EUnetHTA Joint Action 3 WP4

"Rolling Collaborative Review" of Covid-19 treatments

CANAKINUMAB FOR THE TREATMENT OF COVID-19

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Major changes from previous version

Chapter, page no.	Major changes from version 3.0
p.13	One observational study is added

Disclaimer

The content of this “Rolling Collaborative Review” (RCR) represents a consolidated view based on the consensus within the Authoring Team; it cannot be considered to reflect the views of the European Network for Health Technology Assessment (EUnetHTA), EUnetHTA’s participating institutions, the European Commission and/or the Consumers, Health, Agriculture and Food Executive Agency or any other body of the European Union. The European Commission and the Agency do not accept any responsibility for use that may be made of the information it contains.

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Conflict of interest

All authors and co-authors involved in the production of this living document have declared they have no conflicts of interest in relation to the technology and comparator(s) assessed according to the EUnetHTA declaration of interest (DOI) form. Conflict of Interest was evaluated following the EUnetHTA Procedure Guidance for handling DOI form (https://eunethta.eu/doi).

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LIST OF ABBREVIATIONS

AE	Adverse Event
CI	Confidence Interval
DOI	Declaration of interest
EUnetHTA	European Network of Health Technology Assessment
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
HR	Hazard Ratio
ICD	International Classification of Diseases
MD	Mean Difference
MeSH	Medical Subject Headings
NA	Not applicable
NR	Not reported
OR	Odds Ratio
RCT	Randomized Controlled Trial
RCR	Rolling Collaborative Review
REA	Relative Effectiveness Assessment
RR	Relative Risk
SAE	Serious Adverse Event
SD	Standard Deviation
SMD	Standardized Mean Difference
SoC	Standart of care
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	Treatment with canakinumab - a human monoclonal anti-human interleukin-1 beta (IL-1 beta) antibody of the IgG1/κ isotype. Canakinumab binds with high affinity specifically to human IL-1 beta and neutralises the biological activity of human IL-1 beta by blocking its interaction with IL-1 receptors, thereby preventing IL-1 beta-induced gene activation and the production of inflammatory mediators.
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 bi-monthly basis.

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

Population	See project Scope
Intervention	Treatment with canakinumab - a human monoclonal anti-human interleukin-1 beta (IL-1 beta) antibody of the IgG1/κ isotype. Canakinumab binds with high affinity specifically to human IL-1 beta and neutralises the biological activity of human IL-1 beta by blocking its interaction with IL-1 receptors, thereby preventing IL-1 beta-induced gene activation and the production of inflammatory mediators.
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 SMCA 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 SMCA 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

Canakinumab is a human monoclonal anti-human interleukin-1 beta (IL-1 beta) antibody of the IgG1/κ isotype manufactured by Novartis Pharma AG. Canakinumab binds with high affinity specifically to human IL-1 beta and neutralises the biological activity of human IL-1 beta by blocking its interaction with IL-1 receptors, thereby preventing IL-1 beta-induced gene activation and the production of inflammatory mediators [5].

3.2 Regulatory Status

Canakinumab - ATC-code L04AC08 - has orphan designation for familial mediterranean fever; cryopyrin-associated periodic syndromes; juvenile rheumatoid arthritis; inflammation; peroxisomal disorders; familial autosomal dominant periodic fever [5, 6].
Canakinumab has EMA approved indications for:

- Periodic fever syndromes;
- Cryopyrin-associated periodic syndromes;
- Cryopyrin-associated periodic syndromes
- Tumour necrosis factor receptor associated periodic syndrome (TRAPS);
- Hyperimmunoglobulin D syndrome (HIDS)/mevalonate kinase deficiency (MKD);
- Familial Mediterranean fever (FMF)
- Still's disease;
- Gouty arthritis

3.3 Level of Evidence

There are two ongoing studies: Phase II and Phase III – CAN-COVID and Phase III – CAN-COVID with diabetic patients of canakinumab [7, 8]. The purpose of CAN-COVID for diabetic patients is to evaluate whether canakinumab has beneficial effects on patients with Type 2 diabetes mellitus and coronavirus disease 19 (COVID19). One observational study of canakinumab for Covid-19 treatment is included in this updated analysis; however, detailed safety data are lacking [10].

