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EUROPEAN NETWORK FOR HEALTH TECHNOLOGY ASSESSMENT

EUnetHTA Joint Action 3 WP4

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

**TOCILIZUMAB FOR THE TREATMENT OF COVID-19**

**Project ID: RCR03**  
Monitoring Report

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## DOCUMENT HISTORY AND CONTRIBUTORS

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V 2.0	15/09/2020	Second version
V 2.1	08/10/2020	Literature searches, Literature screening, Data extraction
V 2.2	12/10/2020	Data extraction and analysis complete
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V 3.0	15/10/2020	Third version

### Major changes from previous version

Chapter, page no.	Major changes from version 2.0
<b>Methods, Appendix</b>	<p>The description of the search methods for observational and ongoing studies is expanded:</p> <ul style="list-style-type: none"> <li>• Search methods are described in Appendix Table 6-1, Table 6-2 and Table 6-3.</li> <li>• Three flow diagrams are added to describe the study selection process of randomized controlled trials (Appendix Figure 6-1); observational studies (Appendix Figure 6-2); and ongoing studies (Appendix Figure 6-3).</li> </ul>

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## Conflict of interest

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

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## 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 15<sup>th</sup> of the month.

### 2.1 Scope

**Table 2-1 Scope of the RCR**

Description	Project Scope
Population	<p><b>Disease</b></p> <ul style="list-style-type: none"> <li>• SARS-CoV-2 is a novel coronavirus causing a respiratory illness termed Covid-19. The full spectrum of Covid-19 ranges from mild, self-limiting respiratory tract illness to severe progressive pneumonia, multi-organ failure, and death.</li> </ul> <p><b>ICD-Codes</b> (<a href="https://www.who.int/classifications/icd/covid19/en">https://www.who.int/classifications/icd/covid19/en</a>)</p> <ul style="list-style-type: none"> <li>• An emergency ICD-10 code of ‘U07.1 COVID-19, virus identified’ is assigned to a disease diagnosis of COVID-19 confirmed by laboratory testing.</li> <li>• An emergency ICD-10 code of ‘U07.2 COVID-19, virus not identified’ is assigned to a clinical or epidemiological diagnosis of COVID-19 where laboratory confirmation is inconclusive or not available.</li> <li>• Both U07.1 and U07.2 may be used for mortality coding as cause of death. See the International guidelines for certification and classification (coding) of COVID-19 as cause of death following the link below.</li> <li>• In ICD-11, the code for the confirmed diagnosis of COVID-19 is RA01.0 and the code for the clinical diagnosis (suspected or probable) of COVID-19 is RA01.1.</li> </ul> <p><b>MeSH-terms</b></p> <ul style="list-style-type: none"> <li>• COVID-19, Coronavirus Disease 2019</li> </ul> <p><b>Target population</b> (<a href="https://www.covid19treatmentguidelines.nih.gov/overview/management-of-covid-19/">https://www.covid19treatmentguidelines.nih.gov/overview/management-of-covid-19/</a>)</p>

