EUnetHTA Joint Action 3 WP4

“Rolling Collaborative Review” of Covid-19 treatments

ASPIRIN FOR THE TREATMENT OF COVID-19

Project ID: RCR23
Monitoring Report

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DOCUMENT HISTORY AND CONTRIBUTORS

Version	Date	Description of changes
V 1.0	**17/02/2021**	First version
V 2.0	**16/03/2021**	Second version
V 3.0	**22/04/2021**	Third version

Major changes from previous version

Chapter, page no.	Major changes from version 2.0
Summary, 11	The evidence pool has changed • One ongoing phase 3 randomised clinical trial was added (NCT04808895 / Eudract ID 2020-006130-12-IT) • One ongoing adaptive platform trial was added (EudraCT ID 2020-005963-29-DK) which is related to the already identified ASCOT-ADAPT RCT in Australia.

Disclaimer

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Rolling Collaborative Review team

Author(s)	Swiss Network for Health Technology Assessment (SNHTA), Switzerland
Co-Author(s)	Department of Epidemiology Lazio Regional Health Service (DEPLazio), Italy

Further contributors

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

Conflict of interest

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

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

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LIST OF ABBREVIATIONS

AE	Adverse Event
ASA	Acetylsalicylic acid
BID	Bis in die (twice daily)
CI	Confidence Interval
COVID-19	Coronavirus disease 2019
CTRI	Clinical Trials Registry - India
DOI	Declaration of interest
EMA	European Medicines Agency
EUCTR	European Union Clinical Trials Register
EudraCT	European Union Drug Regulating Authorities Clinical Trials Database
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
IRCT	Iranian Registry of Clinical Trials
ISRCTN	International Standard Randomised Controlled Trial Number
IU	International unit
IVM	Ivermectin
kg	kilogram
MD	Mean Difference
MeSH	Medical Subject Headings
mg	milligram
NA	Not applicable
NCT	National Clinical Trial number (Clinicaltrials.gov)r
NR	Not reported
OR	Odds Ratio
PACTR	Pan African Clinical Trials Registry
PCR	Polymerase Reaction Chain
PO	Per os
RCT	Randomized Controlled Trial
RCR	Rolling Collaborative Review
REA	Relative Effectiveness Assessment
RR	Relative Risk
SAE	Serious Adverse Event
SARS	Severe acute respiratory syndrome
SD	Standard Deviation
SMD	Standardized Mean Difference
SNHTA	Swiss Network for Health Technology Assessment
SoC	Standard of care
SOF	Summary of Findings
SOP	Standard Operating Procedure
TNR4	“Terapia Nueva para la Recuperación en la infección por COVID-19, 4 medicamentos”: multidrug-therapy consisting of Ivermectin, Azithromycin, Montelukast and Acetylsalicylic Acid (TNR4 therapy)
WP4	Work Package 4
WHO	World Health Organisation

1 OBJECTIVE

The aim of this EUnetHTA Rolling Collaborative Review is

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

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

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

2 METHODS

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

2.1 Scope

Table 2-1 Scope of the RCR

Description	Project Scope
Population	**Disease** • SARS-CoV-2 is a novel coronavirus causing a respiratory illness termed Covid-19. The full spectrum of Covid-19 ranges from mild, self-limiting respiratory tract illness to severe progressive pneumonia, multi-organ failure, and death. **ICD-Codes** (https://www.who.int/classifications/icd/covid19/en) • An emergency ICD-10 code of 'U07.1 COVID-19, virus identified' is assigned to a disease diagnosis of COVID-19 confirmed by laboratory testing. • An emergency ICD-10 code of 'U07.2 COVID-19, virus not identified' is assigned to a clinical or epidemiological diagnosis of COVID-19 where laboratory confirmation is inconclusive or not available. • Both U07.1 and U07.2 may be used for mortality coding as cause of death. See the International guidelines for certification and classification (coding) of COVID-19 as cause of death following the link below. • In ICD-11, the code for the confirmed diagnosis of COVID-19 is RA01.0 and the code for the clinical diagnosis (suspected or probable) of COVID-19 is RA01.1. **MeSH-terms** • COVID-19, Coronavirus Disease 2019 **Target population** (https://www.covid19treatmentguidelines.nih.gov/overview/management-of-covid-19/)