4 SUMMARY

4.1 Effectiveness and Safety evidence from RCTs

There are no published RCTs related to effectiveness and safety of canakinumab for Covid-19. Only preliminary interim results are presented from the CAN-COVID trial where the CAN-COVID trial failed to meet its primary endpoint showing that treatment with canakinumab plus standard of care (SoC) did not demonstrate a significantly greater chance of survival for patients without the need for invasive mechanical ventilation, compared with placebo plus SoC up to Day 29 [7]. The trial did not meet its key secondary endpoint of reducing the COVID-19-related death rate during the 4-week period after treatment. The safety profiles of canakinumab plus SoC and placebo plus SoC were comparable.

4.2 Safety evidence from observational studies

One observational study of canakinumab for Covid-19 treatment is included in this updated analysis; however, detailed safety data are lacking [10].

4.3 Ongoing studies

Three studies of canakinumab are ongoing: For the Phase III studies, the estimated study completion dates are in December 2020 and September 2023. The estimated completion date of the Phase II study is in December 2020. Also, one observational study (NCT04348448) of canakinumab is planned, but not yet recruiting. The study is configured as a retrospective and prospective observational study. The study will be multi-center and will involve all COVID-19 pneumonia patients treated with canakinumab administered subcutaneously. [7-9].

One observational study (NCT04348448) of canakinumab is planned, but not yet recruiting. The study is configured as a retrospective and prospective observational study. The study will be multi-center and will involve all COVID-19 pneumonia patients treated with canakinumab administered subcutaneously [8].

4.4 Scientific conclusion about status of evidence generation

At the moment, the effectiveness and safety of canakinumab treatment from RCTs in COVID-19 patients could not be assessed. Especially knowing that the CAN-COVID trial failed to meet its primary endpoint, showing that treatment with canakinumab plus standard of care (SoC) did not demonstrate a significantly greater chance of survival for patients without the need for invasive mechanical ventilation, compared with placebo plus SoC up to Day 29.

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

Author, year	Generali et al 2020 [10]
Country	Italy
Sponsor/ lead institution	This research did not receive any specific grant from funding agencies in the public, commercial or not-for-profit sectors. Maurizio Scaltrici is funded by the National Cancer Institute (NCI), USA under the MSK Cancer Center Support Grant/Core Grant
Intervention/Product (drug name)	Canakinumab
Dosage	Canakinumab (150 mg) administered by subcutaneous injection on day 1 and on day 7,
Comparator	Standart of care
Study design	Observational, case-control study
Setting	hospital
Number of pts	33 patients received canakinumab (Cohort 1) and 15 patients (Controls) receive the institutional standard of care (Cohort 2).
Inclusion criteria	Patients with moderate COVID-19-related pneumonia
Exclusion criteria	n.a.
Age of patients (yrs)	Median age was similar in Cohort 1 (70 years, range 29–89) and Cohort 2 (69 years, range 44–85).
Disease severity	Moderate
Follow-up (months)	Hospitalization days (range) <14->21
Lost to follow-up, n (%)	0
RoB	high
Overall AEs, n (%)	n.a
Serious AE (SAE), n (%)	n.a.
Most frequent AEs n (%)	n.a.
Most frequent SAEs, n (%)	n.a.
AEs of special interest, n (%)	n.a.
Death as SAE, n (%)	n.a.
Withdrawals due AEs, n (%)	n.a.