	<ul style="list-style-type: none"> <li>• Asymptomatic or pre-symptomatic Infection: Individuals who test positive for SARS-CoV-2 by virologic testing using a molecular diagnostic (e.g., polymerase chain reaction) or antigen test, but have no symptoms.</li> <li>• Mild Illness: Individuals who have any of the various signs and symptoms of COVID 19 (e.g., fever, cough, sore throat, malaise, headache, muscle pain) without shortness of breath, dyspnoea, or abnormal chest imaging.</li> <li>• Moderate Illness: Individuals who have evidence of lower respiratory disease by clinical assessment or imaging and a saturation of oxygen (SpO<sub>2</sub>) ≥94% on room air at sea level.</li> <li>• Severe Illness: Individuals who have respiratory frequency &gt;30 breaths per minute, SpO<sub>2</sub> &lt;94% on room air at sea level, ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO<sub>2</sub>/FiO<sub>2</sub>) &lt;300 mmHg, or lung infiltrates &gt;50%.</li> <li>• Critical Illness: Individuals who have respiratory failure, septic shock, and/or multiple organ dysfunction.</li> </ul>
<p><b>Intervention</b></p>	<p>Tocilizumab is a humanised IgG1 monoclonal antibody that binds specifically to both soluble and membrane-bound IL-6 receptors (sIL-6R and mL-6R) and inhibits sIL-6R and mL-6R-mediated signalling. Tocilizumab is indicated (EMA-approved) for the treatment of</p> <ul style="list-style-type: none"> <li>• rheumatoid arthritis in adults</li> <li>• giant cell arteritis in adults</li> <li>• active systemic juvenile idiopathic arthritis in patients aged ≥2 years</li> <li>• juvenile idiopathic polyarthritis in patients aged ≥2 years</li> </ul> <p>chimeric antigen receptor (CAR) T cell-induced severe or life-threatening cytokine release syndrome (CRS) in patients aged ≥2 years</p>
<p><b>Comparison</b></p>	<p>Any active treatment, placebo, or standard of care.</p> <p><b>Rationale:</b> Since there is no gold standard treatment any comparator is acceptable as well as the above listed interventions.</p>
<p><b>Outcomes</b></p>	<p><u>Main outcome:</u></p> <ul style="list-style-type: none"> <li>• All-cause Mortality (Survival)</li> </ul> <p><u>Additional Outcomes:</u></p> <p>Efficacy:</p> <ul style="list-style-type: none"> <li>• Length of hospital stay,</li> <li>• Viral burden (2019-nCoV RT-PCR negativity),</li> <li>• Clinical progression (WHO Clinical Progression Scale measured daily over the course of the study),</li> <li>• Rates of hospitalization and of patients entering ICU,</li> <li>• Duration of mechanical ventilation,</li> <li>• Quality of life.</li> </ul> <p>Safety:</p> <ul style="list-style-type: none"> <li>• Adverse events (AE),</li> <li>• Severe adverse events (SAE),</li> <li>• Withdrawals due to AEs,</li> <li>• Most frequent AEs,</li> <li>• Most frequent SAEs.</li> </ul> <p><b>Rationale:</b> We will give priority according to the Core Outcome Set for Clinical Trials on Coronavirus Disease 2019 (<a href="https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7102592/pdf/main.pdf">https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7102592/pdf/main.pdf</a>) and A minimal common outcome measure set for COVID-19 clinical research from the WHO Working Group on the Clinical Characterisation and Management of COVID-19 infection.</p>
<p><b>Study design</b></p>	<p>Efficacy: randomised controlled trials (RCT) Safety: observational studies (comparative or single-arm prospective studies and registries)</p>

## 2.2 Sources of information

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

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

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

The literature search is conducted in the following databases:

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

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

To identify preprints of preliminary reports of work that have not been peer-reviewed, the following sources are searched:

- medRxiv Health Sciences
- bioRxiv Biology

In addition to the sources and strategies described above, registers of ongoing studies are screened. Key conferences and conference proceedings are considered. Appendix Table 6-1 describes in detail the sources searched, the search terms used and the dates at which the searches are executed.

#### Data extraction, Risk of bias assessment, data synthesis:

Two reviewers from DEPLazio are screening search results, assessing full texts of studies and extract study characteristics and outcome data according to pre-defined criteria. The process of study selection is depicted as a flow diagram in Appendix Figure 6-1.

Risk of bias is assessed using the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions [1].

Dichotomous outcomes are analysed by calculating the relative risk (RR) for each trial with the uncertainty in each result being expressed by its 95% confidence interval (CI). Continuous outcomes are analysed by calculating the mean difference (MD) with the relative 95% CI when the study used the same instruments for assessing the outcome.

The standardised mean difference (SMD) is applied when studies used different instruments. Pairwise meta-analyses is performed for primary and secondary outcomes using a random-effects model in RevMan for every treatment comparison [2]. Network meta-analysis (NMA) is performed for the primary outcome. For rating the certainty of the evidence, the GRADE approach is being used [3].

- Sources: <http://deplazio.net/farmacicoVID/index.html> for SoF (or <https://covid-nma.com/>)

## 2. Table(s) on published (peer reviewed) observational studies for safety results:

The literature search is conducted on a monthly basis using the following sources:

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

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

<b>Population</b>	See project Scope
<b>Intervention</b>	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.
<b>Comparison</b>	Any active treatment, placebo, or standard of care.
<b>Outcomes</b>	See project Scope
<b>Study design</b>	Inclusion criteria: Prospective non-randomised controlled trials, prospective case series (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 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 signalling. 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. 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  $\geq 2$  years
- juvenile idiopathic polyarthritis in patients aged  $\geq 2$  years
- chimeric antigen receptor (CAR) T cell-induced severe or life-threatening cytokine release syndrome (CRS) in patients aged  $\geq 2$  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 PaO<sub>2</sub>/FiO<sub>2</sub> 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 is ongoing, and participants are receiving an intervention or being examined, but potential participants are not currently being recruited or enrolled.

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.

