EUnetHTA Joint Action 3 WP4

“Rolling Collaborative Review” of Covid-19 treatments

TOCILIZUMAB FOR THE TREATMENT OF COVID-19

Project ID: RCR03
Monitoring Report

Version 4.0, November 2020

Template version October 2020

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

DOCUMENT HISTORY AND CONTRIBUTORS

Version	Date	Description of changes
V 1.0	**14/08/2020**	First version
V 2.0	**15/09/2020**	Second version
V 3.0	**15/10/2020**	Third version
V 3.1	**09/11/2020**	Literature searches, Literature screening, Data extraction
V 3.2	**11/11/2020**	Data extraction and analysis complete
V 3.3	**12/11/2020**	Check of data extraction and analysis
V 4.0	**23/11/2020**	Fourth version

Major changes from previous version

Chapter, page no.	Major changes from version 3.0
Summary	Table 4 2 Summary of safety from observational studies (AE and SAE) of tocilizumab Table 4 1 Summary of findings (SoF) table for published RCTs related to effectiveness and safety of tocilizumab Table 4 4 Ongoing trials of combination therapies tocilizumab were expanded.

Disclaimer

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

Rolling Collaborative Review team

Author(s)	National Institute of Pharmacy and Nutrition (NIPN), Hungary
Co-Author(s)	Department of Epidemiology Lazio Regional Health Service (DEPLazio), Italy

Further contributors

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

Conflict of interest

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

Copyright

How to cite this assessment

Please cite this assessment as follows:

EUnetHTA Rolling Collaborative Review (RCR03) Authoring Team. Tocilizumab for the treatment of COVID-19. Diemen (The Netherlands): EUnetHTA; 2020.11.12. 32 pages. Report No.: RCR03. Available from: https //www.eunethta.eu

Contact the EUnetHTA Secretariat EUnetHTA@zinl.nl with inquiries about this assessment.

TABLE OF CONTENTS

LIST OF TABLES AND FIGURES

LIST OF ABBREVIATIONS

AE	Adverse Event
ARR	Absolute Risk Reduction
ATC	Anatomical Therapeutic Chemical [Classification System]
ATMP	Advanced therapy medicinal product
CI	Confidence Interval
CRP	C-Reactive Protein
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
ICU	Intensive Care Unit
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
REA	Relative Effectiveness Assessment
RR	Relative Risk
SAE	Serious Adverse Event
SD	Standard Deviation
SMD	Standardized Mean Difference
SmPC	Summary of product characteristics
SoC	Standard of Care
SOP	Standard Operating Procedure
TCZ	Tocilizumab
WP4	Work Package 4

1 OBJECTIVE

The aim of this EUnetHTA Rolling Collaborative Review is

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

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

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

2 METHODS

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

2.1 Scope

Table 2-1 Scope of the RCR

Description	Project Scope
Population	**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	Tocilizumab is a humanised IgG1 monoclonal antibody that binds specifically to both soluble and membrane-bound IL-6 receptors (sIL-6R and mIL-6R) and inhibits sIL-6R and mIL-6R-mediated signalling. Tocilizumab is indicated (EMEA-approved) for the treatment of • rheumatoid arthritis in adults • giant cell arteritis in adults • active systemic juvenile idiopathic arthritis in patients aged ≥2 years • juvenile idiopathic polyarthritis in patients aged ≥2 years chimeric antigen receptor (CAR) T cell-induced severe or life-threatening cytokine release syndrome (CRS) in patients aged ≥2 years
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:

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

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

- https://www.fhi.no/en/qk/systematic-reviews-hta/map/

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

Population	See project Scope
Intervention	Tocilizumab is a humanised IgG1 monoclonal antibody that binds specifically to both soluble and membrane-bound IL-6 receptors (sIL-6R and mIL-6R) and inhibits sIL-6R and mIL-6R-mediated signaling.
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 NIPN extracts the data and assesses the risk of bias using Robins-I (https://training.cochrane.org/handbook/current/chapter-25). For prospective single arm studies the Newcastle-Ottawa Scale (NOS) is used to assess the methodological rigor and applicability.

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 NIPN is searching and extracting the data for the eligible studies. The process of study selection is depicted in a flow diagram (Appendix Figure 6-3). At the drafting stage of each update,

the author team verifies whether the status of previously identified studies has changed. This is done by verifying the date of the last update posted in the trial registers. In addition, trial register IDs of all previously identified studies are entered in both PubMed and Google (google.com) to verify if previously identified studies have been published since the last update. In Google, the first 10 hits are screened for this purpose.

Search methods are described in more detail in Appendix Table 6-3.

Data are presented in tabular form.

3 ABOUT THE TREATMENT

3.1 Mode of Action

Tocilizumab is a humanised IgG1 monoclonal antibody that binds specifically to both soluble and membrane-bound IL-6 receptors (sIL-6R and mIL-6R) and inhibits sIL-6R and mIL-6R-mediated signaling. IL-6 is a pleiotropic, pro-inflammatory cytokine produced by a variety of cell types, including lymphocytes, monocytes, and fibroblasts. Infection by the related SARS-associated coronavirus induces a dose-dependent production of IL-6 from bronchial epithelial cells. Elevations in IL-6 levels may be an important mediator when severe systemic inflammatory responses occur in patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. COVID-19-associated systemic inflammation and hypoxic respiratory failure is associated with heightened cytokine release, as indicated by elevated blood levels of IL-6, C-reactive protein (CRP), D-dimer, and ferritin [4].

3.2 Regulatory Status

The Market Authorisation Holder of tocilizumab is Roche Pharma. Tocilizumab is not approved by the European Medicines Agency (EMA) or the American Food and Drug Administration (FDA) for COVID-19 patients. Tocilizumab is indicated (EMA-approved) for the treatment of:

- rheumatoid arthritis in adults
- giant cell arteritis in adults
- active systemic juvenile idiopathic arthritis in patients aged ≥2 years
- juvenile idiopathic polyarthritis in patients aged ≥2 years
- chimeric antigen receptor (CAR) T cell-induced severe or life-threatening cytokine release syndrome (CRS) in patients aged ≥2 years [5].

Tocilizumab is not authorised in Covid-19 patients (EMA, FDA).

3.3 Level of Evidence

Sixty-three hospitalized adult patients with COVID-19 were enrolled in a prospective, open-label study of tocilizumab for severe COVID-19. Patient received either TCZ IV (8 mg/kg) or SC (324 mg); (the optional second dose within 24 hours 52 of 63 patients), and all of the patients received off-label antiretroviral protease inhibitors. Following administration of tocilizumab, fevers resolved in all but one patient, and CRP, ferritin, and D-dimer levels declined. The mean PaO2/FiO2 ratio of the patients increased between admission (152 +/- 53 mm Hg) and Day 7 of hospitalization (284 +/- 116 mm Hg). No moderate or severe adverse events attributable to tocilizumab were reported. The overall mortality rate was 11% (7 of 63 patients). No details were provided regarding the rate of secondary infections after tocilizumab use. The authors report an association between earlier use of tocilizumab and reduced mortality; however, interpretation of this result is limited because the study results did not describe a comparison group or specify an a priori comparison [6].

