged, as well as the number of patients with any adverse events and the number of patients with serious adverse events (low certainty of evidence). Four small sample size prospective cohort studies with high risk of bias were found related to safety: in one, more patients in the anakinra group developed a thromboembolic event (pulmonary embolism, deep vein thrombosis of the lower limbs, and arterial thrombosis).

High quality evidence from ongoing RCTs is expected to further assess effectiveness and safety of anakinra in COVID-19 patients.

Table 4-1 Summary of findings (SoF) table for published RCTs related to effectiveness and safety of anakinra

Outcome	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Certainty of evidence	Comments
	Risk with Standard treatment	Risk with Anakinra				
All-cause mortality at 28 days	236 per 1000	219 per 1000	**RR 0.93** (0.47 to 1.83)	114 (1 RCT) [a]	⨁⨁◯◯ LOW	**Absolute effect (95% CI) 17 fewer per 1.000** (from 125 fewer to 196 more)
Number of patients discharged	618 per 1000	575 per 1000	**RR 0.93** (0.69 to 1.26)	114 (1 RCT) [a]	⨁⨁◯◯ LOW	**Absolute effect (95% CI) 43 fewer per 1.000** (from 192 fewer to 161 more)
Number of patients with any adverse event	418 per 1000	493 per 1000	**RR 1.18** (0.78 to 1.76)	114 (1 RCT) [a]	⨁⨁◯◯ LOW	**Absolute effect (95% CI) 75 more per 1.000** (from 92 fewer to 318 more)
Number of patients with serious adverse events	382 per 100	458 per 1000	**RR 1.20** (0.77 to 1.85)	114 (1 RCT) [a]	⨁⨁◯◯ LOW	**76 more per 1.000** (from 88 fewer to 325 more)

Source: [13]
[a] [6]
Abbreviations: CI=Confidence interval; RR=Risk ratio
Explanations: **Low certainty of evidence:** Downgraded of one level for high risk of performance bias and unclear risk of selection bias; Downgraded of one level for small sample size (<200)

Table 4-2 Study characteristics of included RCTs

Author, year, reference number/Study name/Study ID	CORIMUNO-19 Collaborative group [6] / CORIMUNO-ANA-1, NCT04341584**
Study design, study phase	RCT
Centres (single centre or multicentre), country, setting	Multicentre, France, inpatient
Patient population (number of included patients/ Mean age and sex/ Disease severity*)	116 patients: 59 were assigned to the anakinra group, and 57 were assigned to the usual care group; 66 years (IQR 59 to 76) and 80 (70%) participants were men; Severe
Inclusion criteria	Adults with mild-to-moderate COVID-19 pneumonia, severe acute respiratory syndrome coronavirus 2 infection confirmed by real-time RT-PCR, requiring at least 3 L/min of oxygen by mask or nasal cannula but without ventilation assistance, a score of 5 on the WHO Clinical Progression Scale (WHO-CPS), and a C-reactive protein serum concentration of more than 25 mg/L not requiring admission to the intensive care unit at admission to hospital
Exclusion criteria	Known hypersensitivity to anakinra or any of its excipients, pregnancy, current documented bacterial infection, an absolute neutrophil count of 1·0 × 10^9 per L or less, a platelet concentration of less than 50 G/L, serum aspartate aminotransferase or serum alanine aminotransferase of more than five-times the upper limit of normal, or severe renal insufficiency defined by an estimated glomerular filtration rate of less than 30 mL/min
Intervention (generic drug name and dosage, time frame; number of randomized/ enrolled patients in subgroups - Mild, Moderate, Severe, Critical COVID-19)	Usual care plus anakinra (200 mg twice a day on days 1–3, 100 mg twice on day 4, 100 mg once on day 5), n=59
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)	Usual care alone, n=57
Primary Outcome(s)	Proportion of patients who had died or needed non-invasive or mechanical ventilation by day 4 (ie, a score of >5 on the WHO-CPS) and survival without need for mechanical or non-invasive ventilation (including high-flow oxygen) at day 14
Patient-relevant secondary outcome(s)	Clinical status assessed with the WHO-CPS at days 4, 7, and 14; overall survival at days 14, 28, and 90; time to discharge from hospital; time to oxygen supply independency; time to negative viral excretion (not assessed due to paucity of data); biological factors (eg, C-reactive protein concentration) and adverse events.
Follow-up (days, months)	Up to 90 days
Sponsor/ lead institution	The Ministry of Health, Programme Hospitalier de Recherche Clinique, Foundation for Medical Research, and AP-HP Foundation

