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“Rolling Collaborative Review” of Covid-19 treatments

LOPINA VIR AND RITONAVIR FOR THE TREATMENT OF COVID-19

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V 1.1	09/2020	Literature searches, Literature screening, Data extraction
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Major changes from previous version

Chapter, page no.	Major changes from version 2.0
Chapter 4., pages 11-18	New tables were added for more comparisons including lopinavir-ritonavir. Also, the list of ongoing trials was expanded.
Methods, Appendix	The description of the search methods for observational and ongoing studies is expanded: <ul style="list-style-type: none"> • Search methods are described in Appendix Table 6-1, Table 6-2 and Table 6-3. • 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).

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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
DOI	Declaration of interest
EUnetHTA	European Network of Health Technology Assessment
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
HR	Hazard Ratio
HRQOL	Health-related Quality of Life
ICD	International Classification of Diseases
ITT	Intention-to-treat
MD	Mean Difference
MeSH	Medical Subject Headings
NA	Not applicable
NR	Not reported
OR	Odds Ratio
PP	Per Protocol
RCT	Randomized Controlled Trial
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
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://eunetha.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	<p>Disease</p> <ul style="list-style-type: none"> • 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. <p>ICD-Codes (https://www.who.int/classifications/icd/covid19/en)</p> <ul style="list-style-type: none"> • 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. <p>MeSH-terms</p> <ul style="list-style-type: none"> • COVID-19, Coronavirus Disease 2019 <p>Target population (https://www.covid19treatmentguidelines.nih.gov/overview/management-of-covid-19/)</p>

	<ul style="list-style-type: none"> 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	Lopinavir - HIV protease inhibitor used in a fixed-dose combination with ritonavir - provides the antiviral activity of Kaletra. Lopinavir is an inhibitor of the HIV-1 and HIV-2 proteases. Ritonavir is an HIV protease inhibitor that works by interfering with the reproductive cycle of HIV. Inhibition of HIV protease prevents cleavage of the gag-pol polyprotein resulting in the production of immature, non-infectious virus. It is also an inhibitor of cytochrome P-450 CYP3A.
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	<p><u>Main outcome:</u></p> <ul style="list-style-type: none"> All-cause Mortality (Survival) <p><u>Additional Outcomes:</u></p> <p>Efficacy:</p> <ul style="list-style-type: none"> 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. <p>Safety:</p> <ul style="list-style-type: none"> Adverse events (AE), Severe adverse events (SAE), Withdrawals due to AEs, Most frequent AEs, Most frequent SAEs. <p>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.pdf) 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>
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, PaO ₂ /FiO ₂ , 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 Intervention [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	Lopinavir-ritonavir as a mono- or combination therapy
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, 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 from 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, Newcastle-Ottawa Scale 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*

Lopinavir provides the antiviral activity of Kaletra. Lopinavir is an inhibitor of the HIV-1 and HIV-2 proteases. Inhibition of HIV protease prevents cleavage of the gag-pol polyprotein resulting in the production of immature, non-infectious virus [4].

3.2 *Regulatory Status*

Lopinavir/ritonavir (ATC-code: J05AR10) is indicated by the EMA in combination with other antiretroviral medicinal products for the treatment of human immunodeficiency virus (HIV-1) infected adults, adolescents and children aged from 14 days and older [4].

3.3 *Level of Evidence*

The safety of lopinavir/ritonavir has been investigated in over 2600 HIV patients in Phase II-IV clinical trials, of which over 700 have received a dose of 800/200 mg (6 capsules or 4 tablets) once daily. Along with nucleoside reverse transcriptase inhibitors (NRTIs), in some studies, lopinavir/ritonavir was used in combination with efavirenz or nevirapine [4].

4 SUMMARY

4.1 *Effectiveness and Safety evidence from RCTs*

The combination of lopinavir and ritonavir has been suggested as a possible treatment in the context of the COVID-19 pandemic recently.

The effectiveness and safety of lopinavir and ritonavir has been studied in a number of clinical trials. A moderate-sized, randomized trial failed to find a virologic or clinical benefit of lopinavir/ritonavir over SOC. Another study of lopinavir and ritonavir (combined with ribavirin) neither supports nor refutes the use of lopinavir/ritonavir with or without ribavirin in patients with COVID-19. Trials usually report their findings on low sample sizes.

4.2 *Safety evidence from observational studies*

There is extensive experience with the use of lopinavir/ritonavir in pregnant women with HIV, and generally, the drug has a good safety profile.

4.3 *Ongoing studies*

According to the database of *clinicaltrials.gov*, there are currently 61 studies (including in other indications than COVID-19) ongoing with lopinavir and ritonavir [5].

As of September 15th, 2020, no observational studies were completed with the combination of lopinavir and ritonavir to assess safety endpoints.

4.4 Scientific conclusion about status of evidence generation

The conclusion is that based on the latest clinical data AbbVie recommends withdrawing Kaletra (lopinavir/ritonavir) from the EUnetHTA RCR list.

The University of Oxford, the World Health Organization and INSERM publicly announced that the Kaletra arms of the RECOVERY, SOLIDARITY and DISCOVERY studies in adults hospitalized with severe COVID-19 will be stopped given the data showed no beneficial effect.