### **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]	144 per 1000	166 per 1000	RR 1.04 (0.70 to 1.55)	565 (2 RCT)	moderate	Compared to SoC there is no effect on all cause mortality
Number of patients with any adverse event at 14-28 days [9]; [11]	659 per 1000	1000 per 1000	RR 1.99 (0.39 to 10.05)	517 (2 RCT)	very low	Compared to standard treatment could increase the number of patients with adverse events
Number of patients with severe adverse events at 14-28 days [9]; [11]	308 per 1000	268 per 1000	RR 0.93 (0.72 to 1.21)	517 (2 RCT)	low	Compared to SoC there is no effect on the risk of severe adverse events
Duration of hospitalization (time to discharge) [9]	n.a.	n.a.	HR: 1.35 (95% CI 1.02, 1.79)	123 (1 RCT)	high	Compared to SoC tocilizumab reduces the number of days of hospitalization

**Source:** [9]; [10]; [11]

**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)	
<b>All-cause mortality</b>											
2 <sup>1,2</sup>	randomised trials	serious <sup>a</sup>	not serious	not serious	not serious	none	60/361 (16.6%)	30/214 (14.0%)	<b>RR 1.04</b> (0.70 to 1.55)	<b>6 more per 1.000</b> (from 42 fewer to 77 more)	⊕⊕⊕○ MODERATE
<b>Number of patients with any adverse event at 14-28 days</b>											
2 <sup>1,3</sup>	randomised trials	very serious <sup>b</sup>	very serious <sup>c</sup>	not serious	not serious	none	248/335 (74.0%)	120/182 (65.9%)	<b>RR 1.99</b> (0.39 to 10.05)	<b>653 more per 1.000</b> (from 402 fewer to 1.000 more)	⊕○○○ VERY LOW
<b>Number of patients with severe adverse events at 14-28 days<sup>100</sup></b>											
2 <sup>1,3</sup>	randomised trials	very serious <sup>b</sup>	not serious	not serious	not serious	none	103/335 (30.7%)	56/182 (30.8%)	<b>RR 0.93</b> (0.72 to 1.21)	<b>22 fewer per 1.000</b> (from 86 fewer to 65 more)	⊕⊕○○ LOW
<b>Duration of hospitalization (time to discharge)</b>											
1 <sup>1</sup>	randomised trials	not serious	not serious	not serious	not serious	none	Time to discharge was 8 days shorter in the tocilizumab group than in the standard treatment group (20 vs 28, HR: 1.35 (95% CI 1.02, 1.79) p = 0.037)			⊕⊕⊕⊕ HIGH	

**Explanations**

<sup>a</sup>. Downgraded of one level for high risk of performance bias and unclear risk of selection bias in one study

<sup>b</sup>. Downgraded of two levels for one study at unclear risk of selection and detection bias and the other study at high risk of performance bias and unclear risk of selection and, attrition and reporting bias

<sup>c</sup>. Downgraded of two levels for high heterogeneity. I<sup>2</sup>: 91%

Source: [12]

**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 [13]	Toniati et al 2020 [8]	Somers et al 2020 [14]	Rossi et al 2020 [15]	Petrak et al [16]
<b>Country</b>	China	China	Italy	USA	France	USA
<b>Sponsor</b>	n.a.	n.a.	n.a.	n.a.	Centre Hospitalier Intercommunal Robert Ballanger Groupe Hospitalier Pitie-Salpetriere	n.a.
<b>Intervention/Product (drug name)</b>	tocilizumab lopinavir/ritonavir; INF- $\alpha$ ; ribavirin;	tocilizumab/ tocilizumab+methylpre dnizolone	tocilizumab+ standard pharmacological protocol	tocilizumab+ standard pharmacological protocol	tocilizumab	tocilizumab+ steroid or vasopressors or hydroxychloroquine and azithromycin
<b>Dosage</b>	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
<b>Comparator</b>	n.a.	n.a.	n.a.	standard pharmacological protocol	standard pharmacological protocol	n.a.
<b>Study design</b>	observational	observational	observational	observational, controlled study	observational	observational
<b>Setting</b>	hospital	hospital	hospital	hospital	hospital	hospital
<b>Number of pts</b>	21	15	100	154	246	145
<b>Inclusion criteria</b>	patients with severe and critical COVID-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
<b>Age of patients (yrs)</b>	56.8 $\pm$ 16.5 (25–88)	73 (62-80)	62 (IQR 57–71])	58 $\pm$ 14.9	67.6 $\pm$ 15.3	58.1
<b>Disease severity</b>	severe	moderate/severe	severe	severe	severe	severe
<b>Follow-up (months)</b>	Hospitalization days (range) 15.1 $\pm$ 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
<b>Loss to follow-up, n (%)</b>	0	0	0	0	n.a.	n.a.
<b>RoB</b>	high	high	high	high	high	high
<b>Overall AEs, n (%)</b>	n.a.	n.a.	100%	n.a.	n.a.	n.a.