**Stopped early

Table 4-3 Summary of safety from observational studies (AE and SAE) of anakinra

Author, year	Huet, 2020 [7]	Bozzi, 2020 [8]	Borie, 2020 [9]	Kooistra, 2020 [10]
Country	France	Italy	France	Netherlands
Sponsor/lead institution	Groupe Hospitalier Paris Saint-Joseph	'COVID-19 NETWORK'' Working Group: Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico	Bichat University Hospital, Paris	Internally funded by the participating departments/ Radboud University Medical Center
Intervention/Product (drug name)	Anakinra	Combination of anakinra and methylprednisolone (MPD)	Combination of anakinra and methylprednisolone (MPD)	Anakinra
Dosage	100 mg twice a day for 72 h, then 100 mg daily for 7 days	Anakinra 200 mg every 8 hours for 3 days, then 100 mg every 8 hours up to day 14 + MPD 1 mg/kg loading dose, then 1 mg/kg/d (fractioned, 2 doses) for 5 days, then 0.5 mg/kg/d (fractioned, 2 doses) for 5 days, followed by 0.25 mg/kg/d (every 24 hours or fractioned) up to day 14	Methylprednisolone alone (120 mg on three consecutive days; at Day 4, switched to orally administered corticosteroids, then tapered with 40mg prednisone-equivalent for 7 days, then 20 mg for 7 days, 10 mg for another 7 days), and methylprednisolone plus anakinra (100mg anakinra daily was added subcutaneously for ≤5 days)	300 mg anakinra intravenously (i.v.), followed by 100 mg i.v. every six hours
Comparator	Standard treatments and supportive care	Standard of care (hydroxychloroquine in most cases and lopinavir/ ritonavir or remdesivir in some)	Standard of care	Standard of care
Study design	Observational prospective cohort study with historical control	Observational prospective cohort study with historical control	Observational prospective cohort study with historical control	Observational prospective cohort study
Setting	Hospital	Hospital	Hospital	Hospital
Number of pts	52 in anakinra group and 44 in historical control	65 in anakinra + MPD and 55 in historical controls	70 in MPD alone and 38 in anakinra + MPD; 63 in historical control	21 in anakinra and 39 in control