The phase III COVACTA (NCT04320615) study of tocilizumab did not meet its primary endpoint of improved clinical status in hospitalised adult patients with severe COVID-19 associated pneumonia. In addition, the key secondary endpoints, which included the difference in patient mortality at week four, were not met; however, there was a positive trend in time to hospital discharge in patients treated with tocilizumab. The COVACTA study did not identify any new safety signals for tocilizumab. The phase III REMDACTA (NCT04409262) study is currently recruiting participants. The phase III EMPACTA (NCT04372186) study has interim results available, and participants are receiving an intervention or are being examined, but potential participants are not currently being recruited or enrolled. The EMPACTA study showed that patients with COVID-19 associated pneumonia who received tocilizumab plus standard of care were less likely to progress to mechanical ventilation or death compared to patients who received placebo plus standard of care (log-rank p-value = 0.0348; HR [95% CI] = 0.56 [0.32, 0.97]). The cumulative proportion of patients who progressed to mechanical ventilation or death by day 28 was 12.2% in the tocilizumab arm versus 19.3% in the placebo arm. The EMPACTA study did not identify any new safety signals for tocilizumab [23].

Currently, no completed, withdrawn, suspended or terminated RCTs on the safety and efficacy of tocilizumab in COVID-19 patients were found in ClinicalTrials.gov and EudraCT registers.

4 SUMMARY

4.1 Effectiveness and Safety evidence from RCTs

There are insufficient data from clinical trials on the use of tocilizumab in patients with COVID-19. The data currently available are presented in Table 4-1. The currently available evidence on all-cause mortality, frequency of adverse events, duration of hospitalization disease severity, hospital discharges is not conclusive, as there is no statistically significant association between these outcomes and the treatment with tocilizumab. For mortality, any adverse events and hospitalization, studies show a trend towards favouring standard of care over tocilizumab, whereas for severe adverse events and the progression of disease, study results tend to favour tocilizumab.

4.2 Safety evidence from observational studies

The primary laboratory abnormalities reported with tocilizumab treatment are elevated liver enzyme levels that appear to be dose dependent. Neutropenia or thrombocytopenia are uncommon. Additional AEs, such as risk for serious infections (e.g., TB, other bacterial pathogens), have been reported only in the context of continuous dosing of tocilizumab. In two prospective cohort study with high risk of bias have been reported safety evidence. A retrospective analysis of data from 21 patients no adverse reaction were observed during the treatment [7]. During the 10-day follow-up Toniati et al. 2020 recorded three cases of severe adverse events: two patients developed septic shock and died, one had gastrointestinal perforation requiring urgent surgery and was alive at day 10 [8].

4.3 Ongoing studies

Several RCTs and interventional nRCTs related to tocilizumab alone or in combination therapy are currently ongoing.

4.4 Scientific conclusion about status of evidence generation

High quality evidence from ongoing RCTs are expected to assess effectiveness and safety of tocilizumab in COVID-19 patients.

Future controlled trials in patients with severe illness are needed to confirm or exclude the possibility of treatment benefit with tocilizumab.

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

Outcome	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Certainty of evidence	Comments
	Risk with standard of care	Risk with tocilizumab				
All-cause mortality [9]; [10]; [11]; [12]; [13]	104 per 1000	114 per 1000 (83 to 157)	RR 1.10 (0.80 to 1.51)	1324 (5 RCTs)	moderate	Compared to SoC there is no effect on all cause mortality
Number of patients with any adverse event [9]; [12]; [13]; [14]	659 per 1000	611 per 1,000 (474 to 789)	RR 1.03 (0.80 to 1.33)	1024 (4 RCTs)	very low	Compared to standard treatment could increase the number of patients with adverse events
Number of patients with severe adverse events [9]; [10]; [11]; [12]; [13]; [14]	238 per 1000	209 per 1,000 (174 to 255)	RR 0.88 (0.73 to 1.07)	1390 (6 RCTs)	moderate	Compared to SoC tocilizumab probably reduces the risk of severe adverse events
Duration of hospitalization (time to discharge) [9]; [12]	n.a.	n.a.	(HR: 1.24 (95% CI 1.03, 1.49) p = 0.42)	(2 RCTs)	high	Compared to SoC there is no effect on the number of days of hospitalization
Progression of disease severity [10]; [11]; [13]	161 per 1,000	110 per 1,000 (69 to 176)	RR 0.68 (0.43 to 1.09)	495 (3 RCT)	moderate	Compared to SoC tocilizumab probably reduces the risk of progression of disease severity
Number of patients discharged [10]; [11]	889 per 1,000	898 per 1,000 (836 to 969)	RR 1.01 (0.94 to 1.09)	365 (2 RCT)	moderate	Compared to SoC there is no effect on the number of patients discharged

Source: [9]; [10]; [11]; [12]; [13]; [14]
Abbreviations: CI=Confidence interval; RR=Risk ratio

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Tocilizumab	Standard treatment	Relative (95% CI)	Absolute (95% CI)	
All-cause mortality											
5 [1,2,3,4,5]	randomised trials	serious [a]	not serious	not serious	not serious	none	102/834 (12.2%)	51/490 (10.4%)	**RR 1.10** (0.80 to 1.51)	**10 more per 1.000** (from 21 fewer to 53 more)	⊕⊕⊕◯ MODERATE
Number of patients with any adverse event											
4 [1,4,5,6]	randomised trials	serious [b]	very serious [c]	not serious	not serious	none	403/648 (62.2%)	223/376 (59.3%)	**RR 1.03** (0.80 to 1.33)	**18 more per 1.000** (from 119 fewer to 196 more)	⊕◯◯◯ VERY LOW
Number of patients with severe adverse events											
6 [1,2,3,4,5,6]	randomised trials	serious [d]	not serious	not serious	not serious	none	190/869 (21.9%)	124/521 (23.8%)	**RR 0.88** (0.73 to 1.07)	**29 fewer per 1.000** (from 64 fewer to 17 more)	⊕⊕⊕◯ MODERATE
Duration of hospitalization (time to discharge)											
2 [1,4]	randomised trials	not serious	not serious	not serious	not serious	none	The duration of hospitalization did not differ between the two groups HR: 1.24 (95% CI 1.03, 1.49) p = 0.42				⊕⊕⊕⊕ HIGH

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Tocilizumab	Standard treatment	Relative (95% CI)	Absolute (95% CI)	
Progression of disease severity											
3 [2,3,5]	randomised trials	serious [e]	not serious	not serious	not serious	none	28/284 (9.9%)	34/211 (16.1%)	**RR 0.69** (0.43 to 1.10)	**50 fewer per 1.000** (from 92 fewer to 16 more)	⊕⊕⊕◯ MODERATE
Number of patients discharged											
2 [2,3]	randomised trials	serious [f]	not serious	not serious	not serious	none	199/221 (90.0%)	128/144 (88.9%)	**RR 1.01** (0.94 to 1.09)	**9 more per 1.000** (from 53 fewer to 80 more)	⊕⊕⊕◯ MODERATE

Explanations
a. Downgraded of one level for performance bias at high risk in two studies and at unclear risk in other two studies, unclear risk of selection bias in three studies
b. Downgraded of one level for performance bias at high risk in two studies and at unclear risk in one study, unclear selection bias in three studies, unclear detection bias in one study and unclear attrition and reporting bias in another study
c. Downgraded of two levels for high heterogeneity: i2=73%
d. Downgraded of one level for performance bias at high risk in three studies and at unclear risk in two studies, unclear selection bias in four studies, unclear detection bias in one study and unclear attrition and reporting bias in another study
e. Downgraded of one level for performance bias at high risk in two studies and at unclear risk in one study
f. Downgraded of one level for performance bias at high risk in one study and at unclear risk in one study
Source: [15]