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

Table 4-2 Ongoing trials of single agent Canakinumab

Active substance	**Canakinumab**	**Canakinumab**	**Canakinumab**
Sponsor	Novartis Pharmaceuticals	The Cleveland Clinic in collaboration with Novartis	University Hospital, Basel, Switzerland in collaboration with Novartis and Swiss National Science Foundation
Trial Identifier	NCT04362813	NCT04365153	NCT04510493
Phase & Intention	Phase III. To assess the efficacy and safety of **canakinumab** in patients with COVID-19-induced pneumonia and CRS.	Phase II. To demonstrate as a proof of concept that early treatment with **canakinumab** prevents progressive heart and respiratory failure in patients with COVID-19 infection. These results will lead to and inform a Phase III randomized placebo-controlled trial.	Phase III. The purpose of this study is to evaluate whether **canakinumab** has beneficial effects on patients with Type 2 diabetes mellitus and coronavirus disease 19 (COVID19).
Study design	**RCT**, multicenter, randomized, double-blind, placebo-controlled study	**RCT**, single center, quadruple-blinded, randomized, placebo- controlled study	**RCT**, parallel assignment, double-blinded, placebo-controlled study
Status trial	Recruiting, started April 30, 2020	Recruiting, started April 24, 2020	Not yet recruiting
Duration/End of Study	Estimated Primary Completion Date: August 28, 2020 Estimated Study Completion Date: December 4, 2020	Estimated Primary Completion Date: December 31, 2020; Estimated Study Completion Date: December 31, 2020	Estimated Primary Completion Date: September 2023 Estimated Study Completion Date: September 2023
Study details			
Number of Patients	Estimated Enrolment n=450 (12 Years and older)	n= 45 (Adult, Older Adult; 18 Years and older)	n= 116 (Adult, Older Adult; 18 Years and older)
Location/Centres	France, Germany, Hungary, Italy, Russian Federation, Spain, United Kingdom, United States	US	Switzerland
Intervention	Canakinumab 450 mg for body weight 40-<60 kg, 600 mg for 60-80 kg or 750 mg for >80 kg in 250 mL of 5% dextrose infused IV over 2 hours. Single dose on Day 1.	Arm 1: Canakinumab Injection 600mg Subjects will be given one-time intravenous infusion of 600 mg of canakinumab (8 mg/kg for patients </= 40 kg) in 250 mL of 5% dextrose infused IV over 2 hours; Arm 2: Canakinumab Injection 300mg Subjects will be given one-time intravenous infusion of 300 mg of canakinumab (4 mg/kg for patients </= 40 kg) in 250 mL of 5% dextrose infused IV over 2 hours	Arm 1: Treatment with Canakinumab i.v. body weight adjusted dose in 250 ml 5% dextrose solution i.v. over 2 hours. Arm 2: Placebo treatment: Aqua ad injectabilia in 250 ml 5% dextrose solution i.v. over 2 hours
Controls	Placebo. 250 mL of 5% dextrose infused IV over 2 hours. Single dose on Day 1.	Placebo. 250 mL of 5% dextrose infused IV over 2 hours.	Placebo. Aqua ad injectabilia in 250 ml 5% dextrose solution i.v. over 2 hours Other Name: Aqua ad injectabilia in 250 ml 5% dextrose solution

Duration of observation/ Follow-up	Study period from initial dose on Day 1 to Day 29 or hospital discharge. Follow-up to Day 127.	The follow-up period is 5 months for each patient enrolled	From randomization up to 4 weeks
Primary Outcomes	Primary outcome: Number of patients with clinical response [Time Frame: Day 3 to Day 29]; Secondary outcomes: COVID-19-related death rate during the 4-week period after study treatment [Time Frame: 4 weeks]; Ratio to baseline in the CRP [Time Frame: Baseline, Day 29]; Ratio to baseline in the serum ferritin [Time Frame: Baseline, Day 29]; Ratio to baseline in the D-dimer [Time Frame: Baseline, Day 29]; Number of participants with AE, SAE, clinically significant changes in laboratory measures, and vital signs [Time Frame: 127 days]	Primary outcome: Time to clinical improvement up to day 14, defined as the time in days from randomization to either an improvement of two points on a seven-category ordinal scale or discharge from the hospital, whichever occurs first. [Time Frame: Up to day 14]; Secondary outcomes: Mortality at day 28 [Time Frame: Up to day 28]	Primary outcome: Unmatched win ratio after treatment with canakinumab compared to Placebo (composite endpoint) [Time Frame: within 4 weeks after treatment with canakinumab or placebo] Treatment and placebo will be compared on the basis of the unmatched win-ratio approach of Pocock. When comparing two patients, the winner will be determined by the first component in which the two patients differ (4 weeks after randomization): a. longer survival time b. longer ventilation-free time c. longer ICU-free time d. shorter hospitalization time Secondary outcomes: Time to clinical improvement [Time Frame: From randomization up to 4 weeks]; Time to clinical improvement [Time Frame: From randomization up to 4 weeks]; Admission to ICU [Time Frame: 4 weeks]; Secondary worsening of disease [Time Frame: 4 weeks]; Prolonged hospital stay [Time Frame: >3 weeks]; Change in ratio to baseline in the glycated hemoglobin [Time Frame: Baseline, Day 29 and Day 90]
Results/Publication	Preliminary interim results from the CAN-COVID trial: The CAN-COVID trial failed to meet its primary endpoint showing that treatment with canakinumab plus standard of care (SoC) did not demonstrate a significantly greater chance of survival for patients without the need for	Not provided.	Not provided