	• Asymptomatic or pre-symptomatic Infection: Individuals who test positive for SARS-CoV-2 by virologic testing using a molecular diagnostic (e.g., polymerase chain reaction) or antigen test, but have no symptoms. • Mild Illness: Individuals who have any of the various signs and symptoms of COVID 19 (e.g., fever, cough, sore throat, malaise, headache, muscle pain) without shortness of breath, dyspnoea, or abnormal chest imaging. • Moderate Illness: Individuals who have evidence of lower respiratory disease by clinical assessment or imaging and a saturation of oxygen (SpO2) ≥94% on room air at sea level. • Severe Illness: Individuals who have respiratory frequency >30 breaths per minute, SpO2 <94% on room air at sea level, ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO2/FiO2) <300 mmHg, or lung infiltrates >50%. • Critical Illness: Individuals who have respiratory failure, septic shock, and/or multiple organ dysfunction.
Intervention	Aspirin, active substance: acetylsalicylic acid (ASA). Any generic equivalent of ASA. Oral intake. MESh terms: aspirin
Comparison	Any active treatment, placebo, or standard of care. **Rationale**: Since there is no gold standard treatment any comparator is acceptable as well as the above listed interventions.
Outcomes	<u>Main outcome:</u> • All-cause Mortality (Survival) <u>Additional Outcomes:</u> Efficacy: • Length of hospital stay, • Viral burden (2019-nCoV RT-PCR negativity), • Clinical progression (WHO Clinical Progression Scale measured daily over the course of the study), • Rates of hospitalization and of patients entering ICU, • Duration of mechanical ventilation, • Quality of life. Safety: • Adverse events (AE), • Severe adverse events (SAE), • Withdrawals due to AEs, • Most frequent AEs, • Most frequent SAEs. **Rationale:** We will give priority according to the Core Outcome Set for Clinical Trials on Coronavirus Disease 2019 (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7102592/pdf/main.pdfc) and A minimal common outcome measure set for COVID-19 clinical research from the WHO Working Group on the Clinical Characterisation and Management of COVID-19 infection.
Study design	Efficacy: randomised controlled trials (RCT) Safety: observational studies (comparative or single-arm prospective studies and registries)

2.2 Sources of information

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

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

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

The literature search is conducted in the following databases:

- PubMed
- MEDLINE, accessed via OVID
- Embase, accessed via OVID

Population	People affected by COVID-19, as defined by the authors of the studies. No limits in terms of gender or ethnicity. SARS-CoV-2 is a novel coronavirus causing a respiratory illness termed Covid-19. It started spreading in December 2019, and was declared a pandemic by the World Health Organisation on 11th March 2020. The full spectrum of Covid-19 ranges from mild, self-limiting respiratory tract illness to severe progressive pneumonia, multi-organ failure, and death.
Intervention	Interventions for the treatment of people affected by COVID-19, including pharmacological interventions (e.g. antibiotics, antibodies, antimalarial, antiviral, antiretroviral, immune-suppressors/modulators, kinase inhibitors) and their combinations.
Comparison	Any active treatment, placebo, or standard of care.
Outcomes	All-cause mortality Additional outcomes: Length of hospital stay, 2019-nCoV RT-PCR negativity, PaO2/FiO2, Duration of mechanical ventilation, radiological imaging, Adverse events, Severe adverse events.
Study design	Randomised controlled trials (RCT); no restriction on language of publication

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

- medRxiv Health Sciences
- bioRxiv Biology

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

Data extraction, Risk of bias assessment, data synthesis:

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

Risk of bias is assessed using the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions [2].

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 [3]. Network meta-analysis (NMA) is performed for the primary outcome. For rating the certainty of the evidence, the GRADE approach is being used [4].

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

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

The literature search is conducted on a monthly basis.

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

Population	See project Scope
Intervention	Aspirin, active substance: acetylsalicylic acid (ASA). Any generic equivalent of ASA. Oral intake. MESh terms: aspirin
Comparison	Any active treatment, placebo, or standard of care.
Outcomes	See project Scope
Study design	Inclusion criteria: Prospective non-randomised controlled trials, prospective case series (i.e. comparative or single-arm prospective studies), registries Exclusion criteria: retrospective studies, case studies/ case reports, observational studies that do not report safety data

Two researchers from NIPHNO carry out title and abstract screening and assess the full texts of all potentially eligible studies. The study selection process is depicted in a flow diagram (Appendix Figure 6-2).
One researcher of SNHTA 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 Johanna Briggs tool for prevalence studies is used to assess the methodological rigor and applicability [5].

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 SNHTA is searching and extracting the data for the eligible studies. At the drafting stage of each update, the author team verifies whether the status of previously identified studies has changed. This is done by verifying the date of the last update posted in the trial registers. In addition, trial register IDs of all previously identified studies are entered in both PubMed and Google

(google.com) to verify if previously identified studies have been published since the last update. In Google, the first 10 hits are screened for this purpose.

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

Data are presented in tabular form.

3 ABOUT THE TREATMENT

3.1 Mode of Action

Aspirin with active substance acetylsalicylic acid belongs to the drug group non-steroidal anti-inflammatory drugs and is a nonselective cyclooxygenase inhibitor [6]. Salicylic acid is the most important active metabolite of aspirin. It is produced by plants upon infection with pathogens and in particular viruses [7, 8]. The production of salicylic acid in turn mediates resistance to viral replication, intercellular spread and systemic movement through so-called pathogenesis-related proteins including the protein Coronatine Insensitive [7]. Aspirin is expected to stimulate cell-autonomous immunity against viral infection.

Apart from its capability to inhibit virus replication and its anti-inflammatory potential, acetylsalicylic acid has analgesic and antipyretic properties. The peripheral analgesic effect is due to the inhibition of cyclooxygenase. This inhibits the formation of prostaglandins (E2 and I2), which are involved in the development of pain [9]. The antipyretic effect is due to a central action on the hypothalamic temperature-regulating centre, resulting in peripheral dilatation of skin vessels with sweating and heat loss [9].