Table 4-2 Summary of safety from observational studies (AE and SAE) of tocilizumab

Author, year	Xu et al 2020 [7]	Luo et al 2020 [16]	Toniati et al 2020 [8]	Somers et al 2020 [17]	Rossi et al 2020 [18]	Petrak et al [19]	Mikulska et al. [20]	Malekzadeh et al. [21]	Perrone et al. [22]
Country	China	China	Italy	USA	France	USA	Italy	Iran	Italy
Sponsor	n.a.	n.a.	n.a.	n.a.	Centre Hospitalier Intercommunal Robert Ballanger Groupe Hospitalier Pitie-Salpetriere	n.a.	n.a.	n.a.	
Intervention/ Product (drug name)	tocilizumab lopinavit/ritonavir; INF-α; ribavirin;	tocilizumab/ tocilizumab+ methylprednizolone	tocilizumab+ standard pharmacological protocol	tocilizumab+ standard pharmacological protocol	tocilizumab	tocilizumab+ steroid or vasopressors or hydroxychloroquine and azithromycin	tocilizumab and/or methylprednisolone+SOC	tocilizumab	tocilizumab
Dosage	4-8 mg/kg max 800 mg	n.a.	8 mg/kg max 800 mg	8 mg/kg max 800 mg	400 mg	4 mg/kg max 800 mg	8 mg/kg max 800 mg, methylprednisolone 1mg/kg for 5 days intravenously, then 0.5mg/kg for 5 days	sc 324 mg tocilizumab <100 kg; ≥100 kg 486 mg + SOC	2 doses of TCZ 8 mg/kg (up to a maximum of 800mg per dose), with an interval of 12 hours
Comparator	n.a.	n.a.	n.a.	standard pharmacological protocol	standard pharmacological protocol	n.a.	standard pharmacological protocol	n.a.	n.a.
Study design	observational	observational	observational	observational, controlled study	observational	observational	observational	observational	observational
Setting	hospital	hospital	hospital	hospital	hospital	hospital	hospital	hospital	hospital
Number of pts	21	15	100	154	246	145	196	126	301

Author, year	Xu et al 2020 [7]	Luo et al 2020 [16]	Toniati et al 2020 [8]	Somers et al 2020 [17]	Rossi et al 2020 [18]	Petrak et al [19]	Mikulska et al. [20]	Malekzadeh et al. [21]	Perrone et al. [22]
Inclusion criteria	patients with severe and criticalCOVID-19	patients infected with COVID-19	infected with COVID-19; absence of contraindication to tocilizumab	patients were admitted to Michigan Medicine from March 9-April 20, 2020 for severe COVID-19 pneumonia ,required invasive mechanical ventilation	patients hospitalized with COVID-19	patients hospitalized with COVID-19	COVID-19 pneumonia	severe or critical COVID-19	patients hospitalized with COVID-19
Age of patients (yrs)	56.8±16.5 (25–88)	73 (62-80)	62 (IQR 57–71])	58±14.9	67.6 ±15.3	58.1	67.9 years (range, 30–100)	median 55 (20–85) years	≤ 60: 122 (40.5%) 61-70: 107 (35.5%) 71 + : 72 (23.9%)
Disease severity	severe	moderate/severe	severe	severe	severe	severe	severe	severe or critical	severe
Follow-up (months)	Hospitalization days (range) 15.1±5.8 (10–31)	1 week after tocilizumab therapy	10-day follow-up	Median follow-up 47 days (28-67).	28-day maximum follow-up	15.3 days length of hospital stay	median follow-up of 53 days (range 4–70, interquartile range 33–57)	median 8 days (5–12)	up to 30 days
Loss to follow-up, n (%)	0	0	0	0	n.a.	n.a.	n.a.	n.a.	n.a.
RoB	high	high	high	high	high	high	high	high	high
Overall AEs, n (%)	n.a	n.a.	100%	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Serious AE (SAE), n (%)	0%	n.a.	3%	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Most frequent AEs n (%)	n.a.	n.a.	100%	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Most frequent SAEs, n (%)	n.a.	n.a.	3%	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.

Author, year	Xu et al 2020 [7]	Luo et al 2020 [16]	Toniati et al 2020 [8]	Somers et al 2020 [17]	Rossi et al 2020 [18]	Petrak et al [19]	Mikulska et al. [20]	Malekzadeh et al. [21]	Perrone et al. [22]
AEs of special interest, n (%)	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Death as SAE, n (%)	n.a.	n.a.	2%	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Withdrawals due AEs, n (%)	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.

Abbreviations: CI=Confidence interval; RR=Risk ratio

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

Table 4-3 Ongoing trials of single agent tocilizumab

Active substance	tocilizumab	tocilizumab	tocilizumab	tocilizumab	tocilizumab	tocilizumab
Sponsor	The First Affiliated Hospital of University of science and technology of China (Anhui Provincial Hospital)	Roche	National Cancer Institute, Naples	Tongji Hospital Collaborators: Hubei Xinhua Hospital Wuhan No.1 Hospital Wuhan central hospital	Università Politecnica delle Marche Collaborator: Azienda Ospedaliera Ospedali Riuniti Marche Nord	Genentech, Inc.
Trial Identifier	ChiCTR2000029765	NCT04320615 COVATA	NCT04317092 TOCIVID-19	NCT04306705	NCT04315480	NCT04372186 EMPACTA
Phase & Intention	Phase 4 A multicenter, randomized controlled trial for the efficacy and safety of tocilizumab in the treatment of new coronavirus pneumonia (COVID-19).	Phase 3 A Randomized, Double-Blind, Placebo-Controlled, Multicenter Study to Evaluate the Safety and Efficacy of Tocilizumab in Patients With Severe COVID-19 Pneumonia	Phase 2 Multicenter single-arm, open-label, phase 2 study on the efficacy and tolerability of tocilizumab in the treatment of patients with COVID-19 pneumonia	A Retrospective Study of Evaluating Safety and Efficacy of Tocilizumab Compared to Continuous Renal Replacement Therapy in Controlling CRS Triggered by COVID-19	Phase 2 Tocilizumab (RoActemra) as Early Treatment of Patients Affected by SARS-CoV2 (COVID-19) Infection With Severe Multifocal Interstitial Pneumonia	Phase III A Randomized, Double-Blind, Placebo-Controlled, Multicenter Study to Evaluate the Efficacy and Safety of Tocilizumab in Hospitalized Patients With COVID-19 Pneumonia
Study design	RCT parallel	RCT parallel, double blind	non randomized	retrospective	non randomized, single arm	RCT parallel
Status of trial	Recruiting	Completed*	Active, not recruiting	Recruiting	Active, not recruiting	Active, not recruiting
Duration/End of Study	n.a.	April 3, 2020-July 28, 2020	December 19, 2020-December 19, 2022	Estimated completion: June 2020	Estimated completion: May 2020	Estimated completion date: September 19, 2020
Study details	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Number of Patients	198	330	301	target sample size: 120	38	379
Disease severity	severe	severe	n.a.	n.a.	severe	n.a.
Setting	Hospital	Hospital	Hospital	Hospital	Hospital	Hospital
Location/Centres	China	Canada, Denmark, France, Germany, Italy, Netherlands, Spain, United Kingdom, United States	Italy	China	Italy	USA, Brazil, Kenya, Mexico, Peru, South Africa