	invasive mechanical ventilation, compared with placebo plus SoC up to Day 29. The trial did not meet its key secondary endpoint of reducing the COVID-19-related death rate during the 4-week period after treatment. The safety profiles of canakinumab plus SoC and placebo plus SoC were comparable. In the trial, the primary endpoint of survival without the need for mechanical ventilation was 88.8% for canakinumab plus SoC vs 85.7% for placebo plus SoC (P=0.29). The key secondary endpoint of COVID-19-related mortality up to 4 weeks was 4.9% for canakinumab plus SoC vs 7.2% for placebo plus SoC (P=0.33). Both the primary and key secondary trended in favor of canakinumab but did not reach statistical significance. No new safety signals for canakinumab were identified.		

Abbreviations: [CRS]=[cytokine release syndrome]; [CRP]=[C-reactive protein]; [AE]=[adverse event]; [SAE]=[serious adverse events]; [SoC]=[standart of care]; [IV]=[intravenous]; [US]=[United States]; [ICU]=[intensive care unit]

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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 (Appendix Table 6-1). DEPLazio searched medRxiv.org (https://www.medrxiv.org/), bioRxiv.org (https://www.bioRxiv.org/), and arXiv.org (https://www.arXiv.org/) for preprints of preliminary reports of randomised trials. The Cochrane Covid-19 Study Register (https://covid-19.cochrane.org/), ClinicalTrials.gov (www.clinicaltrials.gov) and World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictrp/en/) were search in addition. Other sources included journal alerts, contact with researchers, websites such as Imperial College, London School of Hygiene and Tropical Medicine, and Eurosurveillance. We applied no restriction on language of publication.

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

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

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

Table 6-1 Search strategy to identify randomised controlled studies

Database	URL	Search line / Search terms	Date of search
Pubmed	pubmed.ncbi.nlm.nih.gov	1. (coronavirus*[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])	05/02/2021

Database	URL	Search line / Search terms	Date of search
Ovid MEDLINE(R) ALL)	ovidsp.dc2.ovid.com	1. exp coronavirus/ 2. ((corona* or corono*) adj1 (virus* or viral* or virinae*)).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''	05/02/2021
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"	05/02/2021

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 and NIPHNO searches are given at their websites [11,12]. 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	From 1/9/2020 until 3/2/2021 Covering publication dates 01. September 2020

		pneumonia)).mp. or (coronavirus disease 2019 or severe acute respiratory syndrome coronavirus 2).sh,dj.) use oemezd [COVID-19 in Embase] 3 (COVID-19 serotherapy/ or Immunization, Passive/ or tocilizumab/ or camostat/ or nafamostat/ or AP301 peptide/ or Interleukin 1 Receptor Antagonist Protein/ or alunacedase alfa/ or darunavir/ or favipiravir/ or sarilumab/ or exp Interferons/ or 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