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

Outcome	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Certainty of evidence	Comments
	Risk with lopinavir-ritonavir	Risk with umifenovir				
SARS-CoV 2 clearance	853 per 1000	914 per 1000	RR 0,93 (0.78 to 1.11)	69	Moderate	
Clinical progression of COVID-19	235 per 1000	86 per 1000	RR 2.75 (0.79 to 9.49)	69	Moderate	
Number of patients with any adverse events	353 per 1000	143 per 1000	RR 2.47 (0.97 to 6.26)	69	Moderate	
Number of patients with severe adverse events	48 per 1000	0 per 1000	RR 2.32 (0.10 to 53.42)	37	Moderate	

Source: [6]

Abbreviations: RR=risk ratio.

Table 4-2 Summary of findings (SoF) table for published RCTs related to effectiveness and safety of lopinavir-ritonavir + interferone beta 1b

Outcome	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Certainty of evidence	Comments
	Risk with Lopinavir+ritonavir+ ribavirina+ interferone beta-1b	Risk with lopinavir+ ritonavir				
All-cause mortality	0 per 1000	0 per 1000	-	127 (1 RCT)	Moderate	
Length of hospital stay, days	9 days (7 to 13)	14.5 days (9.3 to 16)	HR 2.72 (1.2 to 6.13)	127 (1 RCT)	Moderate	
Time to negative viral load, days (nasopharyngeal swab)	7 days (5 to 11)	12 days (8 to 15)	HR 4.37 (1.86 to 10.24)	127 (1 RCT)	Moderate	
Number of patients with any adverse events	478 per 1000	488 per 1000	RR 0.98 (0.67 to 1.43)	127 (1 RCT)	Moderate	
Number of patients with severe adverse events	0 per 1000	24 per 1000	RR 0.16 (0.01 to 3.87)	127 (1 RCT)	Moderate	

Source [6]

Abbreviations: HR=hazard ratio; RR=risk ratio.

Table 4-3 Summary of findings (SoF) table for published RCTs related to effectiveness and safety of lopinavir-ritonavir compared to SoC

Outcome	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Certainty of evidence	Comments
	Risk with Lopinavir+ritonavir	Risk with SoC				
All-cause mortality	214 per 1000	214 per 1000	RR 1,00 (0,83 to 1,21)	5171 (2 RCTs)	Moderate	
Number of patients with any adverse events	450 per 1000	422 per 1000	RR 2,59 (0,17 to 38,90)	245 (2 RCTs)	Very Low	
Number of patients with severe adverse events	155 per 1000	276 per 1000	RR 0,63 (0,39 to 1,02)	245 (2 RCTs)	Low	
Clinical progression of COVID-19	235 per 1000	59 per 1000	RR 4,00 (0,54 to 29,43)	51 (1 RCT)	Low	
SARS-CoV-2 clearance	481 per 1000	462 per 1000	RR 1.00 (0.75 to 1.32)	250 (2 RCTs)	Moderate	

Source [6]

Abbreviations: RR=risk ratio.

Table 4-4 Summary of findings (SoF) table for published RCTs related to effectiveness and safety of novaferon + lopinavir-ritonavir compared to lopinavir-ritonavir

Outcome	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Certainty of evidence	Comments
	Risk with Lopinavir+ritonavir	Risk with novaferon + lopinavir-ritonavir				
Number of patients with any adverse events	138 per 1000	99 per 1000	RR 0,72 (0,18 to 2,96)	59 (1 RCT)	Low	
Clinical progression of COVID-19	143 per 1000	16 per 1000	RR 0,11 (0,01 to 1,97)	56 (1 RCT)	Very low	

Source: [6]

Abbreviations: RR=risk ratio.

Table 4-5 Summary of findings (SoF) table for published RCTs related to effectiveness and safety of nomaferon compared to lopinavir-ritonavir

Outcome	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Certainty of evidence	Comments
	Risk with nomaferon	Risk with lopinavir+ritonavir				
SARS-CoV-2 clearance	567 per 1000	517 per 1000	RR 1,10 (0,68 to 1,75)	59 (1 RCT)	Very low	
Number of patients with any adverse events	138 per 1000	99 per 1000	RR 0,72 (0,18 to 2,96)	59 (1 RCT)	Low	
Number of patients with severe adverse events	No severe adverse events	No severe adverse events	-	59 (1 RCT)	Very low	
Clinical progression of COVID-19	143 per 1000	16 per 1000	RR 0,11 (0,01 to 1,97)	56 (1 RCT)	Very low	

Source: [6]

Abbreviations: RR=risk ratio.

Table 4-6 Summary of findings (SoF) table for published RCTs related to effectiveness and safety of novaferon+ lopinavir-ritonavir compared to novaferon

Outcome	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Certainty of evidence	Comments
	Risk with novaferon + lopinavir+ritonavir	Risk with novaferon				
SARS-CoV-2 clearance	700 per 1000	517 per 1000	RR 1,35 (0,89 to 2,06)	59 (1 RCT)	Very low	
Number of patients with any adverse events	833 per 1000	897 per 1000	RR 0,93 (0,76 to 1,14)	59 (1 RCT)	Low	
Number of patients with severe adverse events	No severe adverse events	No severe adverse events	-	59 (1 RCT)	Very low	
Clinical progression of COVID-19	0 per 1000	143 per 1000	RR 0,11 (0,01 to 1,97)	56 (1 RCT)	Very low	

Source: [6]

Abbreviations: RR=risk ratio.