Active substance	tocilizumab	tocilizumab	tocilizumab	tocilizumab	tocilizumab	tocilizumab
Intervention drug name and dosage	tocilizumab, n.a	tocilizumab 8 mg/kg IV (max 800 mg), up to 1 additional dose if clinical symptoms worsen or show no improvement.	tocilizumab 2 doses of TCZ 8 mg/kg (up to a maximum of 800mg per dose), with an interval of 12 hours	Tocilizumab or CRRT (continuous renal replacement therapy) or SoC	tocilizumab single intravenous administration 8mg/Kg	tocilizumab 8 mg/kg IV (max 800 mg) + SOC
Comparator (drug name and dosage)	conventional therapy	placebo 1 IV infusion of placebo matched to tocilizumab	n.a.	n.a.	n.a.	placebo+ SOC
Duration of observation/ Follow-up	n.a.	up to 60 days	up to 1 month	up to 28 days	14 days	up to 60 days
Primary Outcomes	cure rate mortality;Ventilator utilization;Hospitalization day	Clinical Status Assessed Using a 7-Category Ordinal Scale to Day 28 Time to Clinical Improvement (TTCI); Time to Improvement of at Least 2 Categories Relative to Baseline on a 7-Category Ordinal Scale of Clinical Status; Incidence of Mechanical Ventilation; Ventilator-Free Days to Day 28; Organ Failure-Free Days to Day 28; Incidence of Intensive Care Unit (ICU) Stay; Duration of ICU Stay; Time to Clinical Failure, Mortality Rate; Time to Hospital	One-month mortality rate; Interleukin-6 level; Lymphocyte count; CRP (C-reactive protein) level; PaO2 (partial pressure of oxygen) / FiO2 (fraction of inspired oxygen, FiO2) ratio (or P/F ratio); Change of the SOFA (Sequential Organ Failure Assessment); Number of participants with treatment-related side effects as assessed by Common Terminology Criteria for Adverse Event (CTCAE) version 5.0; Radiological response; Duration of hospitalization; Remission of respiratory symptoms	Proportion of Participants With Normalization of Fever and Oxygen Saturation Through Day 14; Duration of hospitalization; Proportion of Participants With Normalization of Fever Through Day 14; Time to first negative in 2019 novel Corona virus RT-PCR test; Change from baseline in white blood cell and differential count ; in hsCRP; in cytokines IL-1β, IL-10, sIL-2R, IL-6, IL-8 and TNF-α; in proportion of CD4+CD3/CD8+CD3 T cells	arrest in deterioration of pulmonary function; improving in pulmonary function; need of oro-tracheal intubation; death	Cumulative Proportion of Participants Requiring Mechanical Ventilation by Day 28

Active substance	tocilizumab	tocilizumab	tocilizumab	tocilizumab	tocilizumab	tocilizumab
		Discharge; Duration of Time on Supplemental Oxygen; Percentage of Participants with Adverse Events; COVID-19 (SARS-CoV-2) Viral Load Over Time; Time to Reverse-Transcriptase Polymerase Chain Reaction (RT-PCR) Virus Negativity; Proportion of Participants with Post-Treatment Infection Serum Concentration of IL-6; sIL-6R; Feritin; CRP; TCZ				
Results/Publication	n.a.	n.a.	**Perrone et al. [22]**	n.a.	.patients with COVID-19 associated pneumonia who received Actemra/RoActemra plus standard of care were 44% less likely to progress to mechanical ventilation or death compared to patients who received placebo plus standard of care (log-rank p-value = 0.0348; HR [95% CI] = 0.56 [0.32, 0.97]).[23]	n.a.

Abbreviations: n.a.=not applicable;
** COVATA study did not meet its primary endpoint of improved clinical status in hospitalised adult patients with severe COVID-19 associated pneumonia.*

Table 4-4 Ongoing trials of combination therapies tocilizumab

Active substance	tocilizumab, hydroxychloroquine, azithromycin	anakinra +/- ruxolitinib tocilizumab +/- ruxolitinib	remdesivir + tocilizumab	favipiravir + tocilizumab	heparin+tocilizumab
Sponsor	Fundació Institut de Recerca de l'Hospital de la Santa Creu i Sant Pau	Assistance Publique Hopitaux De Marseille	Hoffmann-La Roche	Peking University First Hospital	University of Sao Paulo
Trial Identifier	NCT04332094	NCT04424056	NCT04409262 REMDACTA	NCT04310228	NCT04600141
Phase & Intention	Phase 2, Pilot, Randomized, Multicenter, Open-label	Phase 3 open label randomized therapeutic trial	Phase III, Randomized, Double-Blind, Multicenter Study	Not Applicable Phase, Multicenter, RCT	Phase III, Parallel Assignment
Study design	RCT parallel, open label	RCT parallel, open label	RCT parallel, double blind	RCT parallel, open label	RCT parallel, open label
Status of trial	Recruiting	Not yet recruiting	Recruiting	Recruiting	Not yet recruiting
Duration/End of Study	September 2020	November 1, 2022	September 10, 2020	May 2020	October 20, 2021
Study details	n.a.	n.a	n.a	n.a	n.a.
Number of Patients	276	216	450	150	308
Disease severity	Severity 3-4 according to the WHO 7-point ordinal scale	COVID19 infection pneumonia at stage 2b or advanced stage 3	severe COVID-19 pneumonia	n.a.	severe COVID-19 infection
Setting	hospital	hospital	hospital	hospital	hospital
Location/Centres	Spain	France	Brazil, Russian Federation, United States	China	Brazil
Intervention drug name and dosage	tocilizumab, hydroxychloroquine, azithromycin	anakinra +/- ruxolitinib tocilizumab +/- ruxolitinib	remdesivir + tocilizumab	favipiravir + tocilizumab	Tocilizumab iv 8mg/kg/dose + Therapeutic dosage heparin
Comparator (drug name and dosage)	hydroxychloroquine, azithromycin	standard of care	remdesevir	favipiravir, tocilizumab	Heparin - Therapeutic dosage (Group 1) and Heparin - Prophylactic dosage (Group 2)
Duration of observation/ Follow-up	2 weeks	28 days	60 days	3 months	90 days
Primary Outcomes	in-hospital mortality	ventilation free days at D28	Clinical Status as Assessed by the Investigator Using a 7-Category Ordinal Scale of Clinical Status on Day 2	Clinical cure rate	Proportion of patients with clinical improvement in 30 days
Results/Publication	n.a.	n.a.	n.a.	n.a.	n.a.

5 REFERENCES

[1.] Higgins JPT TJ, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.0 (updated July 2019): Cochrane; 2019. Available from: http://www.training.cochrane.org/handbook.

[2.] DerSimonian R LN. Meta-analysis in clinical trials. Controlled Clinical Trials 1986;7:177-88.

[3.] Balshem H HM, Schünemann HJ, Oxman AD, Kunz R, Brozek J, Vist GE, Falck-Ytter Y, Meerpohl J, Norris S, Guyatt GH. GRADE guidelines: 3. Rating the quality of evidence. Journal of Clinical Epidemiology 2011;64:401-6.