Author, year	Huet, 2020 [7]	Bozzi, 2020 [8]	Borie, 2020 [9]	Kooistra, 2020 [10]
Inclusion criteria	Aged 18 years or older and admitted to Groupe Hospitalier Paris Saint-Joseph with severe COVID-19-related bilateral pneumonia on chest x-ray or lung CT scan; either laboratory-confirmed SARS-CoV-2 or typical lung infiltrates on a lung CT scan, and either an oxygen saturation of 93% or less under oxygen 6 L/min or more, or aggravation (saturation ≤93% under oxygen 3 L/min) with a loss of 3% of oxygen saturation in ambient air over the previous 24 h.	Age more than 18 years; evidence of pneumonia; ferritin greater than or equal to 1000 ng/mL and/or CRP greater than 10 mg/dL; respiratory failure with need of supplemental oxygen (oxygen therapy from 0.4 FiO2 Venturi mask to invasive MV)	Positive SARS-CoV-2 RT-PCR; non-ICU patients; symptom duration ≥5 days; bilateral pneumonia based on non-injected thoracic CT scan, need for ≥3 L/min oxygen supply in view of ≥94% oxygen saturation measured by pulse oximetry; hyper-inflammation assessed by C-reactive protein (CRP) blood levels ≥50mg/L, or CRP between 20 and 50mg/L and increased blood ferritin (>500 µg/L) or Ddimers levels (>500 ng/mL)	Mechanically ventilated COVID-19 patients; Indication for starting treatment with anakinra was based on clinical judgment of features of hyperinflammation (including persistent high fever and/or a high plasma level of ferritin and/or progressive organ dysfunction with no apparent reason apart from hyperinflammation)
Exclusion criteria	Refusal of the patient to participate, patients who were bedridden and near the end of life, patients with respiratory failure explained by an alternative aetiology, and patients already admitted to the ICU.	Data available for less than 48 hours or death within 48 hours from inclusion; symptoms for less than 7 days; uncontrolled bacterial infections (ie, sepsis/septic shock); treatment with anakinra or MPD alone	Not meet inclusion criteria	Patients with a pre-existing immunosuppressed status or other comorbidities that could strongly influence prognosis
Age of patients (yrs)	71.0 in anakinra group vs 71.1 in historical group	62 years (interquartile range, 54.5-70 years), 80.0% (96 of 120) males	Overall, 67.1 (56.7–78.1)	63 [55–71] years in anakinra and 67 [59–72] in control group
Disease severity	Severe COVID-19-related bilateral pneumonia requiring oxygen therapy	Severe and critical: Hyperinflammation and respiratory failure	Severe	Critical
Follow-up (months)	Until discharge from hospital or death	Until day 28 or death	15 days	Until day 28
Loss to follow-up, n (%)	None	None	None	None
RoB	High	High	High	High
	Safety – Outcomes*			

Author, year	Huet, 2020 [7]	Bozzi, 2020 [8]	Borie, 2020 [9]	Kooistra, 2020 [10]
Overall AEs, n (%)	Increase in liver aminotransferases: Seven (13%) patients in the anakinra group vs four (9%) patients in the historical group Thromboembolic event: Ten (19%) patients in the anakinra group vs five (11%) in the historical group (among the anakinra group, seven (13%) had a pulmonary embolism, three (6%) had deep vein thrombosis of the lower limbs, and one (2%) had arterial thrombosis)	Grade 3 or greater gamma-glutamyl transferase increase (27.7%), anemia (24.6%), alanine transaminase increase (6.2%), and granulocytopenia (1.5%) in treated patients (comparable proportion observed within controls) Nine bloodstream infections (13.8%) in the anakinra + MPD group vs (7.3%) in controls (p=0.23)	Prospective cohort: Pre-existing diabetes exacerbation occurred in 29 of 108 patients (26.9%) Pseudomonas aeruginosa pneumonia and invasive aspergillosis in one patient Abdominal varicella-zoster in one patient	Secondary infection during the first 28 days after alignment day Seven patients (33%) of the anakinra group vs nine patients (23%) of the control group (p=0.54)
Serious AE (SAE), n (%)	Not reported as such (see above)	Not reported as such (see above)	Not reported as such (see above)	Not reported as such (see above)
Most frequent AEs n (%)	See above	See above	See above	See above
Most frequent SAEs, n (%)	Not reported as such (see above)	Not reported as such (see above)	Not reported as such (see above)	Not reported as such (see above)
AEs of special interest, n (%)	Not reported as such (see above)	Not reported as such (see above)	Not reported as such (see above)	Not reported as such (see above)
Death as SAE, n (%)	Not reported	Not reported	Not reported	Not reported
Withdrawals due AEs, n (%)	Not reported	Not reported	Not reported	Not reported

Abbreviations: RoB=Risk of Bias (Robins-I: https://training.cochrane.org/handbook/current/chapter-25)
**by arms*