Table 4-7 Summary of findings (SoF) table for published RCTs related to effectiveness and safety of ribavirin + lopinavir-ritonavir + interferon alfa

Outcome	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Certainty of evidence	Comments
	Risk with ribavirin + lopinavir-ritonavir + interferon alfa	Risk with ribavirin + interferon alfa				
All-cause mortality	0 per 1000	0 per 1000	-	-	Low	
SARS-CoV-2 clearance	469 per 1000	515 per 1000	RR 0,91 (0,55 to 1,49)	65 (1 RCT)	Low	
Clinical progression of COVID-19	63 per 1000	30 per 1000	RR 2,06 (0,20 to 21,64)	65 (1 RCT)	Low	
Number of patients with any adverse events	938 per 1000	697 per 1000	RR 1,35 (1,06 to 1,71)	65 (1 RCT)	Low	
Number of patients with severe adverse events	No severe adverse events	No severe adverse events	-	65 (1 RCT)	Low	

Source: [6]

Abbreviations: RR=risk ratio.

Table 4-8. Summary of findings (SoF) table for published RCTs related to effectiveness and safety of ribavirin + lopinavir-ritonavir + interferon alfa

Outcome	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Certainty of evidence	Comments
	Risk with ribavirin + lopinavir-ritonavir + interferon alfa	Risk with lopinavir-ritonavir + interferon alfa				
All-cause mortality	0 per 1000	0 per 1000	-	-	Low	
SARS-CoV-2 clearance	469 per 1000	611 per 1000	RR 0.77 (0.49 to 1.20)	68 (1 RCT)	Low	
Clinical progression of COVID-19	63 per 1000	56 per 1000	RR 1.13 (0.17 to 7.53)	68 (1 RCT)	Low	
Number of patients with any adverse events	938 per 1000	722 per 1000	RR 1.30 (1.04 to 1.62)	68 (1 RCT)	Low	
Number of patients with severe adverse events	No severe adverse events	No severe adverse events	-	65 (1 RCT)	Low	

Source: [6]

Abbreviations: RR=risk ratio.

Table 4-9. Summary of findings (SoF) table for published RCTs related to effectiveness and safety azithromycin + lopinavir/ritonavir + hydroxychloroquine

Outcome	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Certainty of evidence	Comments
	Risk with azithromycin + lopinavir / ritonavir + hydroxychloroquine	Risk with lopinavir / ritonavir + hydroxychloroquine				
All-cause mortality	0 per 1000	2 per 1000	RR 0.33 (0.01 to 7.87)	111 (1 RCT)	Very Low	
Length of hospital stay, days	4.61 days (CI95% 3.93 to 5.28)	5.96 days (CI95% 3.11 to 6.81)	SMD 0.46 lower (0.84 lower to 0.08 lower)	111 (1 RCT)	Very Low	

Source: [6]

Abbreviations: RR=risk ratio.

Table 4-10. Summary of findings (SoF) table for published RCTs related to effectiveness and safety of lopinavir/ritonavir + interferon alfa

Outcome	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Certainty of evidence	Comments
	Risk with lopinavir/ritonavir +interferon alfa	Risk with ribavirin +interferon alfa				
All-cause mortality	0 per 1000	0 per 1000	No death reported	-	Low	
SARS-CoV-2 clearance	611 per 1000	515 per 1000	RR 1.19 (0.78 to 1.81)	99 (1 RCT)	Low	
Clinical progression of COVID-19	56 per 1000	30 per 1000	RR 1.83 (0.17 to 19.29)	99 (1 RCT)	Low	
Number of patients with any adverse events	722 per 1000	697 per 1000	RR 1.04 (0.77 to 1.40)	99 (1 RCT)	Low	
Number of patients with severe adverse events	No severe adverse events	No severe adverse events	-	99 (1 RCT)	Low	

Source: [6]

Abbreviations: RR=risk ratio.

Table 4-11. Summary of safety from observational studies (AE and SAE) of lopinavir-ritonavir

Author, year	M. Stoldick , F. Lamoureux , M. Robert , F. Caron , M. Étienne ,I. Gueit, 2020.[7]	Tian et al [8]
Country	France	EU27 (countries reporting adverse events Eudravigilance)
Sponsor	Hospital Center University De Rouen	n.a.
Intervention/Product (drug name)	lopinavir/ritonavir	lopinavir/ritonavir
Dosage	400/100 mg for 10-14 days	n.a.
Comparator	n.a.	n.a.
Study design	observational, single arm	Retrospective data analysis
Setting	Hospital (inpatient)	n.a.
Number of pts	69	3 753
Inclusion criteria	COVID-19 infection with severe pneumonia (O ₂ > 3 L/min), no contraindications for the treatment	n.a.
Age of patients (yrs)	64	18-64
Disease severity	Patients with COVID-19 and severe pneumonia	n.a.
Follow-up (months)	Treatment duration (maximum 14 days)	n.a.
Loss to follow-up, n (%)	n.a.	n.a.
RoB	high	high
Safety Outcomes		
Overall AEs, n (%)	n.a	n.a
Serious AE (SAE), n (%)	n.a	n.a
Most frequent AEs n (%)	n.a	n.a
Most frequent SAEs, n (%)	n.a	n.a
AEs of special interest, n (%)	n.a	n.a
Death as SAE, n (%)	n.a	n.a
Withdrawals due AEs, n (%)	n.a	n.a