[4.] Yoshikawa T., Hill T., Li K., Peters C.J., Tseng C.T. Severe acute respiratory syndrome (SARS) coronavirus-induced lung epithelial cytokines exacerbate SARS pathogenesis by modulating intrinsic functions of monocyte-derived macrophages and dendritic cells. J Virol. 2009;83(7):3039-3048. doi:10.1128/JVI.01792-08.

[5.] European Medicines Agency. EMA. RoActemra (tocilizumab) 2020 [Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/roactemra

[6.] Sciascia S., Aprà F., Baffa A., al. e. Pilot prospective open, single-arm multicentre study on off-label use of tocilizumab in patients with severe COVID-19. Clin Exp Rheumatol. 2020;38(3):529-32

[7.] Xu X., Han M., Li T., Sun W., Dongsheng W., Fu B., et al. Effective Treatment of Severe COVID-19 Patients with Tocilizumab. Proc Natl Acad Sci U S A. 2020;117(20):10970-10975. doi:10.1073/pnas.2005615117

[8.] Toniati P., Piva S., Cattalini M., Garrafa E., Regola F., Castelli F., et al. Tocilizumab for the treatment of severe COVID-19 pneumonia with hyperinflammatory syndrome and acute respiratory failure: A single center study of 100 patients in Brescia, Italy. . Autoimmunity Reviews 2020.

[9.] Rosas I, Bräu N, Waters M, Go RC, Hunter BD, Bhagani S, et al. Tocilizumab in Hospitalized Patients With COVID-19 Pneumonia. medRxiv. 2020:2020.08.27.20183442.

[10.] Salvarani C, Dolci G, Massari M, Merlo DF, Cavuto S, Savoldi L, et al; RCT-TCZ-COVID-19 Study Group. Effect of Tocilizumab vs Standard Care on Clinical Worsening in Patients Hospitalized With COVID-19 Pneumonia: A Randomized Clinical Trial. JAMA Intern Med. 2020 Oct 20:e206615. doi: 10.1001/jamainternmed.2020.6615. Epub ahead of print. PMID: 33080005; PMCID: PMC7577199.

[11.] Stone JH, Frigault MJ, Serling-Boyd NJ, Fernandes AD, Harvey L, Foulkes AS, et al; BACC Bay Tocilizumab Trial Investigators. Efficacy of Tocilizumab in Patients Hospitalized with Covid-19. N Engl J Med. 2020 Oct 21. doi: 10.1056/NEJMoa2028836. Epub ahead of print. PMID: 33085857.

[12.] Salama C, Han J, Yau L, Reiss WG, Kramer B, Neidhart JD, et al. Tocilizumab in nonventilated patients hospitalized with Covid-19 pneumonia. medRxiv. 2020:2020.10.21.20210203.

[13.] Hermine O, Mariette X, Tharaux PL, Resche-Rigon M, Porcher R, Ravaud P; CORIMUNO-19 Collaborative Group. Effect of Tocilizumab vs Usual Care in Adults Hospitalized With COVID-19 and Moderate or Severe Pneumonia: A Randomized Clinical Trial. JAMA Intern Med. 2020 Oct 20:e206820. doi: 10.1001/jamainternmed.2020.6820. Epub ahead of print. PMID: 33080017; PMCID: PMC7577198

[14.] Wang D, Fu B, Peng Z, Yang D, Han M, Li M, et al. Tocilizumab Ameliorates the Hypoxia in COVID-19 Moderate Patients with Bilateral Pulmonary Lesions: A Randomized, Controlled, Open-Label, Multicenter Trial.. The Lancet. 2020 . Available at SSRN: https://ssrn.com/abstract=3667681 or http://dx.doi.org/10.2139/ssrn.3667681

[15.] Cruciani F, De Crescenzo F., Vecchi S., Saulle R., Mitrova Z., Amato L., et al. Efficacy of Early Administration of Tocilizumab in COVID-19 Patients. 2020 [Available from: https://www.aifa.gov.it/web/guest/-/covid-19-studio-randomizzato-italiano-nessun-beneficio-dal-tocilizumab

[16.] Luo P., Liu Y., Qiu L., Liu X., Liu D., J. L. Tocilizumab treatment in COVID-19: A single center experience. . Journal of medical virology. 2020. [6.] Xu X., Han M., Li T., Sun W., Dongsheng W., Fu B., et al. Effective Treatment of Severe COVID-19 Patients with Tocilizumab. Proc Natl Acad Sci U S A. 2020;117(20):10970-10975. doi:10.1073/pnas.2005615117

[17.] Somers E.C., Eschenauer G.A., Troost J.P., al. e. Tocilizumab for treatment of mechanically ventilated patients with COVID-19 Clin Infect Dis. 2020.

[18.] Rossi B., Nguyen L., Zimmermann P., Boucenna F., Baucher L., Dubret L., et al. Effect of tocilizumab in hospitalized patients with severe pneumonia COVID-19: a cohort study. medRxiv. 2020

[19.] Petrak RM, Skorodin NC, Van Hise NW et al. Tocilizumab as a Therapeutic Agent for Critically Ill Patients Infected with SARS-CoV-2. Clin Transl Sci. 2020 Sep 12. doi: 10.1111/cts.12894. Epub ahead of print. PMID: 32918792.

[20.] Mikulska M, Nicolini LA, Signori A et al. Tocilizumab and steroid treatment in patients with COVID-19 pneumonia. PLoS One. 2020 Aug 20;15(8):e0237831. doi:

[21.] Malekzadeh R, Abedini A, Mohsenpour B et al. Subcutaneous tocilizumab in adults with severe and critical COVID-19: A prospective open-label uncontrolled multicenter trial. Int Immunopharmacol. 2020 Oct 13;89(Pt B):107102. doi: 10.1016/j.intimp.2020.107102. Epub ahead of print. PMID: 33075713; PMCID: PMC7553010.

[22.] Perrone F, Piccirillo MC, Ascierto PA, et al.; TOCIVID-19 investigators, Italy. Tocilizumab for patients with COVID-19 pneumonia. The single-arm TOCIVID-19 prospective trial. J Transl Med. 2020 Oct 21;18(1):405. doi: 10.1186/s12967-020-02573-9. PMID: 33087150; PMCID: PMC7576974.

[23.] F Hoffman-La Roche Ltd. Roche's phase III EMPACTA study showed Actemra/RoActemra reduced the likelihood of needing mechanical ventilation in hospitalised patients with COVID-19 associated pneumonia. Published September 18, 2020. Accessed September 19, 2020. https://www.roche.com/investors/updates/inv-update-2020-09-18.htm

6 APPENDIX

6.1 Search strategy to identify randomised controlled trials

DEPLazio, the Department of Epidemiology of the Regional Health Service Lazio in Rome, Italy is responsible for setting up the search strategy to identify randomised controlled trials (RCTs). DEPLazio performed a search in Medline, PubMed, and Embase, which has been updated weekly from March 2020 (Appendix Table 6-1). DEPLazio searched medRxiv.org (https://www.medrxiv.org/), bioRxiv.org (https://www.bioRxiv.org/), and arXiv.org (https://www.arXiv.org/) for preprints of preliminary reports of randomised trials. The Cochrane Covid-19 Study Register (https://covid-19.cochrane.org/), ClinicalTrials.gov (www.clinicaltrials.gov) and World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictrp/en/) were search in addition. Other sources included journal alerts, contact with researchers, websites such as Imperial College, London School of Hygiene and Tropical Medicine, and Eurosurveillance. We applied no restriction on language of publication.