Table 4-4 Ongoing trials of single agent anakinra

Trial Identifier/registry ID(s)/contact	NCT04443881, EudraCT 2020-001825-29 (ANA-COVID-GEAS)	NCT04412291, EudraCT 2020-001748-24 (ImmCoVA) Study	NCT04364009, EudraCT 2020-001734-36 (ANACONDA)	NCT04324021 EudraCT 2020-001167-93
Study design, study phase	RCT, phase 2/3	RCT, phase 2	RCT, phase 3	RCT, phase 2/3
Recruitment status	Recruiting	Recruiting	**Terminated (Efficiency and safety reasons)**	**Terminated (recruitment issues)**
Number of Patients, Disease severity*	180, Severe	120, Severe	240, COVID19, Mixed	54, Mixed
Setting (hospital, ambulatory,..)	Hospital	Hospital	Hospital	Hospital
Intervention (generic drug name and dosage)	Anakinra (100 mg/ 6 hours) i.v infusión during 15 days plus standard of care	Anakinra total dose of 400mg per day (divided in 4 doses of 100 mg iv every 6 hours) for 7 days + Standard of care	Anakinra 400mg from Day 1 to Day 3 (two injections of 100 mg each 12 hours) and 200mg the remaining 7 days plus Optimized Standard of Care (oSOC)	Anakinra i.v infusion four times daily for 15 days. 400 mg/day in total, divided into 4 doses given every 6 hours + Standard of care Emapalumab i.v infusion every 3rd day for a total 5 infusions. Day 1: 6mg/kg. Days 4, 7, 10 and 13: 3 mg/kg + Standard of care
Comparator (standard care or generic drug name and dosage)	Standard of care	Tocilizumab: 8mg/kg for a single infusion iv up to max 800 mg + Standard of care Standard of care alone	Optimized Standard of Care (oSOC)	Standard of care
Primary Outcome(s)	Treatment success, defined as number of patients not requiring mechanical ventilation by Day 15; Number of patients not requiring mechanical ventilation; Time to mechanical ventilation; Time to oxygen	Time to recovery [Time Frame: Day 1 through Day 29]	Treatment success [Time Frame: After 14 days of treatment]	Treatment success [Time Frame: Up to Day 15],
Sponsor/ lead institution, country (also country of recruitment if different)	Fundacion Miguel Servet, Spain	Karolinska University Hospital, Sweden	University Hospital, Tours, France	Swedish Orphan Biovitrum, Italy

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

Table 4-5 Ongoing trials of single agent anakinra (continued)

Trial Identifier/registry ID(s)/contact	NCT04339712, EudraCT 2020-001039-29 (ESCAPE)	NCT04603742 (SOBI)	NCT04362111	NCT04341584 (CORIMUNO-ANA)
Study design, study phase	nRCT interventional study, phase 2	RCT, phase 2	RCT, phase 3	RCT, phase 2
Recruitment status	**Completed**	Not yet recruiting	Recruiting	**Completed**
Number of Patients, Disease severity*	40, Critical	100, Severe	30, Severe	240, Mixed (severe and critical)
Setting (hospital, ambulatory,..)	Hospital	Hospital	Hospital	Hospital
Intervention (generic drug name and dosage)	Anakinra 200mg three times daily (every eight hours) for 7 days Tocilizumab 8mg/kg body weight once up to a maximum of 800mg	Anakinra 100 mg IV 4 times a day for 7 days	Anakinra 100 mg subcutaneously every 6-12 hours for a period of 10 days	Anakinra two IV infusions / day 200mg (total 400 mg) at day 1 (D1), D2 and D3, two IV infusions / day 100mg (total 200 mg) at day 4 (D4), and one IV infusion 100mg (total 100 mg) at day 5 (D5)
Comparator (standard care or generic drug name and dosage)	No comparator	Normal saline IV	Normal saline placebo subcutaneously every 6-12 hours for period of 10 days	Standard of care
Primary Outcome(s)	Change of baseline total sequential organ failure assessment (SOFA) score; Improvement of lung involvement measurements; Increase of pO2/FiO2 ratio	Number of subjects alive without having required mechanical ventilation [Time Frame: 28 days post randomization]	Percentage of patients discharged from the hospital alive and without the need for mechanical ventilation [Time Frame: Variable up to Day 28]	Survival without needs of ventilator utilization at day 14 [Time Frame: 14 days]; WHO progression scale ≤ 5 [Time Frame: 4 days]; Cumulative incidence of successful tracheal extubation; Decrease of at least one point in WHO progression scale score [Time Frame: 4 days]
Sponsor/ lead institution, country (also country of recruitment if different)	Hellenic Institute for the Study of Sepsis, Greece	Weill Medical College of Cornell University, US	University of Alabama at Birmingham, US	Assistance Publique - Hôpitaux de Paris, France