An additional mechanism of action is based on anti-platelet aggregation. Acetylsalicylic acid has an antithrombotic effect by inhibiting thromboxane A2 synthesis in platelets [10]. Accumulating data suggests COVID-19 to be profoundly prothrombotic. Microthrombosis due to a hypercoagulable state has been repeatedly reported in patients with COVID 19 [11]. Furthermore, the likelihood of progressing to severe disease and COVID-19 severity appears to be in part driven by direct injury to the cardiovascular system. Due to its anti-thrombotic effects, cardioprotective and lung-injury protective effects of aspirin in COVID-19 are expected.

3.2 Regulatory Status

Aspirin, produced by Bayer, is not currently approved for the treatment of COVID-19[12]. Beside the Brand-name “Aspirin” there are generic equivalents of acetylsalicylic acid on the market, but they have the same therapeutic indications and limitations as the original "Aspirin" (e.g. Alcacyl, Aspégic, Aspro, ASS Cardio Mepha). It is approved for the treatment of mild to moderately severe acute pain (headache, toothache, pain in the area of joints and ligaments, back pain) and for symptomatic treatment of fever and/or pain in colds. In adolescents aged 12 years and over, aspirin is indicated only after a doctor's prescription and only as a second-line treatment. Aspirin chewable tablets and granules are approved for self-medication for short-term treatment of a maximum of 3 days. Aspirin is marketed as Aspirin, Aspirin-C, Aspirin S, Aspirin Complex and Aspirin 500 Instant-tablets. In children aged 9 years and over and in adolescents, aspirin-C is approved only after a doctor's prescription and only as a second-line treatment (swissmedicinfo.ch).

Aspirin Cardio 100, Aspirin Cardio 300 of Bayer are approved for the following indication (swissmedicinfo.ch):

- Thrombosis prevention (reocclusion prophylaxis) after aortocoronary bypass, percutaneous transluminal coronary angioplasty (PTCA) and arteriovenous shunt in dialysis patients.
- Prophylaxis of cerebrovascular insults after precursor stages have occurred (transient ischaemic attacks, TIA).
- Reduction of the risk of further coronary thrombosis after a heart attack (reinfarction prophylaxis).

- Myocardial infarction prophylaxis in conjunction with other therapeutic measures in patients with a very high cardiovascular risk according to the benefit-risk assessment by the attending physician.
- Unstable angina pectoris.
- Prophylaxis of arterial thrombosis after vascular surgery.
- In acute myocardial infarction, as part of standard therapy.
- Prevention of vascular occlusion in arterial occlusive disease.

3.3 Level of Evidence

We did not identify any RCT with published outcome data in any of the sources searched (Table 6-1).

The searches by NIPHNO identified one observational study (Table 6-2) [1]. This prospective comparative trial was conducted in Mexico and evaluated the effectiveness of a multidrug therapy consisting of ivermectin, azithromycin, montelukast and 100 mg of acetylsalicylic acid (TNR4) to prevent hospitalization and death among ambulatory COVID-19 patients. Control patients were those who refused TNR4 treatment because they were asymptomatic or had already started self-medication. The search in trial registries identified another study to which a non-peer reviewed preprint report was found when using the trial registration number as search term in google.com (IDEA; NCT04425863) [11]. This single arm prospective study conducted in Argentina has documented the effectiveness and safety of Aspirin. This study evaluated a combined therapy of 24 mg Ivermectin plus 250 mg Aspirin in outpatients with mild COVID-19 cases. The study also evaluated Ivermectin, Dexamethasone, Aspirin and oxygen therapy in hospitalized patients with moderate COVID-19 and another combination therapy without aspirin in patients with severe symptoms. The outcome data from the sample with moderate COVID-19 symptoms could not be extracted as the authors reported all outcome data for the combined group with moderate and severe symptoms. Detailed information of the two included observational studies and eligible safety data are described in Table 4-1. In the previous version of this report, we excluded one study because of sample size being below 50 [13].

We identified 30 reports to 19 ongoing studies in international clinical trial registries and through searching other sources (Table 4-2 to Table 4-9).

4 SUMMARY

4.1 Effectiveness and Safety evidence from RCTs

None of the RCTs identified in trial registries has posted outcome data in any of the sources searched.

4.2 Safety evidence from observational studies

Ivermectin, Azithromycin, Montelukast and ASA (TNR4 therapy)

The non-randomised comparative trial focused on effectiveness and reported safety outcome data incompletely and confusingly. Only outcome data on the most frequently occurring adverse events were extractable in part, for the TNR4 group only. Only percentages could be extracted, without confidence intervals or denominators. As no comparison could be made for our outcomes of interest, the extracted outcome data were considered to be derived from a single arm study. The critical appraisal of the study was thus assessed with the JBI tool for prevalence studies [5], and the trial was judged to be at high risk of bias (Table 4-1). The most frequently occurring adverse events were gastrointestinal issues such as abdominal pain, nausea, vomiting, diarrhea, constipation, diarrhea and constipation (5.9%); headache and dizziness (3.1%); asthenia, fatigue, and confusion (1.4%); urticarial and itchy feeling (0.9%).