Table 4-12 Ongoing trials of single agent Lopinavir + Ritonavir

Active substance	Lopinavir+ Ritonavir	Lopinavir + Ritonavir	Lopinavir + Ritonavir	Lopinavir + Ritonavir
Sponsor	Tongji Hospital		Darrell Tan	
Trial Identifier	NCT04255017	NCT04315948	NCT04321174	ChiMCTR2000002940
Phase & Intention	Phase 4 study to Compare the Efficacy of Three Antiviral Drugs (Abidol Hydrochloride (Umifenovir), Oseltamivir and Lopinavir/Ritonavir) in the Treatment of 2019-nCoV Pneumonia.			
Study design	Single blinded, Prospective, Randomised Controlled Cohort Study	Adaptive, randomised open clinical trial to one of 4 treatments	Open label randomised trial	
Status of trial	Recruiting	Recruiting	Not yet recruiting	Not Recruiting
Duration/End of Study	Estimated study completion: July 1, 2020	Estimated study completion: March 2023	Estimated Primary Completion: March 31, 2021	Estimated study completion: Dec 31, 2020
Study details				
Number of Patients	N=400 patients with CT manifestation of viral pneumonia + mCoV positive randomised to Abidol hydrochloride, Oseltamivir, or Lopinavir/ritonavir	N=3200	N=1220	N=60 randomised to traditional Chinese medicine, Lopinavir/ritonavir, or traditional Chinese medicine + lopinavir/ritonavir
Disease severity			High risk close contact with a confirmed COVID-19 case	
Setting			Post exposure prophylaxis	
Location/Centres	Tongji Hospital, Hubei, China	EU: France, Spain, UK, Germany, Belgium, Netherlands, Luxembourg, Norway	Canada, Ontario	Wuhan, China
Intervention drug name and dosage				
Comparator (drug name and dosage)				
Duration of observation/ Follow-up				

Active substance	Lopinavir+ Ritonavir	Lopinavir + Ritonavir	Lopinavir + Ritonavir	Lopinavir + Ritonavir
Primary Outcomes	Rate of disease remission (Time Frame: two weeks) Time for lung recovery (Time Frame: two weeks)	Subject clinical status (on a 7-point ordinal scale) on Day 15	Microbiologic evidence of infection [Time Frame: 14 days]	The rate of remission
Results/Publication				

Table 4-13 Ongoing trials of single agent Lopinavir + Ritonavir (continued)

Active substance	Lopinavir+ Ritonavir	Lopinavir + Ritonavir	Lopinavir + Ritonavir	Lopinavir + Ritonavir
Sponsor			First Affiliated Hospital of Zhejiang University	Bassett Healthcare
Trial Identifier	NCT04252885	NCT04276688	NCT04261907 ChiCTR2000029603	NCT04328012
Phase & Intention				Phase 2-3
Study design	Open label	Phase 2 study Open-label randomised controlled trial	Randomised, Open-label, Multi-centre Clinical Trial	Randomized, double-blind, placebo-controlled, multi-center, Phase 2-like, investigator-directed trial
Status of trial	Recruiting	Recruiting;	Recruiting (according to Chinese website that was updated)	Recruiting
Duration/End of Study	Estimated study completion: July 31, 2020	Estimated study completion: July 31,2022	Estimated study completion: June 30, 2020	Estimated Primary Completion Date: January 1, 2021
Study details				
Number of Patients	125 patients Randomised 2:2:1 to Lopinavir /Ritonavir Tablets, Arbidol, or ordinary treatment	N=70 hospitalised patients with confirmed covid 19 infection randomised to Lopinavir/ritonavir, Ribavirin, or Interferon Beta-1B	N=160 patients with pneumonia caused by covid-19 randomised to ASC09/ritonavir or lopinavir/ritonavir	N=4000 hospitalized adult patients with laboratory confirmed SARS-CoV-2 infection
Disease severity				
Setting				
Location/Centres	Guangdong, China	Hong Kong	Zhejiang University, China	United States
Intervention drug name and dosage				lopinavir/ritonavir 400mg/200mg mg po BID X 5-14 days depending on availability
Comparator (drug name and dosage)		Ribavirin, or Interferon Beta-1B		losartan 25 mg po QD X 5-14 days depending on availability placebo BID X 14 days
Duration of observation/ Follow-up				
Primary Outcomes Secondary Outcomes	The rate of virus inhibition	Time to negative nasopharyngeal swab (NPS) 2019-n-CoV coronavirus viral RT- PCR	The incidence of composite adverse outcome (time frame 14 days)	National Institute of Allergy and Infectious Diseases COVID-19 Ordinal Severity Scale (NCOSS)
Results/Publication				

Table 4-14 Ongoing trials of single agent Lopinavir + Ritonavir (continued)