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

Table 4-6 Ongoing trials of single agent anakinra (continued)

Trial Identifier/registry ID(s)/contact	ISRCTN67000769; NCT02735707; EudraCT2015-002340-14 (REMAP-CAP)	NCT04643678	NCT04680949, EudraCT2020-00528-11, (SAVE-MORE)	NCT04381936 RECOVERY EudraCT 2020-001113-21 ISRCTN50189673
Study design, study phase	RCT, phase 4	RCT, phase 2/3	RCT, phase 3	RCT, phase 2/3
Recruitment status	Recruiting	Recruiting	Recruiting	Recruiting
Number of Patients, Disease severity*	7100, Severe	80, Critical	600, Moderate and Severe	20000, Mixed
Setting (hospital, ambulatory...)	Hospital	Hospital	Hospital	Hospitalised
Intervention (generic drug name and dosage)	Anakinra (loading dose 300mg, followed by maintenance doses of 100mg administered every 6 hours) (as COVID-19 immune modulation – pandemic) (As one intervention among other drugs in pandemic - antivirals, immune modulation, immunoglobulin therapy, anticoagulation, simvastatin, vitamin C therapy, corticosteroids, antibiotic domain, macrolide domain...)	Anakinra 100 mg SC injection every 12 hours for 3 days, then 100 mg once daily from day 4 to day 7 plus Standard of Care	Anakinra 100 mg once daily for 10 days + Standard of care	Lopinavir-Ritonavir, Hydroxychloroquine, Corticosteroids, Azithromycin, IV Immunoglobulin (children >44 weeks gestational age with PIMS-TS only), Convalescent plasma, Synthetic neutralizing antibodies (REGN-COV2) single dose of REGN10933 + REGN10987 8 g, Tocilizumab, Aspirin, Colchicine, Baricitinib 4 mg, Anakinra (children with PIMS-TS only)
Comparator (standard care or generic drug name and dosage)	No immune modulation for COVID-19	Standard care alone	Placebo + Standard of care	Standard care
Primary Outcome(s)	All-cause mortality; Days alive and outside of ICU	Treatment Success at day 14 [Time Frame: Day 14]	Comparison of the distribution of frequencies of each score of a 5-scale patient state evaluated from the 11-point WHO Clinical Progression ordinal Scale (CPS) between the two arms of treatment [Time Frame: 28 days]	All-cause mortality [Within 28 days after randomisation]
Sponsor/ lead institution, country (also country of recruitment if different)	Hospital/treatment centre, Australia, Belgium, Canada, Croatia, Germany, Hungary, Ireland, Netherlands, New Zealand, Portugal, Romania, Spain, United Kingdom	Hamad Medical Corporation, Qatar	Hellenic Institute for the Study of Sepsis, Greece	University of Oxford United Kingdom

*Mixed COVID-19, Mild, Moderate, Severe, Critical COVID-19; PIMS-TS=hyperinflammatory syndrome associated with COVID-19 in children

Table 4-7 Ongoing trials of singe agent anakinra (continued) and combination therapies