Ivermectin + 250 mg aspirin

In one single arm prospective study at high risk of bias that evaluated a combined therapy of 24 mg Ivermectin + 250 mg aspirin in outpatients with mild COVID-19 cases, none of the 135 patients experienced a serious adverse event (SAE), none was withdrawn because of a SAE and none died because of a SAE.

4.3 Ongoing studies

Searches across clinical trial registries resulted in the identification of 57 entries, the search at covid-nma.com in 13 entries (Table 6-3). An additional three reports were found when using trial acronyms and clinical trial registration numbers in google.com, scholar.google.com and pubmed.gov. The search in the Cochrane COVID-19 register resulted in 17 additional citations. After deduplication, 30 reports to 19 ongoing studies were included. Two newly identified RCTs compared colchicine plus aspirin with aspirin alone. As the effect of aspirin cannot be distilled from such comparison, the trials were excluded CTRI ID 2021/03/032060; CTRI ID 2021/03/032059). Another ongoing RCT was excluded as aspirin was provided in all trial arms (LEAD COVID-19; NCT04363840). The LEAD COVID-19 trial evaluates aspirin and vitamin D in vitamin D deficient COVID-19 patients and will be addressed in EUnetHTA RCR20 [14]. The 19 included studies involved 5 platform adaptive RCTs (Table 4-2, Table 4-3); ten studies evaluating aspirin as a single agent (Table 4-4 to Table 4-7), three studies evaluating a combination therapy with aspirin (Table 4-8

Table 4-8) and one observational study where it is not yet clear if eligible safety data will be addressed (Table 4-9

Table 4-9). Three platform randomized trials and two RCTs recruited (part of) the patients in Europe. Thirteen of the ongoing RCTs evaluated Aspirin in daily doses of 75 to 160mg. Latter doses are typically used to obtain antiplatelet effects and are used for cardioprotection. One RCT used a lower dose by using Aggrenox twice daily for a total daily dose of 400 mg Dipyridamole and 50mg aspirin (NCT04410328). One trial used a daily dose of 325 mg, a dosage used to elicit both antiplatelet and anti-inflammatory action (CTRI/2020/09/028088). The dose used in the ASCOT-ADAPT platform trial in Denmark remains unclear (EudraCT: 2020-005963-29-DK) but it likely the same as used in the ASCOT-ADAPT with recruitment in Australia, which is 100 mg (NCT04483960 / ACTRN12620000445976). The remaining trial did not describe the dose in detail, but it was clear that the Aspirin dose was to obtain anti-inflammatory effects (NCT04554433).The severity of COVID-19 in the study population varied between trials, the majority studied hospitalized patient with moderate to critical COVID-19, one RCTs focused on outpatients (NCT04498273) and another on both outpatients and hospitalized patients (NCT04324463).

4.4 Scientific conclusion about status of evidence generation

None of the identified RCTs has published outcome data on effectiveness and the safety outcome data. Evidence of the two observational studies is incomplete and interpretation is hampered by risk of bias and the quality of reporting. The current evidence base is not sufficient to decide to support the use of aspirin as monotherapy or combination therapy for COVID-19.

Table 4-1 Summary of safety from observational studies (AE and SAE) of combination therapy with Aspirin

Author, year	Carvallo 2020 [11]; NCT04425863; IDEA	Lima-Morales 2021 [1];
Country	Argentina	Mexico
Sponsor/ lead institution	Eurnekian Public Hospital, Buenos Aires, Argentina	Sponsor not reported, likely Ministry of Health of the Tlaxcala state, Mexico
Intervention/ Product (drug name)	Mild cases: Ivermectin + aspirin, outpatient treatment Moderate cases: Ivermectin, Dexamethasone, aspirin and Low Flow Washed Oxygen or Oxygen Concentrator, inpatient treatment Severe cases: Ivermectin, Dexamethasone, enoxaparin and inpatient treatment with mechanical ventilation in ICU.	N=481 multidrug-therapy consisting of Ivermectin, Azithromycin, Montelukast and Acetylsalicylic Acid (TNR4 therapy) All participants received home visits and/or phone calls for clinical evaluation during the 14 days after enrollment. Non standardised concomittant drug use: 2.71% used nonsteroidal anti-inflammatory drugs (NSAIDs), 1.90% took medications to treat cold and flu symptoms, 0.9% used antibiotics, and 0.74% used antivirals.
Dosage	Ivermectin on day 0 (day the patient starts treatment) and 7: Mild: 25 mg, oral; Moderate 36 mg, oral; Severe 48 mg via gastric cannulae Aspirin: 250 mg tablets, 1 table daily for 30 days Dexamethason: 4-mg injection daily until discharge Enoxaparin: injection 100 IU/kg (ca. 1 mg/kg) daily until transfer to ward care	TNR4 therapy with Ivermectin, 12 mg single dose plus Azithromycin 500 mg for 4 days plus Montelukast, 60 mg on the first day and then 10 mg between days 2 to 21 plus acetylsalicylic acid, 100 mg for 30 days.
Comparator	None**	N=287 Control: “participants who did not accept the TNR4 therapy because they were asymptomatic, were already taking another treatment, or they had self-medicated for cold and flu. However, they agreed to take part in the follow up portion of the study.” All participants received home visits and/or phone calls for clinical evaluation during the 14 days after enrollment. Non standardised concomittant drug use: 19% did not take any medications, 61.4% used NSAIDs, 14.4% combined antibiotics with NSAIDs or corticosteroids, and 5.2% took antiviral drugs along with NSAIDs or corticosteroids.
Study design	Prospective single center uncontrolled cohort. Recruitment from May to July 2020.	Comparative prospective non-randomised study. Recruitment from May 11 to September 19 2020.
Setting	Outpatient, hospital ward & ICU	Oupatients
Number of pts	N=167	N=768
Inclusion criteria	Patients with positive oral/nasal swabs; able to provide informed consent; not enrolled in another clinical study	• Laboratory confirmed COVID-19 of those suspected of COVID-19 in the catchement area