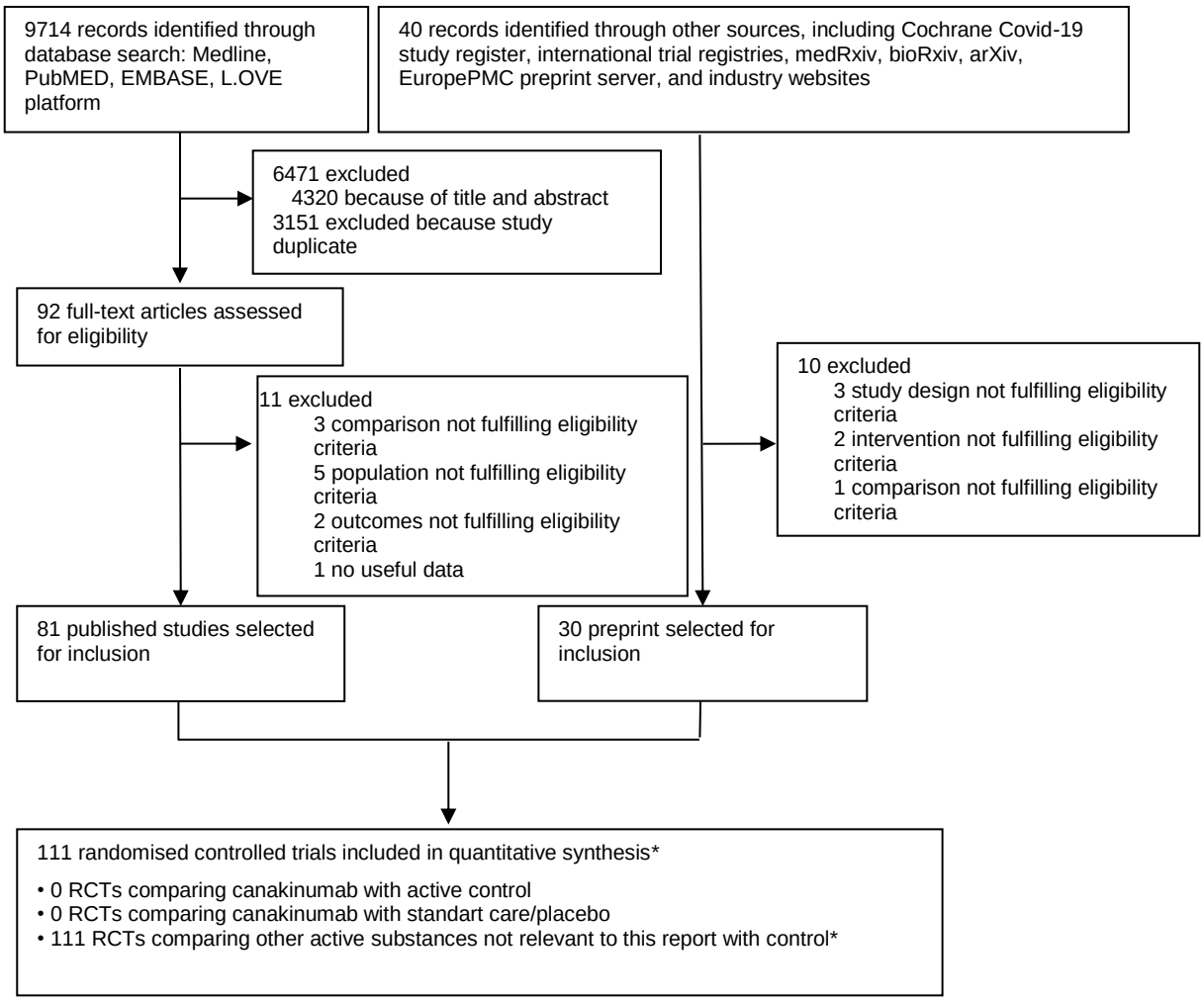
SMCA is responsible for searching in trial registries to identify ongoing and unpublished studies. The combination of search terms related to COVID-19 and Canakinumab are described in Appendix Table 6-3.