Trial Identifier/registry ID(s)/contact	NCT04330638, EudraCT 2020-001500-41 (COV-AID)	EudraCT 2020-001754-21, NCT04424056 (INFLAMMACOV)	EudraCT 2020-001963-10, NCT04366232 (JAKINCOV)
Study design, study phase	RCT, phase 3	RCT, phase 3	RCT, phase 3
Recruitment status	Active, not recruiting	Ongoing	**Terminated (Investigator decision)**
Number of Patients, Disease severity*	342, Critical	150, Severe (stage 2b and 3)	54, Mixed (severe and Critical)
Setting (hospital, ambulatory...)	Hospital	Hospital	Hospital
Intervention (generic drug name and dosage)	Anakinra alone (as a daily subcutaneous injection of 100 mg for 28 days or until hospital discharge, whichever is first) Siltuximab alone (via single IV infusion at a dose of 11 mg/kg) Tocilizumab alone (via single IV infusion at a dose of 8 mg/kg with a maximum infusion of 800 mg/injection) Anakinra + Siltuximab Anakinra + Tocilizumab	Anakinra alone Tocilizumab alone or in combination with Ruxolitinib	Anakinra with or without Ruxolitinib
Comparator (standard care or generic drug name and dosage)	Usual care	Standard of care	Standard of care
Primary Outcome(s)	Time to Clinical Improvement [Time Frame: at day 15]	Ventilation free days at D28 (VFD28) (an increase of 5 days VFD28 is expected)	Biological criteria: validation if at least 3 parameters are met including CRP and/or Ferritin 1) CRP: decrease > 50% 2) Ferritinemia: decrease > 1/3 3) Serum creatinine: decrease > 1/3 4) AST/ALT: decrease > 50% 5) Eosinophils > 50 /mm3 6) Lymphocytes > 1000 /mm3
Sponsor/ lead institution, country (also country of recruitment if different)	University Hospital, Ghent / Belgium Health Care Knowledge Centre, Belgium	Assistance Publique Hôpitaux de Marseille, France	Centre Hospitalier Intercommunal de Toulon La Seyne-sur-mer, France

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

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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/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 [14] and NIPHNO [15] 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]	From 4/2/2021 until 26/2/2021

		3 (COVID-19 serotherapy/ or Immunization, Passive/ or tocilizumab/ or camostat/ or nafamostat/ or AP301 peptide/ or Interleukin 1 Receptor Antagonist Protein/ or alunacedase alfa/ or darunavir/ or favipiravir/ or sarilumab/ or exp Interferons/ or gimsilumab/ or canakinumab/ or 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