Author, year	Carvallo 2020 [11]; NCT04425863; IDEA	Lima-Morales 2021 [1];
Exclusion criteria	Children under 5 years old; pregnant women; previous reports of allergy to any of the drugs used in the clinical trial	• who refused to participate (n=251) • who were under 18 years or older than 80 years (n=44) • those who initiated the treatment on the same day or one day before they were hospitalized or died (n=84)
Age of patients (yrs)	Mild: 55.7 years; 48.5% females Moderate to severe: 59.7 years; 57.5% females	TNR4: 41.3 years; 226 (47.5%) males Control: 46.2 years; 161 (57.8%) males At least one comorbidity: TNR4: 185 (38.5%) / control: 131 (45.6%)
Disease severity	Mild to severe symptoms	mild or moderate symptoms of COVID-19
Follow-up (months)	Up to 30 days	Up to 14 days
Loss to follow-up, n (%)	None reported	Not addressed in the paper
RoB**	High RoB. Unclear sampling methods, too small sampe size to measure safety outcomes, non-standard definitions of COVID-19 severity. In addition to the JBI criteria, concerns raised regarding selective outcome reporting as data for moderate and severe samples were reported jointly. As the study sample with severe symptoms did not receive Aspirin, outcome data on SAE for this joint group could not be considered.	High RoBł. Main concerns regarded wether valid methods were used for the identification of AEs; wether these were measured in a reliable way for all particants. In addition to the JBI criteria, concerns raised regarding selective outcome reporting as safety data were reported not clearly and incompletely and because no protocol nor trial registration was found.
Safety – Outcomes		
Overall AEs, n (%)	-	- not extracted, unclearly reported
Serious AE (SAE), n (%)	Treatment related SAE: Mild: 0 / 135	-
Most frequent AEs n (%)	-	In the TNR4 group: • gastrointestinal issues such as abdominal pain, nausea, vomiting, diarrhea, constipation, diarrhea and constipation (5.9%) • headache and dizziness (3.1%) • asthenia, fatigue, and confusion (1.4%) • urticarial and itchy feeling (0.9%). In the control group: • Not reported
Most frequent SAEs, n (%)	-	-

Author, year	Carvallo 2020 [11]; NCT04425863; IDEA	Lima-Morales 2021 [1];
AEs of special interest, n (%)	-	-
Death as SAE, n (%)	Mild: 0 / 135; Moderate to severe: 0 / 32	-
Withdrawals due AEs, n (%)	Mild: 0 / 135; Moderate to severe: 0 / 32	-

*** The authors descriptively compare the outcome data with external controls and published data, which are both ignored in this report**

**** by arms, if available, (Robins-I): https://training.cochrane.org/handbook/current/chapter-25; for single arm studies the JBI checklist for prevalence studies is used[5].**

ł Although the study design was comparative, the eligible safety outcome data was only reported for the TNR4 group. For this reason, the JBI checklist for prevalence studies was applied.

Abbreviations: n=number; yrs=years; RoB=risk of biasAE=adverse event; SAE=serious adverse events;.