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

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

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

Table 6-1 Search strategy to identify randomised controlled studies

Database	URL	Search line / Search terms	Date of search
Pubmed	pubmed.ncbi.nlm.nih.gov	1. (((((((("Coronavirus"[Mesh]) OR (coronavirus*[Title/Abstract] OR coronovirus*[Title/Abstract] OR coronavirinae*[Title/Abstract] OR Coronavirus*[Title/Abstract] OR Coronovirus*[Title/Abstract] OR Wuhan*[Title/Abstract] OR Hubei*[Title/Abstract] OR Huanan[Title/Abstract] OR "2019-nCoV"[Title/Abstract] OR 2019nCoV[Title/Abstract] OR nCoV2019[Title/Abstract] OR "nCoV-2019"[Title/Abstract] OR "COVID-19"[Title/Abstract] OR COVID19[Title/Abstract] OR "CORVID-19"[Title/Abstract] OR CORVID19[Title/Abstract] OR "WN-CoV"[Title/Abstract] OR WNCoV[Title/Abstract] OR "HCoV-19"[Title/Abstract] OR HCoV19[Title/Abstract] OR CoV[Title/Abstract] OR "2019 novel*"[Title/Abstract] OR Ncov[Title/Abstract] OR "n-cov"[Title/Abstract] OR "SARS-CoV-2"[Title/Abstract] OR "SARSCoV-2"[Title/Abstract] OR "SARSCoV2"[Title/Abstract] OR "SARS-CoV2"[Title/Abstract] OR SARSCov19[Title/Abstract] OR "SARS-Cov19"[Title/Abstract] OR "SARSCov-19"[Title/Abstract] OR "SARS-Cov-19"[Title/Abstract] OR Ncovor[Title/Abstract] OR Ncorona*[Title/Abstract] OR Ncorono*[Title/Abstract] OR NcovWuhan*[Title/Abstract] OR NcovHubei*[Title/Abstract] OR NcovChina*[Title/Abstract] OR NcovChinese*[Title/Abstract])) OR ((((respiratory*[Title/Abstract] AND (symptom*[Title/Abstract] OR disease*[Title/Abstract] OR illness*[Title/Abstract] OR condition*))[Title/Abstract] OR "seafood market*"[Title/Abstract] OR "food market*")[Title/Abstract] AND (Wuhan*[Title/Abstract] OR Hubei*[Title/Abstract] OR China*[Title/Abstract] OR Chinese*[Title/Abstract] OR Huanan*))[Title/Abstract])) OR ("severe acute respiratory syndrome*")) OR ((corona*[Title/Abstract] OR corono*)[Title/Abstract] AND (virus*[Title/Abstract] OR viral*[Title/Abstract] OR virinae*)[Title/Abstract])) AND (((((((randomized controlled trial [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])	9/11/2020

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"	9/11/2020
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	9/11/2020

Database	URL	Search line / Search terms	Date of search
		8. 4 and 7 9. limit 8 to yr="2019 -Current"	

6.2 Search strategy to identify observational studies

As of October 2020, NIPHNO is responsible for setting up the search strategy to identify observational studies. We receive studies that EPPI Centre has screened after searching weekly in Medline and Embase. We supplement these studies with a weekly search in Scopus. The retrieved hits were imported into an Endnote database and combined with generic names of the 15 included COVID-19 drugs.

Table 6-2 Search strategy to identify observational studies

Database	URL	Search terms / Search modality	Date of search
OVID Medline	Imported from EPPI Centre	1 exp Coronavirus/ 2 exp Coronavirus Infections/ 3 (coronavirus* or corona virus* or OC43 or NL63 or 229E or HKU1 or HCoV* or ncov* or covid* or sars-cov* or sarscov* or Sars-coronavirus* or Severe Acute Respiratory Syndrome Coronavirus*).mp. 4 (or/1-3) and ((20191* or 202*).dp. or 20190101:20301231.(ep).) 5 4 not (SARS or SARS-CoV or MERS or MERS-CoV or Middle East respiratory syndrome or camel* or dromedar* or equine or coronary or coronal or covidence* or covidien or influenza virus or HIV or bovine or calves or TGEV or feline or porcine or BCoV or PED or PEDV or PDCoV or FIPV or FCoV or SADS-CoV or canine or CCov or zoonotic or avian influenza or H1N1 or H5N1 or H5N6 or IBV or murine corona*).mp. 6 ((pneumonia or covid* or coronavirus* or corona virus* or ncov* or 2019-ncov or sars*).mp. or exp pneumonia/) and Wuhan.mp. 7 (2019-ncov or ncov19 or ncov-19 or 2019-novel CoV or sars-cov2 or sars-cov-2 or sarscov2 or sarscov-2 or Sars-coronavirus2 or Sars-coronavirus-2 or SARS-like coronavirus* or coronavirus-19 or covid19 or covid-19 or covid 2019 or ((novel or new or nouveau) adj2 (CoV on nCoV or covid or coronavirus* or corona virus or Pandemi*2)) or ((covid or covid19 or covid-19) and pandemic*2) or (coronavirus* and pneumonia)).mp. 8 COVID-19.rx,px,ox. or severe acute respiratory syndrome coronavirus 2.os. 9 ("32240632" or "32236488" or "32268021" or "32267941" or "32169616" or "32267649" or "32267499" or "32267344" or "32248853" or "32246156" or "32243118" or "32240583" or "32237674" or "32234725" or "32173381" or "32227595" or "32185863" or "32221979" or "32213260" or "32205350" or "32202721" or "32197097" or "32196032" or "32188729" or "32176889" or "32088947" or "32277065" or "32273472" or "32273444" or "32145185" or "31917786" or "32267384" or "32265186" or "32253187" or "32265567" or "32231286" or "32105468" or "32179788" or "32152361" or "32152148" or "32140676" or "32053580" or "32029604" or "32127714" or "32047315" or "32020111" or "32267950" or "32249952" or "32172715").ui. 10 or/6-9 11 5 or 10	27/09/2020 until 25/10/2020
OVID EMBASE		1 exp Coronavirus Infections/ 2 exp coronavirinae/ 3 (coronavirus* or corona virus* or OC43 or NL63 or 229E or HKU1 or HCoV* or ncov* or covid* or sars-cov* or sarscov* or Sars-coronavirus* or Severe Acute Respiratory Syndrome Coronavirus*).mp. 4 or/1-3 5 4 not (SARS or SARS-CoV or MERS or MERS-CoV or Middle East respiratory syndrome or camel* or dromedar* or equine or coronary or coronal or covidence* or covidien or influenza virus or HIV or bovine or calves or TGEV or feline or porcine or BCoV or PED or PEDV or PDCoV or FIPV or FCoV or SADS-CoV or canine or CCov or zoonotic or avian influenza or H1N1 or H5N1 or H5N6 or IBV or murine corona*).mp. 6 ((pneumonia or covid* or coronavirus* or corona virus* or ncov* or 2019-ncov or sars*).mp. or exp pneumonia/) and Wuhan.mp.	27/09/2020 until 25/10/2020