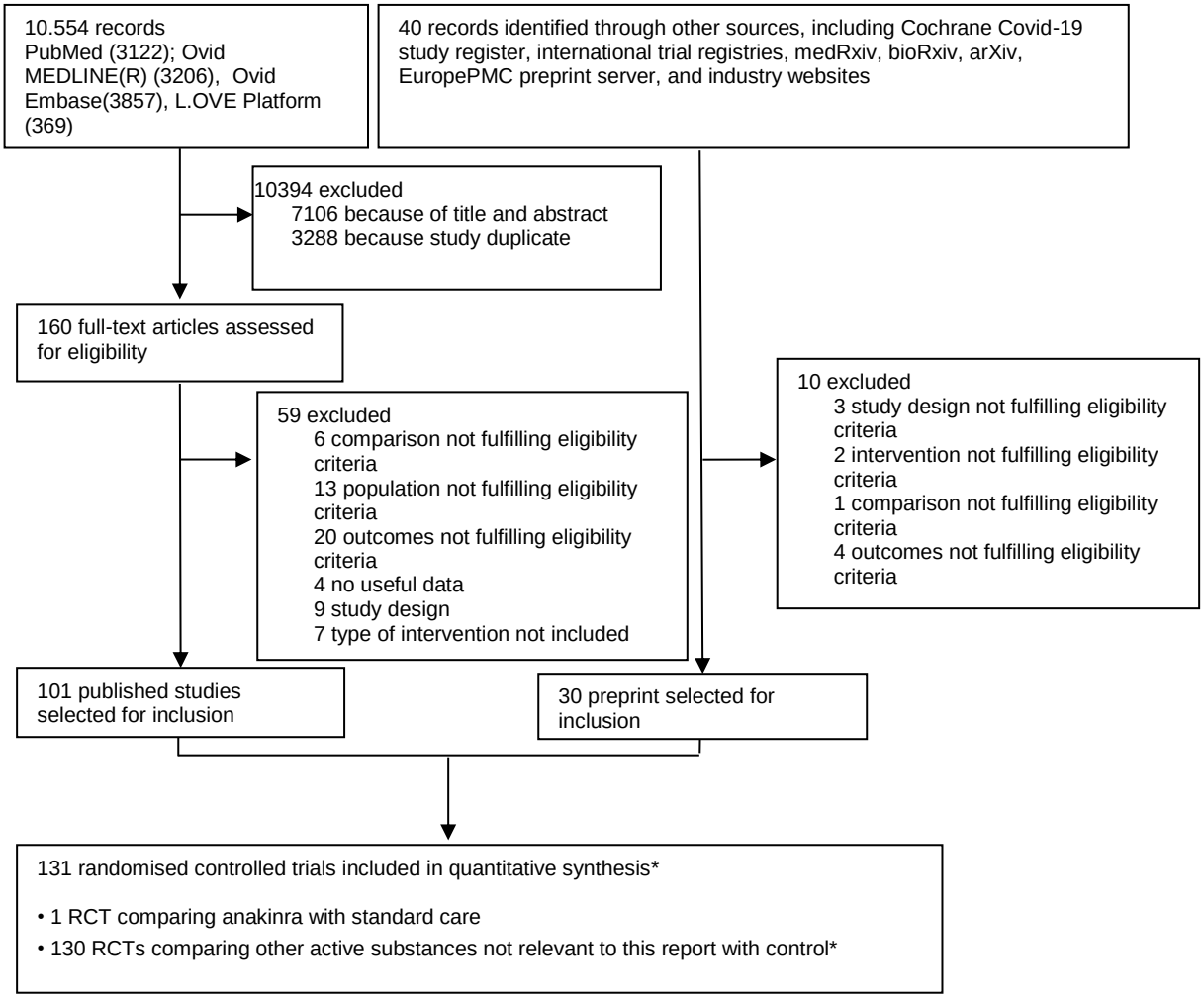
AIHTA is responsible for searching in trial registries to identify ongoing and unpublished studies. The combination of search terms related to COVID-19 and anakinra are described in Appendix Table 6-3.

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": • Anakinra • IL-1RA	10/03/2021	28 1 new
ISRCTN	https://www.isrctn.com/	Basic search mode Search terms: 1. covid-19 and Anakinra 2. covid-19 and Kineret 3. covid-19 and Kinaret 4. covid-19 and IL-1RA 5. covid-19 and rIL-1ra 6. SARS-CoV-2 and Anakinra 7. SARS-CoV-2 and Kineret 8. SARS-CoV-2 and Kinaret 9. SARS-CoV-2 and IL-1RA 10. SARS-CoV-2 and rIL-1ra	10/03/2021	3 1 new
European Clinical Trials Registry	https://www.clinicaltrialsregister.eu/	Basic search mode Search terms: 1. covid-19 and Anakinra 2. covid-19 and Kineret 3. covid-19 and Kinaret 4. covid-19 and IL-1RA 5. covid-19 and rIL-1ra 6. SARS-CoV-2 and Anakinra 7. SARS-CoV-2 and Kineret 8. SARS-CoV-2 and Kinaret 9. SARS-CoV-2 and IL-1RA 10. SARS-CoV-2 and rIL-1ra	10/03/2021	16 1 new