Table 4-2 Ongoing platform RCTs involving Aspirin

Trial Identifier/registry ID(s)/contact	**NCT04381936 / EudraCT2020-001113-21-GB / ISRCTN50189673** **RECOVERY** **Contact: Contact: Richard Haynes; +44 (0)1865 743743; recoverytrial@ndph.ox.ac.uk**	**NCT04498273** **ACTIV4-Outpatient** **Contact: Jean Connors(617) 732-5190; jconnors@bwh.harvard.edu**	**NCT02735707 / EudraCT: 2015-002340-14-IT** **REMAP—COVID** **Contact: Cameron Green; info@remapcap.org**
Study design, study phase	Phase 2/3 RCT, multicentre open label adaptive platform trial with factorial assignment	Phase 3 RCT, multicentre quadruple blinded adaptive platform trial with parallel assignment Pharmacological and standard of care comparators Masing: Participant, Care Provider, Investigator, Outcomes Assessor	Phase 4 Randomized, Embedded, Multifactorial Adaptive Platform Trial Masking: none
Recruitment status	Recruiting (last update at trial registry on 2 March 2021)	Recruiting (last update at trial registry on 26 Feb. 2021)	Recruiting (last update at trial registry at 12 Oct. 2020)
Number of Patients, Disease severity*	40’000 Disease severity: not specified	7’000 Mild-Moderate	N=7100 in main trial, N=unclear in COVID-19 sub-platform Severe to critical
Setting (hospital, ambulatory,..)	Hospital	Outpatient	Hospital, ICU
Intervention (generic drug name and dosage)**	• Lopinavir-Ritonavir • Corticosteroid • Hydroxychloroquine • Azithromycin • Biological: Convalescent plasma • Tocilizumab • Biological: Immunoglobulin • Synthetic neutralising antibodies • **Aspirin**: 150 mg by mouth (or nasogastric tube) or per rectum once daily until discharge, for adults ≥18 years old. • Colchicine • Baricitinib • Anakinra • dimethyl fumarate (UK adults only; early phase assessment)	Apixaban 2.5 MG Apixaban 5MG • Aspirin: low dose aspirin 81mg oral, twice daily for 45 days	• Aspirin administered at either 75mg or 100mg once per day for 14 days or until hospital discharge, whichever occurs first Other active trial arms • Fixed-duration Hydrocortisone • Shock-dependent hydrocortisone • Ceftriaxone • Moxifloxacin or Levofloxacin • Piperacillin-tazobactam • Ceftaroline • Amoxicillin-clavulanate • Macrolide administered for 3-5 days • Macrolide administered for up to 14 days • Five-days oseltamivir • Ten-days oseltamivir • Lopinavir/ritonavir • Hydroxychloroquine

Trial Identifier/registry ID(s)/contact	**NCT04381936 / EudraCT2020-001113-21-GB / ISRCTN50189673 RECOVERY Contact: Contact: Richard Haynes; +44 (0)1865 743743; recoverytrial@ndph.ox.ac.uk**	**NCT04498273 ACTIV4-Outpatient Contact: Jean Connors(617) 732-5190; jconnors@bwh.harvard.edu**	**NCT02735707 / EudraCT: 2015-002340-14-IT REMAP—COVID Contact: Cameron Green; info@remapcap.org**
			• Hydroxychloroquine + lopinavir/ritonavir • Interferon-β1a • Anakinra • Fixed-duration higher dose Hydrocortisone • Tocilizumab • Sarilumab • Vitamin C • Therapeutic anticoagulation • Simvastatin • Biological: Convalescent plasma • Other: Protocolised mechanical ventilation strategy • Eritoran • Apremilast • Clopidogrel, Prasugrel or Ticagrelor
Comparator (standard care or generic drug name and dosage)	Standard care: usual hospital care	• Placebo	• No intervention: patients will not receive any antiplatelet agent or NSAID for 14 days while patient remains in hospital • Active comparator: P2Y12 inhibitor, patients will receive either clopidogrel, prasugrel, or ticagrelor (as per site preference).
Primary Outcome(s)	All-cause mortality [Time Frame: Within 28 days after randomisation]	Composite endpoint of need for hospitalization for cardiovascular/pulmonary events, symptomatic deep venous thrombosis, pulmonary embolism, arterial thromboembolism, myocardial infarction, ischemic stroke, and all-cause mortality for up to 45 days after initiation of assigned treatment.	• All-cause mortality [Time Frame: Day 90] Days alive and not receiving organ support in ICU [Time Frame: Day 21]
Sponsor/ lead institution, country	University of Oxford, UK	University of Pittsburgh, USA	MJM Bonten, , UMC Utrecht, the Netherlands

Trial Identifier/registry ID(s)/contact	**NCT04381936 / EudraCT2020-001113-21-GB / ISRCTN50189673** **RECOVERY** **Contact: Contact: Richard Haynes; +44 (0)1865 743743; recoverytrial@ndph.ox.ac.uk**	**NCT04498273** **ACTIV4-Outpatient** **Contact: Jean Connors(617) 732-5190; jconnors@bwh.harvard.edu**	**NCT02735707 / EudraCT: 2015-002340-14-IT** **REMAP—COVID** **Contact: Cameron Green; info@remapcap.org**
(also country of recruitment if different)	Recruitment in Indonesia, Nepal, United Kingdom		Recruitment in USA, Australia, Belgium, Canada, Croatia, Germany, Hungary, Ireland, the Netherlands; New Zealand, Portugal, Romania, Spain, United Kingdom

*Mixed COVID-19, Mild, Moderate, Severe, Critical COVID-19
** Description on dose and route of administration for interventions other than aspirin are found on the trial registration site.
Abbreviations: see list of abbreviation on page 5.