Active substance	Lopinavir+ Ritonavir	Lopinavir+ Ritonavir	Lopinavir+ Ritonavir	Lopinavir + Ritonavir
Sponsor	OHSU Knight Cancer Institute	Vanderbilt University Medical Center	Tongji Hospital	Centre Hospitalier Universitaire de Saint Etienne
Trial Identifier	NCT04455958	NCT04372628	NCT04255017	NCT04328285
Phase & Intention	Phase 2	Phase 2	Phase 4	Phase 3
Study design	Double-Blind, Randomized, Placebo-Controlled Phase II Study	Blinded, multicenter, placebo-controlled randomized clinical trial	Open, Prospective/Retrospective, Randomized Controlled Cohort Study	Allocation: Randomized Intervention Model: Parallel Assignment Intervention Model Description: A randomized double-blind placebo-controlled clinical trial Masking: Triple (Participant, Investigator, Outcomes Assessor) Primary Purpose: Prevention
Status of trial	Not yet recruiting	Recruiting	Recruiting	Active, not recruiting
Duration/End of Study	July 1, 2021	May 1, 2021	July 1, 2020	November 30, 2020
Study details				
Number of Patients	75	600	400	1200
Disease severity	COVID-19 positive patients with cancer and a weakened immune system (immune-suppression) in the last year and have mild or moderate symptoms caused by COVID-19.	Non-hospitalized COVID-19 outpatients	Mild and severe COVID-19 patients	Health care workers with prolonged or repeated close contact to SARS-CoV2 patients
Setting				
Location/Centres	OHSU Knight Cancer Institute Portland, Oregon, United States	University of Colorado School of Medicine, Beth Israel Deaconess Medical Center, University of Mississippi Medical Center, Oregon Health & Science University, Vanderbilt University Medical Center	Tongji Hospital, China	Centre Hospitalier Universitaire de Saint Etienne
Intervention drug name and dosage	lopinavir/ritonavir orally (PO) twice daily (BID) for 14 days	Lopinavir/Ritonavir 400 mg/100 mg	500mg once, twice a day, 2 weeks	Lopinavir/ritonavir 200/50 mg

Active substance	Lopinavir+ Ritonavir	Lopinavir+ Ritonavir	Lopinavir+ Ritonavir	Lopinavir + Ritonavir
Comparator (drug name and dosage)	placebo	placebo	Abidol hydrochloride (0.2g once, 3 times a day,2 weeks) Oseltamivir (75mg once, twice a day,2 weeks)	Hydroxychloroquine 200 mg Placebo
Duration of observation/ Follow-up	3 months	15 days		2.5 months
Primary Outcomes	Severity of symptoms	Modified COVID Ordinal Outcomes Scale:		Occurrence of an symptomatic or asymptomatic SARS-CoV-2 infection among healthcare workers (HCWs)
Results/Publication	N/A	N/A	N/A	N/A

Table 4-15 Ongoing trials of combination therapies Lopinavir + Ritonavir

Active substance	Lopinavir + Ritonavir in combination with Interferon-beta	Lopinavir + Ritonavir vs Interferon 1 β vs Low-dose Corticosteroids vs Hydroxychloroquine.
Sponsor		University of Oxford
Trial Identifier	NCT04315948	EudraCT 2020-001113-21
Phase & Intention		
Study design	Adaptive, randomised open clinical trial to one of 4 treatments	Adaptive, open label randomised controlled trial.
Status of trial	Recruiting	Ongoing
Duration/End of Study	Estimated study completion: March 2023	Estimated Primary Completion: March 31, 2021
Study details		
Number of Patients	EU: France, Spain, UK, Germany, Belgium, Netherlands, Luxembourg, Norway N=3200	N=2000 hospitalised patients with covid-19 are randomised to 1 of 5 treatment arms in addition to usual standard of care:
Disease severity		
Setting		
Location/Centres		UK
Intervention drug name and dosage		Lopinavir-Ritonavir
Comparator (drug name and dosage)		No additional treatment, Interferon 1 β , Low-dose Corticosteroids, or Hydroxychloroquine.
Duration of observation/ Follow-up		
Primary Outcomes	Subject clinical status (on a 7-point ordinal scale) on Day 15	In-hospital death, discharge, and need for ventilation. Time frame 28 days
Results/Publication		

5 REFERENCES

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- [7] M. Stoldick, F. Lamoureux, M. Robert, F. Caron, M. Étienne, and I. Gueit, "Relation concentration-tolérance du lopinavir/ritonavir dans le traitement des COVID-19 sévères," *Médecine Mal. Infect.*, vol. 50, no. 6, pp. S91–S92, Sep. 2020.
- [8] T. Xiao-jiang *et al.*, "A quick data mining and analysis of lopinavir/ritonavir(LPV/r) adverse events based on Eudravigilance Medicines Safety Database," *Chinese J. New Drugs*, no. 9, pp. 1073–1080, 2020.