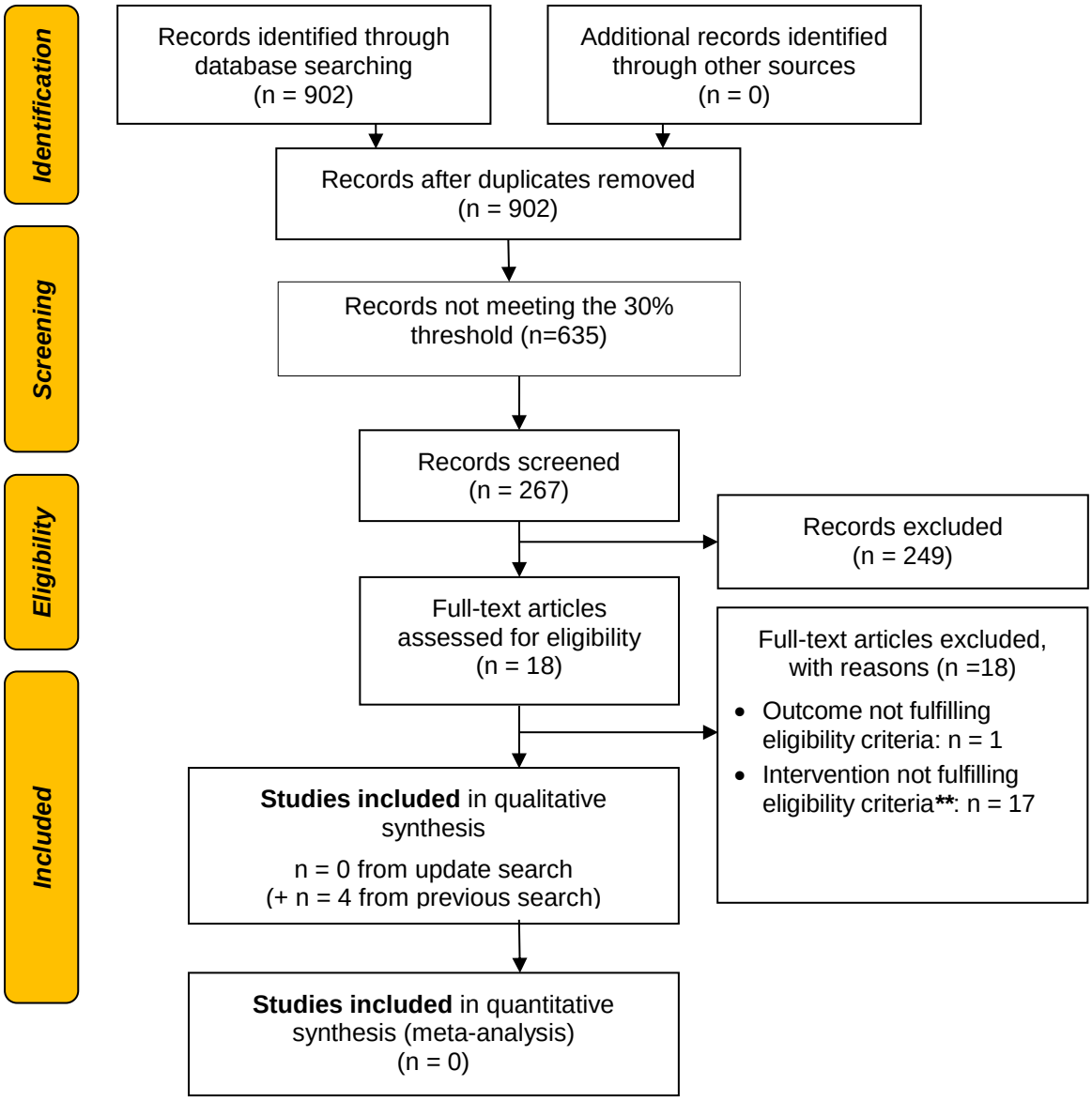
*****In Basic search mode, one term was added to the field "condition or disease" and one term in the field "other terms".*

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