Table 4-3 Ongoing platform RCTs involving Aspirin, continued

Trial Identifier/registry ID(s)/contact	**NCT04483960 / ACTRN12620000445976** **ASCOT-ADAPT** **Contact: Naomi Perry ;+61 3 83442647; naomi.perry@unimelb.edu.au**	**EudraCT: 2020-005963-29-DK (new)** **ASCOT-ADAPT (in Denmark)** **Contact: Charlotte Kastberg Levin; +4530477341; charlotte.kastberg.levin.01@regionh.dk**
Study design, study phase	Phase 3 RCT, multicentre open label adaptive platform trial with factorial assignment Pharmacological and standard of care comparators.	Phase 3 RCT. Current: Randomised single center national multistage adaptive platform Trial with 3 arms. Planned: center involvement of Ausralia, India a d New Zealand
Recruitment status	Recruiting (last update at trial registry on 25 Jan. 2021)	Ongoing (trial registry assessed at 20 April 2021)
Number of Patients, Disease severity*	2'400 Non critical	N=20 in Denmark N=2400 overall Not described, but non-critical
Setting (hospital, ambulatory,..)	Hospital	Acute Care Hospital
Intervention (generic drug name and dosage)**	• Nafamostat Mesilate • Biological: Convalescent plasma • Enoxaparin • Dalteparin • Tinzaparin • Aspirin: In addition to standard dose thromboprophylaxis, patients randomised to this arm will also receive 100mg aspirin daily.	• Standard dose thromboprophylaxis + Aspirin. Standard dose thromboprophylaxis not described but involving Tinzeparin, Enoxaparin, Dalteparin. In the platform trial, the addition of Acetylsalicylic Acid is described as comparator.
Comparator (standard care or generic drug name and dosage)	• Anticoagulation - standard dose thromboprophylaxis: low molecular weight heparin, choice of agent according to availability and local practice at the participating site.	• Standard dose thromboprophylaxis • Intermediate dose thromboprophylaxis

Trial Identifier/registry ID(s)/contact	**NCT04483960 / ACTRN12620000445976** **ASCOT-ADAPT** **Contact: Naomi Perry ;+61 3 83442647; naomi.perry@unimelb.edu.au**	**EudraCT: 2020-005963-29-DK (new)** **ASCOT-ADAPT (in Denmark)** **Contact: Charlotte Kastberg Levin; +4530477341; charlotte.kastberg.levin.01@regionh.dk**
	• Other pharmacological interventions and standard of care as listed above	
Primary Outcome(s)	• Proportion of participants alive and not having required new intensive respiratory support (invasive or non-invasive ventilation) or vasopressors/inotropic support [Time Frame: 28 days]	• The primary endpoint for this trial is death from any cause or requirement of new intensive respiratory support (invasive or non-invasive ventilation) or vasopressor/inotropic support in the 28 days after randomisation.
Sponsor/ lead institution, country (also country of recruitment if different)	University of Melbourne/ The Peter Doherty Institute for Infection and Immunity; Australasian Society for Infectious Diseases	University of Melbourne, Australia, recruitment in Denmark. Planned future recruitment in Australia, India and New Zealand

*Mixed COVID-19, Mild, Moderate, Severe, Critical COVID-19
** Description on dose and route of administration for interventions other than aspirin are found on the trial registration site.
Abbreviations: see list of abbreviation on page 5.

Table 4-4 Ongoing trials of single agent: Aspirin

Trial Identifier/registry ID(s)/contact	**CTRI/2020/07/026791[15]** **RESIST** **Deepti Siddharthan; 9968774019; deeptikailath@gmail.com**	**NCT04365309** **PEAC** **Contact: Cai Yue; the first affiliated hospital of the Air force medical university**	**NCT04324463** **ACT COVID-19** **Contact: ACT COVID-19 Study Coordinator; 905-297-3479; ACT.ProjectTeam@PHRI.ca**
Study design, study phase	Phase 2/3 RCT. Single center 4-arm open label trial with parallel group assignment Randomisation: computer-generated permuted block randomization with mixed block size Concealment: Sequentially numbered, sealed, opaque envelopes	Phase 2-3 Randomized controlled trial with parallel group assignment Masking: none	Two parallel randomised controlled trials Outpatient trial: 2x2 factorial design Inpatient trial: 2x2x2 factorial design Masking: none
Recruitment status	Open to recruitment (last update at trial registry at 11 Oct. 2020)	Enrolling by invitation (last update at trial registry at 28 April 2020)	Recruiting (last update at trial registry at 8 Oct. 2020)
Number of Patients, Disease severity*	N=800 Non-critical	N=128 Moderate to severe COVID-19	N= 4000 overall Outpatient study: symptomatic severity not described, symptomatic with COVID-19 in the community who are at high risk of disease progression