6 APPENDIX

6.1 Search strategy to identify randomised controlled trials

DEPLazio, the Department of Epidemiology of the Regional Health Service Lazio in Rome, Italy is responsible for setting up the search strategy to identify randomised controlled trials (RCTs). DEPLazio performed a search in Medline, PubMed, and Embase, which has been updated weekly from March 2020 (Appendix Table 6-1). DEPLazio searched medRxiv.org (<https://www.medrxiv.org/>), bioRxiv.org (<https://www.biorxiv.org/>), and arXiv.org (<https://www.arxiv.org/>) for preprints of preliminary reports of randomised trials. The Cochrane Covid-19 Study Register (<https://covid-19.cochrane.org/>), ClinicalTrials.gov (www.clinicaltrials.gov) and World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (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*[Title/Abstract] 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"> 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 Ncover 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" 	21 September 2020
OID EMBASE	ovidsp.dc2.ovid.com	<ol style="list-style-type: none"> 1. exp Coronavirinae/ or exp Coronavirus/ 2. exp Coronavirus infection/ 3. (((("Corona virinae" or "corona virus" or Coronavirinae or coronavirus or COVID or nCoV) adj4 ("19" or "2019" or novel or new)) or (("Corona virinae" or "corona virus" or Coronavirinae or coronavirus or COVID or nCoV) and (wuhan or china or chinese)) or "Corona virinae19" or "Corona virinae2019" or "corona virus19" or "corona virus2019" or Coronavirinae19 or Coronavirinae2019 or coronavirus19 or coronavirus2019 or COVID19 or COVID2019 or nCOV19 or nCOV2019 or "SARS Corona virus 2" or "SARS Coronavirus 2" or "SARS-COV-2" or "Severe Acute Respiratory Syndrome Corona virus 2" or "Severe Acute Respiratory Syndrome Coronavirus 2").ti,ab,kw. 4. or/1-3 5. Clinical-Trial/ or Randomized-Controlled-Trial/ or Randomization/ or Single-Blind-Procedure/ or Double-Blind-Procedure/ or Crossover-Procedure/ or Prospective-Study/ or Placebo/ 6. (((clinical or control or controlled) adj (study or trial)) or ((single or double or triple) adj (blind\$3 or mask\$3)) or (random\$ adj (assign\$ or allocat\$ or group or grouped or patients or study or trial or distribut\$)) or (crossover adj (design or study or trial)) or placebo or placebos).ti,ab. 7. 5 or 6 8. 4 and 7 9. limit 8 to yr="2019 -Current" 	21 September 2020

		<p>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 cvidence* or covidien or influenza virus or HIV or bovine or calves or TGEV or feline or porcine or BCoV or PED or PEDV or PDCoV or FIPV or FCoV or SADS-CoV or canine or CCov or zoonotic or avian influenza or H1N1 or H5N1 or H5N6 or IBV or murine corona*).mp. 6 ((pneumonia or covid* or coronavirus* or corona virus* or ncov* or 2019-ncov or sars*).mp. or exp pneumonia/) and Wuhan.mp. 7 (2019-ncov or ncov19 or ncov-19 or 2019-novel CoV or sars-cov2 or sars-cov-2 or sarscov2 or sarscov-2 or Sars-coronavirus2 or Sars-coronavirus-2 or SARS-like coronavirus* or coronavirus-19 or covid19 or covid-19 or covid 2019 or ((novel or new or nouveau) adj2 (CoV on nCoV or covid or coronavirus* or corona virus or Pandemi*2) or ((covid or covid19 or covid-19) and pandemic*2) or (coronavirus* and pneumonia)).mp. 8 6 or 7 9 5 or 8</p>		
Scopus		<p>TITLE-ABS-KEY(((pneumonia OR covid* OR coronavirus* OR "corona virus*" OR ncov* OR 2019-ncov OR sars*) AND Wuhan) OR 2019-ncov OR ncov19 OR ncov-19 OR "2019-novel CoV" OR 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)</p>	24 August and 27 September 2020	

6.3 Search strategy to identify ongoing studies

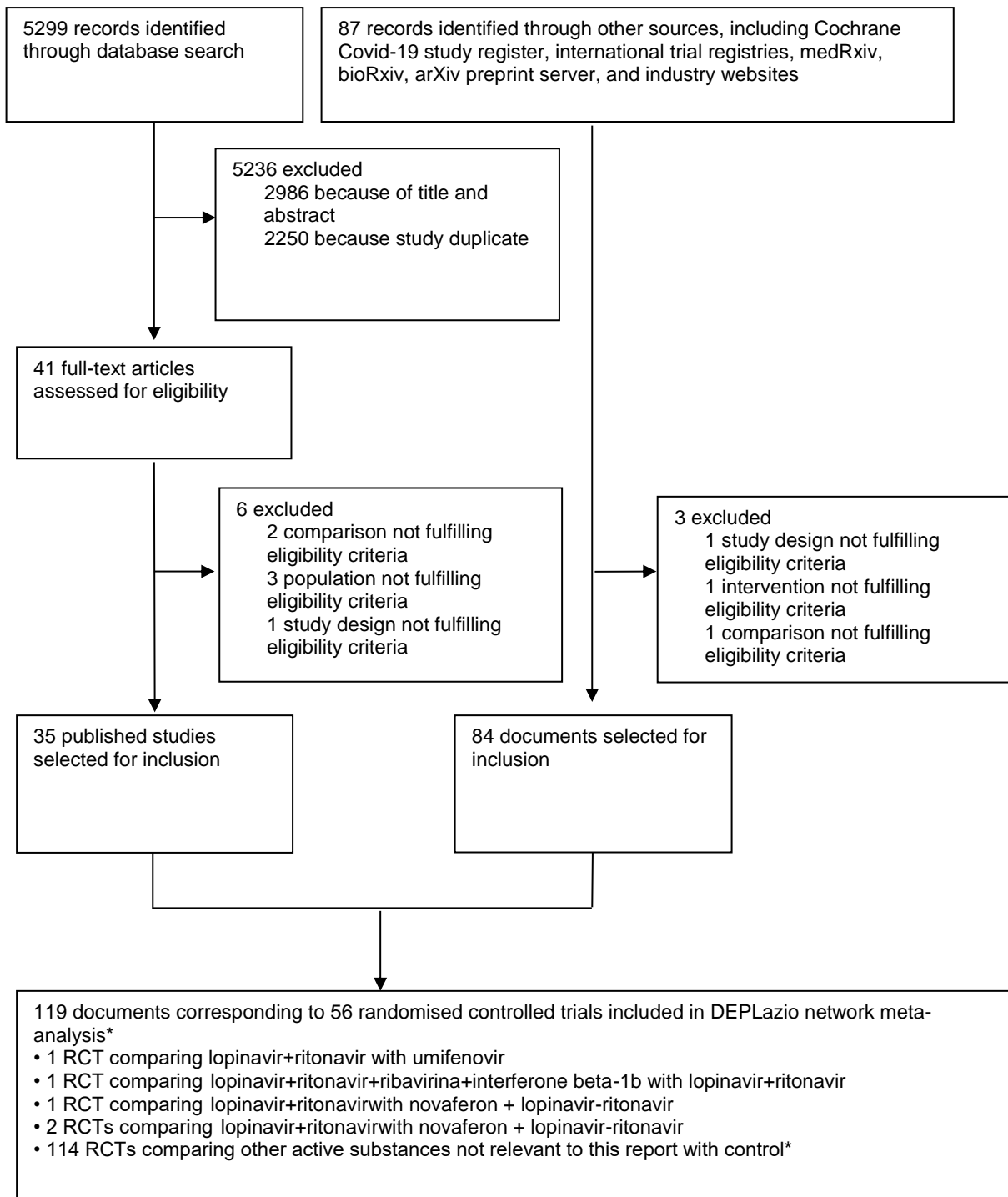
NIPN is responsible for searching in trial registries to identify ongoing and unpublished studies. The combination of search terms related to COVID-19 and lopinavir+ritonavir are described in Appendix Table 6-3.