Author, year	Xu et al 2020 [7]	Luo et al 2020 [13]	Toniati et al 2020 [8]	Somers et al 2020 [14]	Rossi et al 2020 [15]	Petrak et al [16]
<b>Serious AE (SAE), n (%)</b>	0%	n.a.	3%	n.a.	n.a.	n.a.
<b>Most frequent AEs n (%)</b>	n.a.	n.a.	100%	n.a.	n.a.	n.a.
<b>Most frequent SAEs, n (%)</b>	n.a.	n.a.	3%	n.a.	n.a.	n.a.
<b>AEs of special interest, n (%)</b>	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
<b>Death as SAE, n (%)</b>	n.a.	n.a.	2%	n.a.	n.a.	n.a.
<b>Withdrawals due AEs, n (%)</b>	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
<b>Sponsor</b>	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.
<b>Trial Identifier</b>	ChiCTR2000029765	NCT04320615 COVATA	NCT04317092	NCT04306705	NCT04315480	NCT04372186 EMPACTA
<b>Phase &amp; Intention</b>	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
<b>Study design</b>	RCT parallel	RCT parallel, double blind	non randomized	retrospective	non randomized, single arm	RCT parallel
<b>Status of trial</b>	Recruiting	Completed*	Recruiting	Recruiting	Active, not recruiting	Active, not recruiting
<b>Duration/End of Study</b>	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
<b>Study details</b>	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
<b>Number of Patients</b>	198	330	target sample size: 330	target sample size: 120	38	379
<b>Disease severity</b>	severe	severe	n.a.	n.a.	severe	n.a.
<b>Setting</b>	Hospital	Hospital	Hospital	Hospital	Hospital	Hospital
<b>Location/Centres</b>	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
<b>Intervention drug name and dosage</b>	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
<b>Comparator (drug name and dosage)</b>	conventional therapy	placebo 1 IV infusion of placebo matched to tocilizumab	n.a.	n.a.	n.a.	placebo+ SOC
<b>Duration of observation/ Follow-up</b>	n.a.	up to 60 days	up to 1 month	up to 28 days	14 days	up to 60 days
<b>Primary Outcomes</b>	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-1 $\beta$ , IL-10, sIL-2R, IL-6, IL-8 and TNF- $\alpha$ ; 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; Ferritin; CRP; TCZ				
<b>Results/Publication</b>	n.a.	n.a.	n.a.	n.a.	n.a.	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**

<b>Active substance</b>	tocilizumab, hydroxychloroquine, azithromycin	anakinra +/- ruxolitinib tocilizumab +/- ruxolitinib	remdesivir + tocilizumab	favipiravir + tocilizumab
<b>Sponsor</b>	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
<b>Trial Identifier</b>	NCT04332094	NCT04424056	NCT04409262 REMDACTA	NCT04310228
<b>Phase &amp; Intention</b>	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, Randomized and Controlled Clinical Trial
<b>Study design</b>	RCT parallel, open label	RCT parallel, open label	RCT parallel, double blind	RCT parallel, open label
<b>Status of trial</b>	Recruiting	Not yet recruiting	Recruiting	Recruiting
<b>Duration/End of Study</b>	September 2020	November 1, 2022	September 10, 2020	May 2020
<b>Study details</b>	n.a.	n.a.	n.a.	n.a.
<b>Number of Patients</b>	276	216	450	150
<b>Disease severity</b>	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.
<b>Setting</b>	hospital	hospital	hospital	hospital
<b>Location/Centres</b>	Spain	France	Brazil, Russian Federation, United States	China
<b>Intervention drug name and dosage</b>	tocilizumab, hydroxychloroquine, azithromycin	anakinra +/- ruxolitinib tocilizumab +/- ruxolitinib	remdesivir + tocilizumab	favipiravir + tocilizumab
<b>Comparator (drug name and dosage)</b>	hydroxychloroquine, azithromycin	standard of care	remdesivir	favipiravir, tocilizumab
<b>Duration of observation/ Follow-up</b>	2 weeks	28 days	60 days	3 months
<b>Primary Outcomes</b>	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
<b>Results/Publication</b>	n.a.	n.a.	n.a.	n.a.