		7 (2019-ncov or ncov19 or ncov-19 or 2019-novel CoV or sars-cov2 or sars-cov-2 or sarscov2 or sarscov-2 or Sars-coronavirus2 or Sars-coronavirus-2 or SARS-like coronavirus* or coronavirus-19 or covid19 or covid-19 or covid 2019 or ((novel or new or nouveau) adj2 (CoV on nCoV or covid or coronavirus* or corona virus or Pandemi*2)) or ((covid or covid19 or covid-19) and pandemic*2) or (coronavirus* and pneumonia)).mp. 8 6 or 7 9 5 or 8	
Scopus		TITLE-ABS-KEY(((pneumonia OR covid* OR coronavirus* OR "corona virus*" OR ncov* OR 2019-ncov OR sars*) AND Wuhan) OR 2019-ncov OR ncov19 OR ncov-19 OR "2019-novel CoV" OR 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) W/1 (CoV OR nCoV OR covid OR coronavirus* OR "corona virus*" OR pandemi*)) OR ((covid OR covid19 OR covid-19) AND pandemic*) OR ((coronavirus* OR "corona virus*") AND pneumonia)) AND ORIG-LOAD-DATE > 20200920[date changes from week to week] AND ORIG-LOAD-DATE < 20200928 [date changes from week to week] AND NOT INDEX(medline)	27/09/2020 until 25/10/2020

6.3 Search strategy to identify ongoing studies

NIPN is responsible for searching in trial registries to identify ongoing and unpublished studies. The combination of search terms related to COVID-19 and tocilizumab are described in Appendix

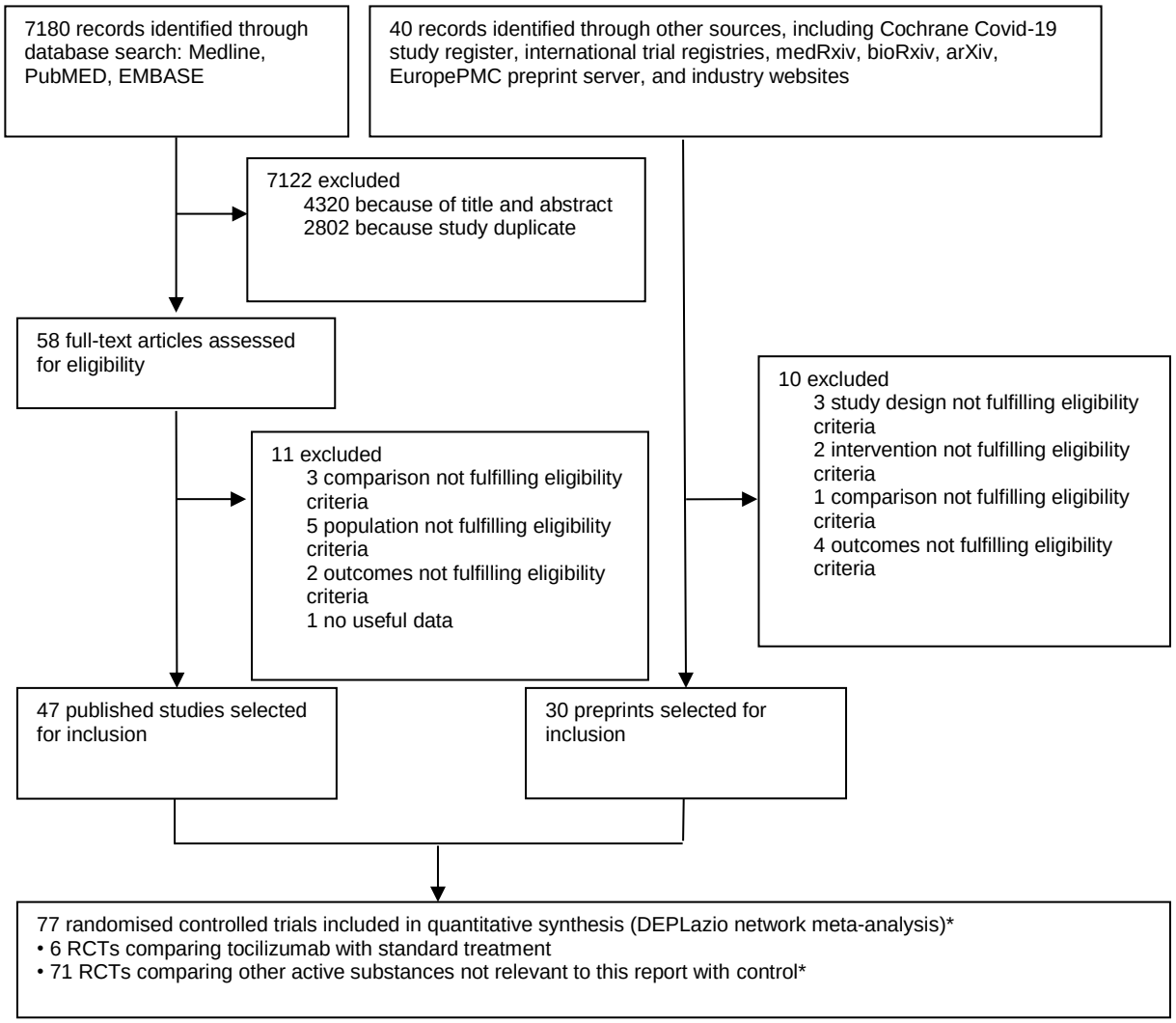
Table **6-3**.

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: • covid19 Terms used at "other terms": • tocilizumab • Actemra	11/11/2020	54 1 new
ISRCTN	https://www.isrctn.com/	Basic search mode Search terms: 1. covid-19 and tocilizumab 2. covid-19 and Actemra 3. SARS-CoV-2 and tocilizumab 4. SARS-CoV-2 and Actemra	11/11/2020	2 0 new
European Clinical Trials Registry	https://www.clinicaltrialsregister.eu/	Basic search mode Search terms: 1. covid-19 and tocilizumab 2. covid-19 and Actemra 3. SARS-CoV-2 and tocilizumab 4. SARS-CoV-2 and Actemra	11/11/2020	33 0 new