Table 6-3 Search strategy to identify ongoing studies

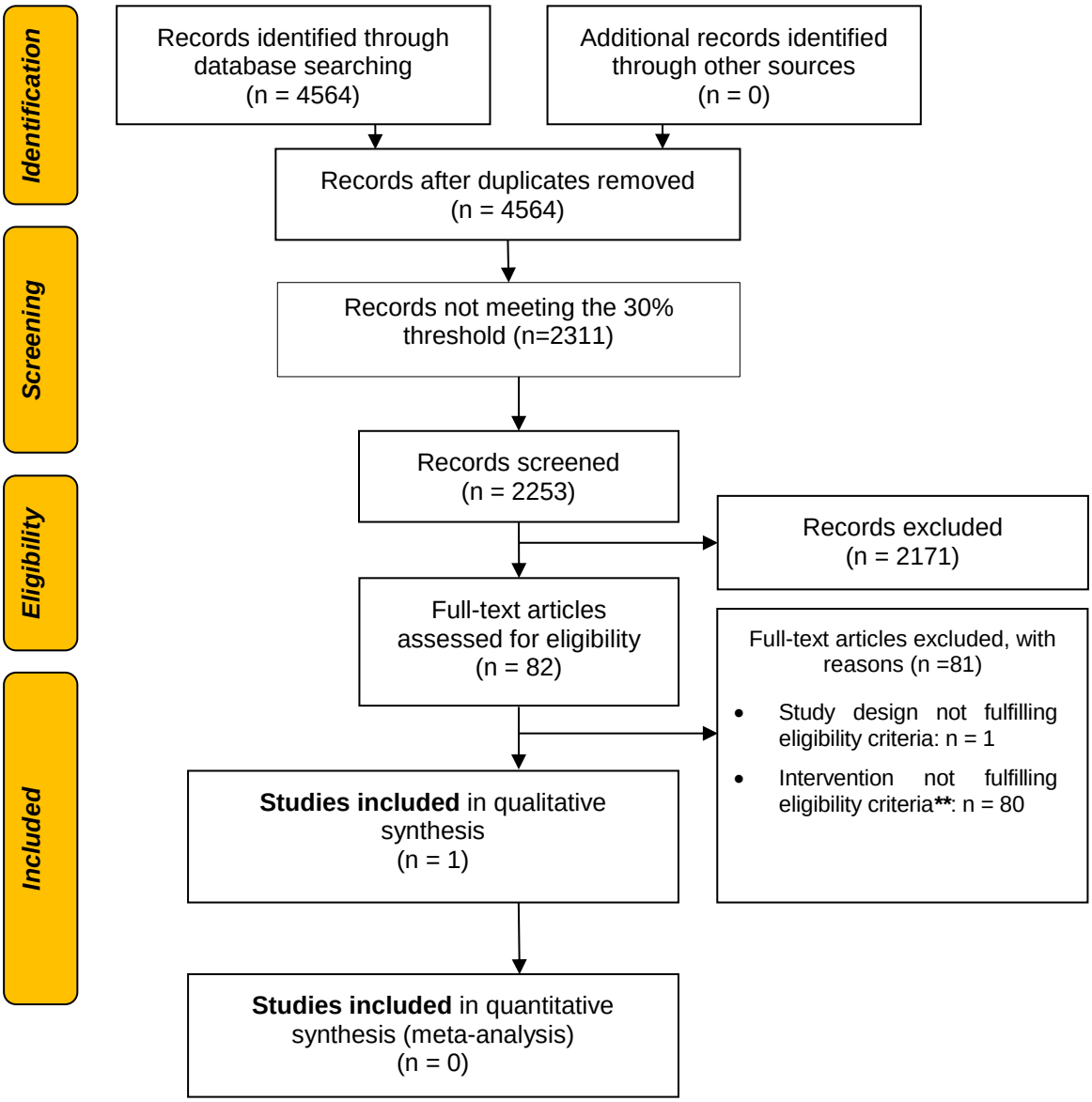
Database	URL	Search line / search terms	Date of search	Hits retrieved
ClinicalTrials.gov	https://clinicaltrials.gov/	Basic search mode* Terms used at Condition or disease: • covid-19 Terms used at "other terms": • Canakinumab; • anti IL-1beta	08/02/2021	6 0 new
ISRCTN	https://www.isrctn.com/	Basic search mode [adapt if you used "Advanced search mode"] Search terms: 1. covid-19 and canakinumab 2. covid-19 and Ilaris 3. covid-19 and Ilaris 4. covid-19 and anti IL-1beta 5. covid-19 and anti IL-1beta 6. SARS-CoV-2 and canakinumab 7. SARS-CoV-2 and Ilaris 8. SARS-CoV-2 and Ilaris 9. SARS-CoV-2 and anti IL-1beta 10. SARS-CoV-2 and anti IL-1beta	08/02/2021	0 0 new
European Clinical Trials Registry	https://www.clinicaltrialsregister.eu/	Basic search mode [adapt if you used "Advanced search mode"] Search terms: 1. covid-19 and canakinumab 2. covid-19 and Ilaris 3. covid-19 and Ilaris 4. covid-19 and anti IL-1beta 5. covid-19 and anti IL-1beta 6. SARS-CoV-2 and canakinumab 7. SARS-CoV-2 and Ilaris 8. SARS-CoV-2 and Ilaris 9. SARS-CoV-2 and anti IL-1beta 10. SARS-CoV-2 and anti IL-1beta	08/02/2021	2 0 new

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

6.4 Flow diagrams



Appendix Figure 6-1. Flow diagram depicting the selection process of RCTs
RCT = randomised controlled trial;
* The selection process was part of an external project, see https://www.deplazio.net/farmacicovid and Prospero ID CRD42020176914.



Appendix Figure 6-2. Flow diagram depicting the selection process of observational studies
** studies evaluating active substances relevant to other EUnetHTA rolling collaborative reviews