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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](http://www.clinicaltrials.gov)) and World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) ([www.who.int/ictcp/en/](http://www.who.int/ictcp/en/)) were search in addition. Other sources included journal alerts, contact with researchers, websites such as Imperial College, London School of Hygiene and Tropical Medicine, and Eurosurveillance. We applied no restriction on language of publication.

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

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

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

**Table 6-1 Search strategy to identify randomised controlled studies**

Database	URL	Search line / Search terms	Date of search
Pubmed	pubmed.ncbi.nlm.nih.gov	<p>1. ((((((("Coronavirus"[Mesh]) OR (coronavirus*[Title/Abstract] OR coronavirus*[Title/Abstract] OR coronavirinae*[Title/Abstract] OR Coronavirus*[Title/Abstract] OR Coronavirus*[Title/Abstract] OR Wuhan*[Title/Abstract] OR Hubei*[Title/Abstract] OR Huanan[Title/Abstract] OR "2019-nCoV"[Title/Abstract] OR 2019nCoV[Title/Abstract] OR nCoV2019[Title/Abstract] OR "nCoV-2019"[Title/Abstract] OR "COVID-19"[Title/Abstract] OR COVID19[Title/Abstract] OR "CORVID-19"[Title/Abstract] OR CORVID19[Title/Abstract] OR "WN-CoV"[Title/Abstract] OR WNCov[Title/Abstract] OR "HCoV-19"[Title/Abstract] OR HCoV19[Title/Abstract] OR CoV[Title/Abstract] OR "2019 novel"*[Title/Abstract] OR Ncov[Title/Abstract] OR "n-cov"[Title/Abstract] OR "SARS-CoV-2"[Title/Abstract] OR "SARSCoV-2"[Title/Abstract] OR "SARSCoV2"[Title/Abstract] OR "SARS-CoV2"[Title/Abstract] OR SARSCov19[Title/Abstract] OR "SARS-Cov19"[Title/Abstract] OR "SARSCov-19"[Title/Abstract] OR "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])</p>	21 September 2020

Database	URL	Search line / Search terms	Date of search
Ovid MEDLINE(R) ALL)	ovidsp.dc2.ovid.com	<ol style="list-style-type: none"> <li>1. exp coronavirus/</li> <li>2. ((corona* or corono*) adj1 (virus* or viral* or virinae*)).ti,ab,kw.</li> <li>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.</li> <li>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.</li> <li>5. ((outbreak* or wildlife* or pandemic* or epidemic*) adj1 (China* or Chinese* or Huanan*).ti,ab,kw.</li> <li>6. "severe acute respiratory syndrome".ti,ab,kw.</li> <li>7. or/1-6</li> <li>8. randomized controlled trial.pt.</li> <li>9. controlled clinical trial.pt.</li> <li>10. random*.ab.</li> <li>11. placebo.ab.</li> <li>12. clinical trials as topic.sh.</li> <li>13. random allocation.sh.</li> <li>14. trial.ti.</li> <li>15. or/8-14</li> <li>16. exp animals/ not humans.sh.</li> <li>17. 15 not 16</li> <li>18. 7 and 17</li> <li>19. limit 18 to yr="2019 -Current"</li> </ol>	21 September 2020
OVID EMBASE	ovidsp.dc2.ovid.com	<ol style="list-style-type: none"> <li>1. exp Coronavirinae/ or exp Coronavirus/</li> <li>2. exp Coronavirus infection/</li> <li>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.</li> <li>4. or/1-3</li> <li>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/</li> </ol>	21 September 2020

Database	URL	Search line / Search terms	Date of search
		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"	

## 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	Hits retrieved
FHI Live COVID-19 Evidence Map	<a href="https://www.fhi.no/en/qk/systematic-reviews-hta/map/">https://www.fhi.no/en/qk/systematic-reviews-hta/map/</a>	Endnote file of hits retrieved in Medline + Embase + Scopus, combined with generic drug names	24 August and 27 September 2020	460
OVID Medline	Imported from EPPI Centre	<p>1 exp Coronavirus/                  2 exp Coronavirus Infections/                  3 (coronavirus* or corona virus* or OC43 or NL63 or 229E or HKU1 or HCoV* or ncov* or covid* or 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</p>	24 August and 27 September 2020	

		"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		
OID 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. 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	24 August and 27 September 2020	
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	24 August and 27 September 2020	

		< 20200928 [date changes from week to week] AND NOT INDEX(medline)		
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### 6.3 Search strategy to identify ongoing studies