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: <ul style="list-style-type: none"> • covid-19 Terms used at "other terms": <ul style="list-style-type: none"> • lopinavir + ritonavir 	14/10/2020	87 1 new
ISRCTN	https://www.isrctn.com/	Basic search mode Search terms: <ol style="list-style-type: none"> 1. covid-19 and lopinavir+ritonavir 2. covid-19 and Kaletra 3. SARS-CoV-2 and lopinavir+ritonavir 4. SARS-CoV-2 and Kaletra 	14/10/2020	3
European Clinical Trials Registry	https://www.clinicaltrialsregister.eu/	Basic search mode Search terms: <ol style="list-style-type: none"> 1. covid-19 and lopinavir+ritonavir 2. covid-19 and Kaletra 3. SARS-CoV-2 and lopinavir+ritonavir 4. SARS-CoV-2 and Kaletra 	14/10/2020	21

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

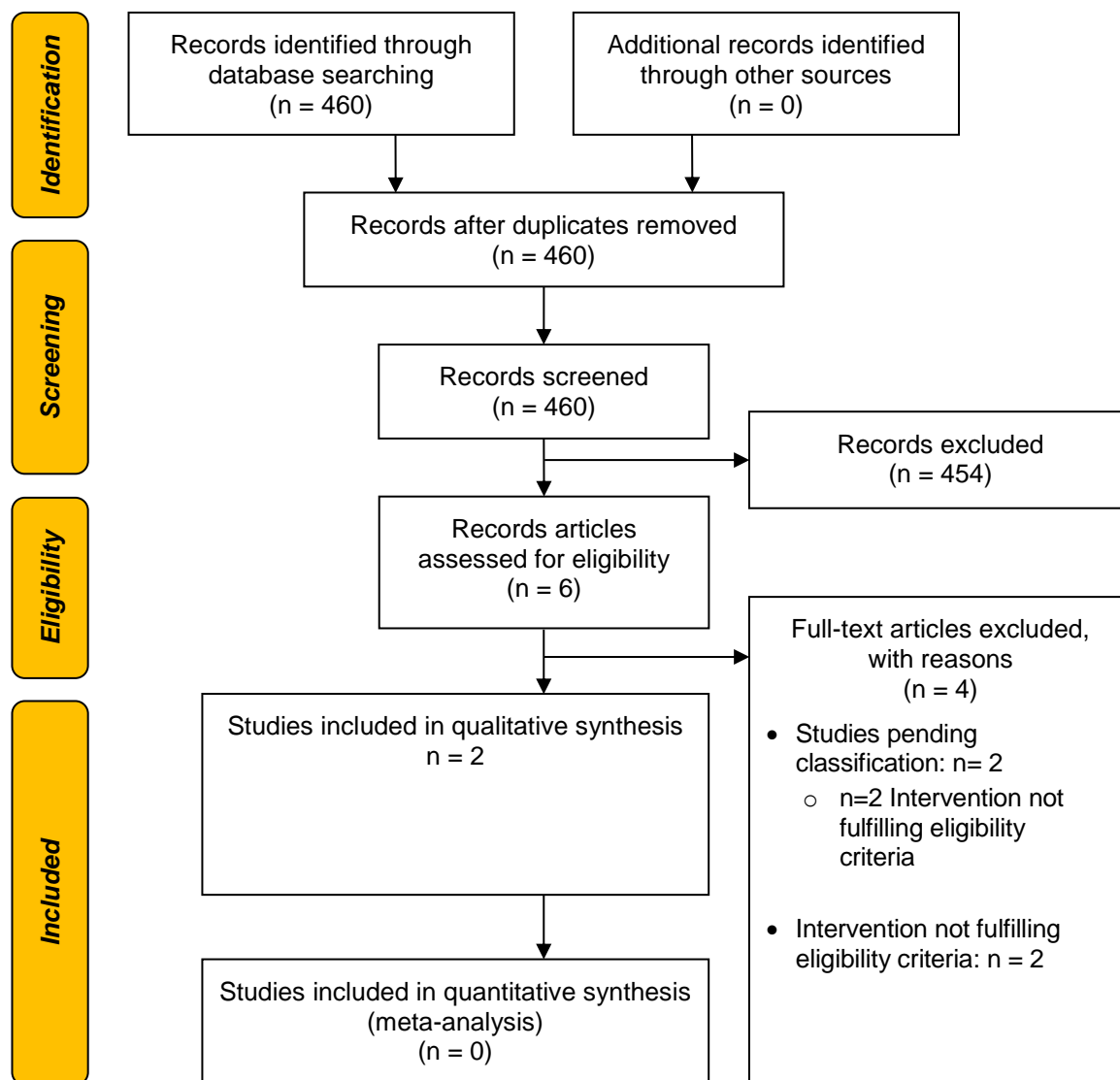
6.4 Flow diagrams



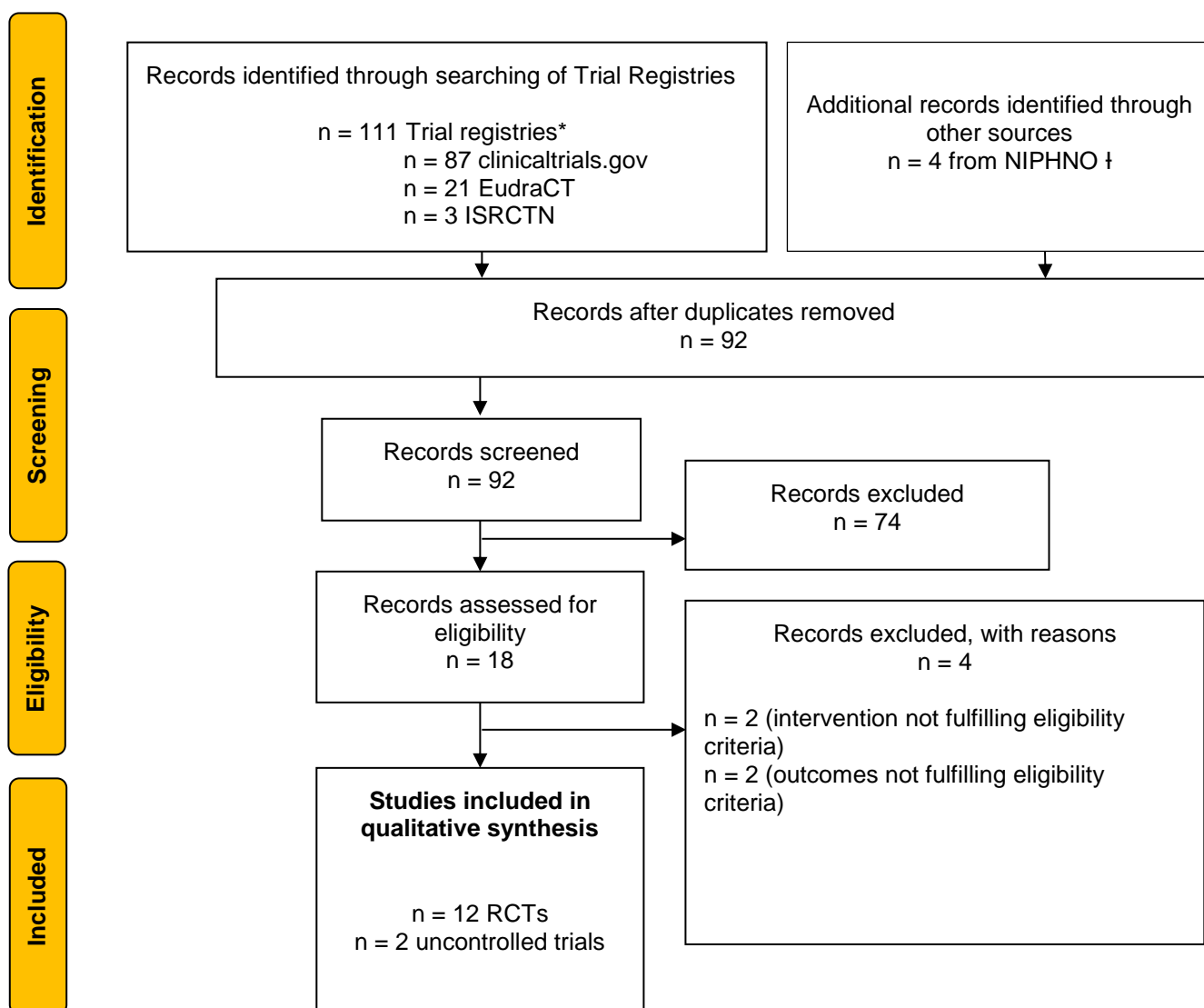
Appendix Figure 6-1. Flow diagram depicting the selection process of RCTs

Abbreviation: RCT=randomised controlled trial;

* The selection process was part of an external project, see <https://www.deplazio.net/farmacocovid> 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



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;