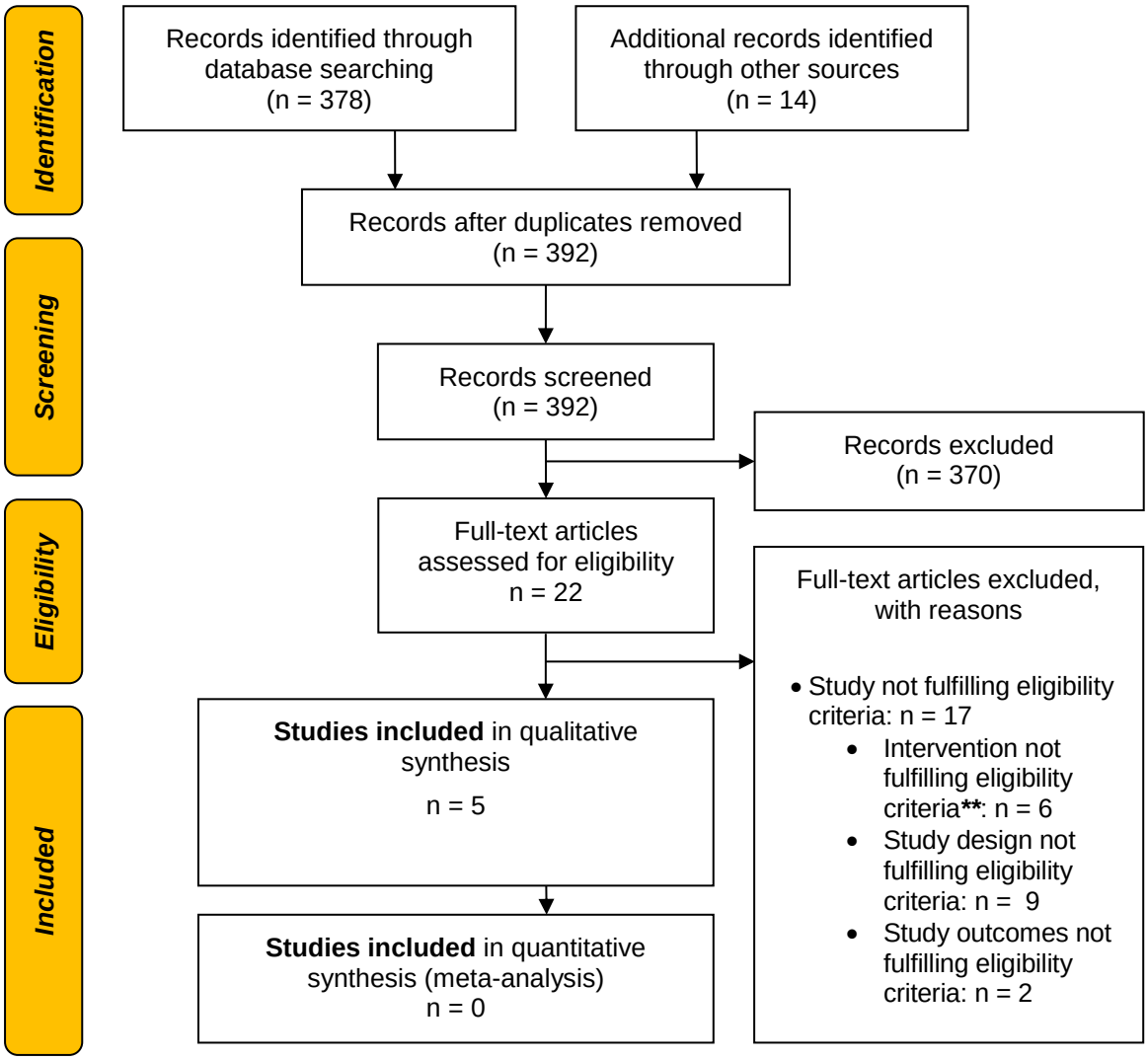
***** *In Basic Search mode, one term was added to the field "condition or disease" and one term in the field "other terms".*

6.4 Flow diagrams



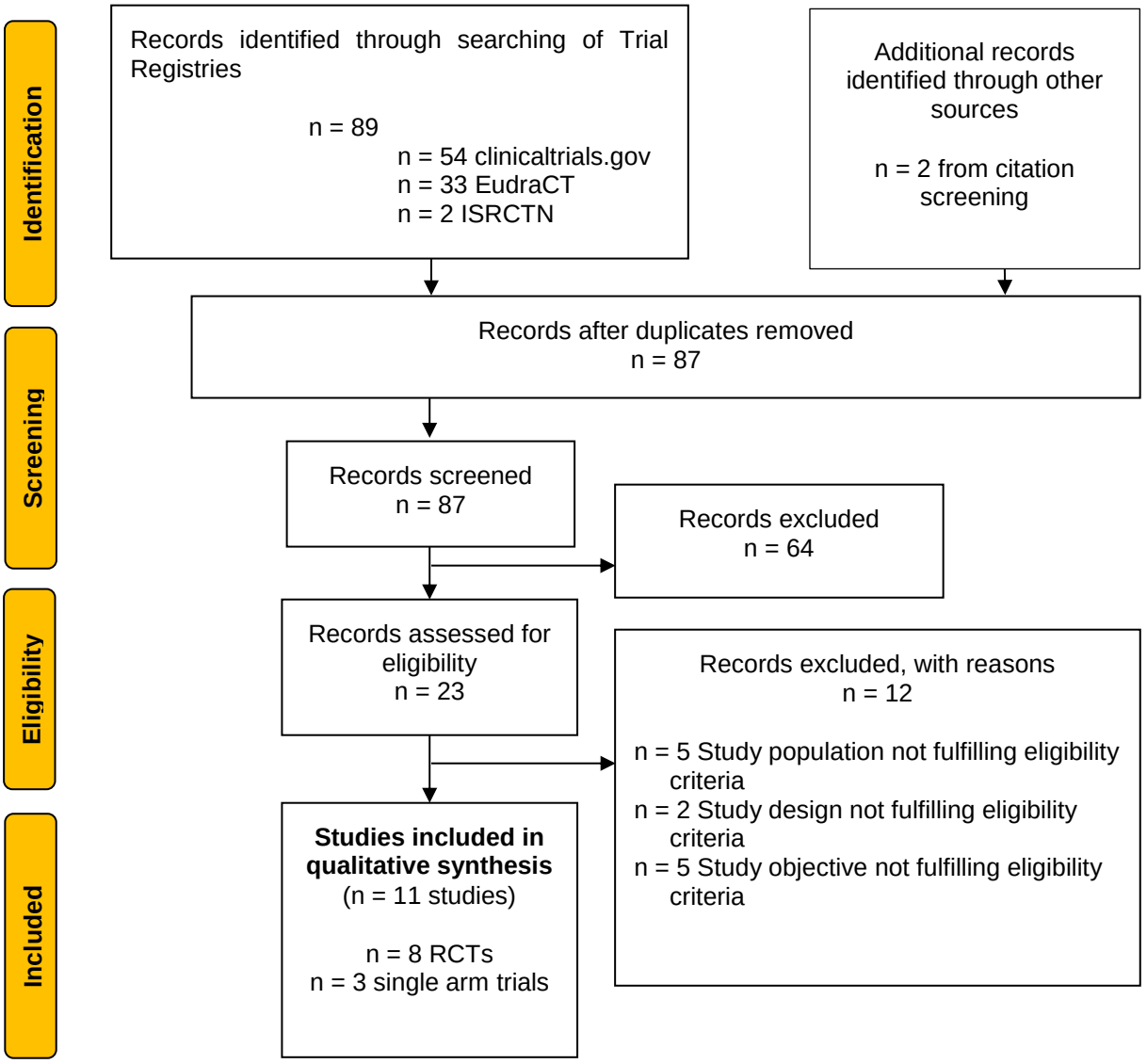
Appendix Figure 6-1. Flow diagram depicting the selection process of RCTs

Abbreviation: RCT=randomised controlled trial
**The selection process was part of an external project, see https://www.deplazio.net/farmacicovid and Prospero ID CRD42020176914.*



Appendix Figure 6-2. Flow diagram depicting the selection process of observational studies for the period 27/09/2020 to 25/10/2020

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



Appendix Figure 6-3. Flow diagram depicting the selection process of ongoing studies

Abbreviation: RCT=randomised controlled trial