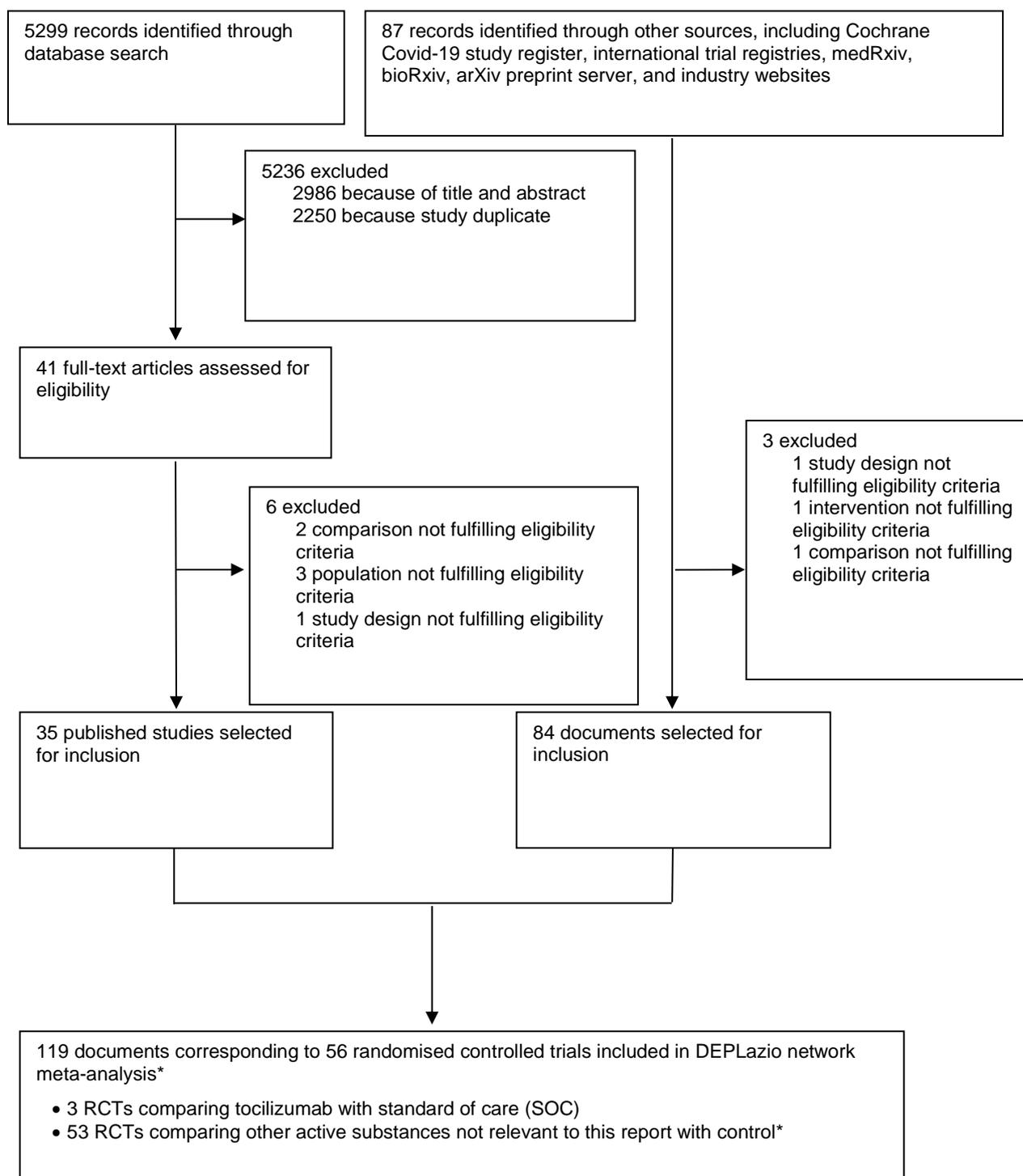
NIPN is responsible for searching in trial registries to identify ongoing and unpublished studies. The combination of search terms related to COVID-19 and tocilizumab are described in **Table 6-3**.

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

Database	URL	Search line / search terms	Date of search	Hits retrieved
ClinicalTrials.gov	<a href="https://clinicaltrials.gov/">https://clinicaltrials.gov/</a>	"Basic search mode*" Terms used at Condition or disease: <ul style="list-style-type: none"> <li>• covid19</li> </ul> Terms used at "other terms": <ul style="list-style-type: none"> <li>• tocilizumab</li> <li>• Actemra</li> </ul>	08/10/2020	56 2 new
ISRCTN	<a href="https://www.isrctn.com/">https://www.isrctn.com/</a>	Basic search mode Search terms: <ol style="list-style-type: none"> <li>1. covid-19 and tocilizumab</li> <li>2. covid-19 and Actemra</li> <li>3. SARS-CoV-2 and tocilizumab</li> <li>4. SARS-CoV-2 and Actemra</li> </ol>	08/10/2020	2 0 new
European Clinical Trials Registry	<a href="https://www.clinicaltrialsregister.eu/">https://www.clinicaltrialsregister.eu/</a>	Basic search mode Search terms: <ol style="list-style-type: none"> <li>1. covid-19 and tocilizumab</li> <li>2. covid-19 and Actemra</li> <li>3. SARS-CoV-2 and tocilizumab</li> <li>4. SARS-CoV-2 and Actemra</li> </ol>	08/10/2020	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".

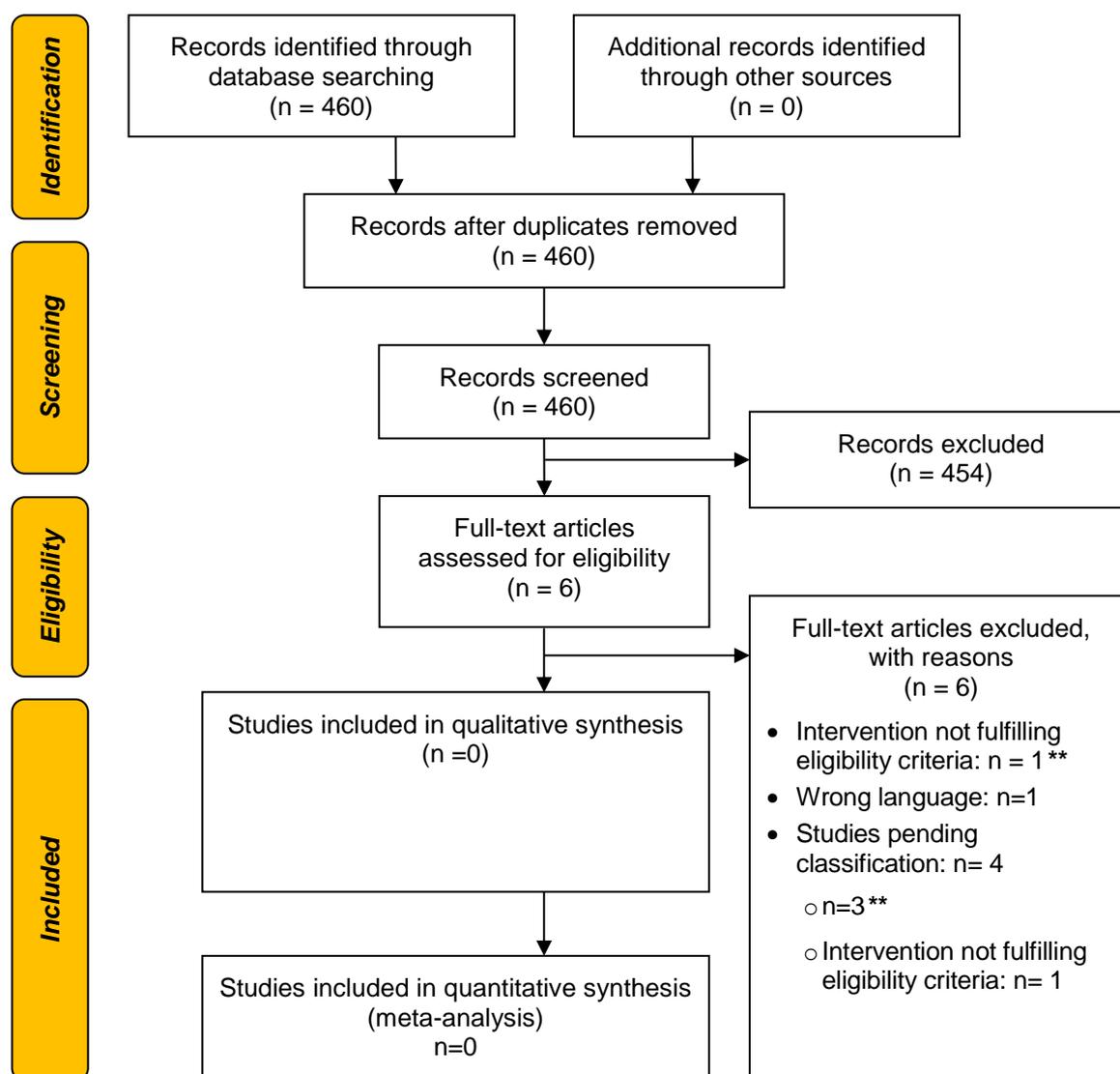
## 6.4 Flow diagrams



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

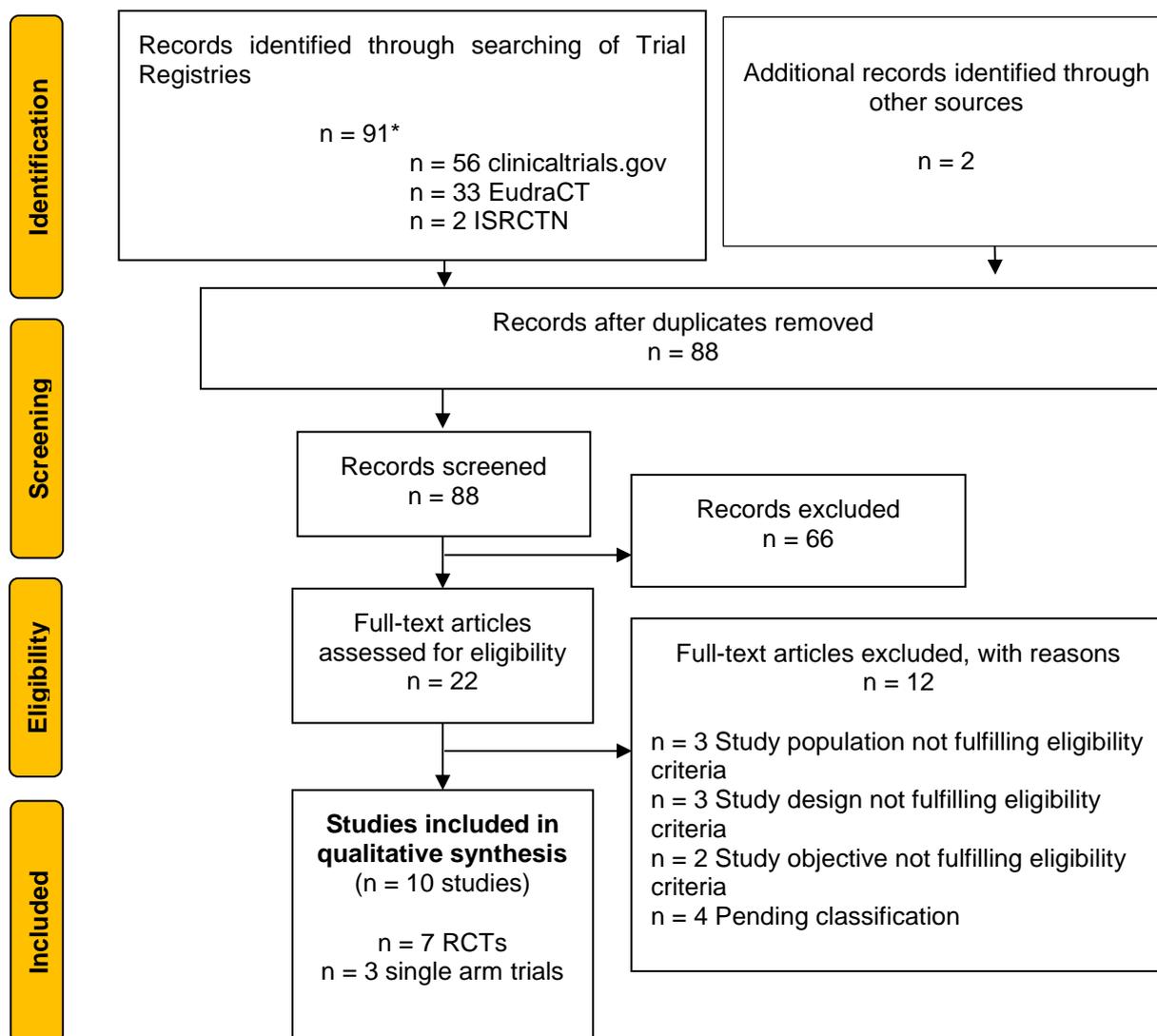
**Abbreviation:** RCT=randomised controlled trial

\*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 24 August to 27 September**

\*\* 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

\* 2 added in this update; † = ongoing study identified by the search strategy on observational studies