Trial Identifier/registry ID(s)/contact	**CTRI/2020/07/026791[15]** **RESIST** **Deepti Siddharthan; 9968774019; deeptikailath@gmail.com**	**NCT04365309** **PEAC** **Contact: Cai Yue; the first affiliated hospital of the Air force medical university**	**NCT04324463** **ACT COVID-19** **Contact: ACT COVID-19 Study Coordinator; 905-297-3479; ACT.ProjectTeam@PHRI.ca**
			Inpatient study: severity not described, symptomatic with COVID-19
Setting (hospital, ambulatory,..)	Hospital	Hospital	Hospital and Outpatients
Intervention (generic drug name and dosage)	• Aspirin with standard of care: Aspirin tablet 75mg once daily for ten days or till discharge whichever is later. • Atorvastatin (Statin) with standard of care: Atorvastatin 40mg tablet once daily for ten days or till discharge whichever is later • Aspirin + atorvastatin with standad of care	Aspirin administered orally with 100 mg per day on top of standard of care for COVID-19 at admission until 14 days after discharge	Outpatient study: • Trial arm Colchicine: 0.5 or 0.6 mg twice daily for 3 days, then o.5 or 0.6 mg once daily for 25 days (total 28 days). • Trial arm ASA: 75 to 100 mg once daily for 28 days. For inpatients: • Trial arm Interferon-β: 0.25 mg by subcutaneous injection on days 1, 3, 5 & 7 • Trial arm Colchicine: 1 or 1.2 mg followed by 0.5 or 0.6 mg 2 hours later, then 0.5 or 0.6 mg twice daily for 28 days. • Trial am combination of ASA and rivaroxaban: ASA 75 to 100 mg once daily for 28 days; 2.5 mg twice daily for 28 days.
Comparator (standard care or generic drug name and dosage)	Standard of care: conventional therapy for COVID-19 infected patients	Standard of care without aspirin	No Intervention: Usual Care (Control) Outpatients and Inpatients: No constraints for treating physicians on the therapies within the standard of care arm. All key co-interventions will be documented.
Primary Outcome(s)	• Clinical deterioration characterised by progression to WHO clinical improvement ordinal score more than or equal to 6 (i.e., endotracheal intubation, non-invasive mechanical ventilation, pressor agents, RRT, ECMO, and mortality). Time frame: 10	• clinical recovery time (TTCR) defined as the study treatment (oral aspirin enteric-coated tablet) began to fever, breathing rate, blood oxygen saturation recovery, and cough relieving for at least 72 hours. [Time Frame: not more than 14 days]	Outpatient trial Colchicine vs. control & ASA vs. control • composite of hospitalization or death. [Time Frame: 45 days post randomization] Inpatient trial

Trial Identifier/registry ID(s)/contact	CTRI/2020/07/026791[15] RESIST Deepti Siddharthan; 9968774019; deeptikailath@gmail.com	NCT04365309 PEAC Contact: Cai Yue; the first affiliated hospital of the Air force medical university	NCT04324463 ACT COVID-19 Contact: ACT COVID-19 Study Coordinator; 905-297-3479; ACT.ProjectTeam@PHRI.ca
	days or until discharge whichever is longer	• the time of SARS-CoV2 overcasting defined as Time of SARS-CoV2 in upper respiratory tract specimens overcasting detected by RT-PCR. [Time Frame: not more than 37 days]	Interferon-β vs. control & Colchicine vs. control & ASA and rivaroxaban vs. control • composite of invasive mechanical ventilation or death. [Time Frame: 45 days post randomization]
Sponsor/ lead institution, country (also country of recruitment if different)	All India Institute of Medical Sciences (AIIMS), New Delhi, India	Xijing Hospital, China	Sponsor: Population Health Research Institute, Canada Collaborator: Bayer Countries of recruitment: Brazil, Canada, Chile, Colombia, Ecuador, Egypt, India, Pakistan, Philippines, Russian Federation, Saudi Arabia, United Arab Emirates

*Mixed COVID-19, Mild, Moderate, Severe, Critical COVID-19; **The duration and dose of empiric antibiotics will be determined by the treating clinician and local guidelines or practice.
Abbreviations: see list of abbreviation on page 5. REMAP-COVID=sub-platform of REMAP-CAP evaluating treatments specific for COVID-19; REMAP-CAP=Randomized, Embedded, Multifactorial Adaptive Platform Trial for Community- Acquired Pneumonia

Table 4-5 Ongoing trials of single agent: Aspirin, continued

Trial Identifier/registry ID(s)/contact	NCT04703608 / PACTR202101544570971 PaTS-COVID Contact: Gibbi Sey; +220 4495442 ext 2204; gsey@mrc.gm	NCT04333407 C-19-ACS Contact: Alena Marynina; 07776 224520; alena.marynina@nhs.net	CTRI/2020/08/027503 Contact: Souvik Maitra; souvikmaitra@live.com
Study design, study phase	RCT. Multicenter single blinded trial with parallel group assignment Permuted block randomization; central allocation; masking: participant, blinding with non-identical placebo	Multicenter RCT with parallel group assignment Masking: none	RCT. Two-arm single center pilot trial with parallel group assignment Stratified block randomization Concealment: sequentially numbered, sealed, opaque envelopes Masking: outcome assessor
Recruitment status	Recruiting (last update at trial registry 18 Feb. 2021)	Recruiting (last update at trial registry 9 April 2020)	Not yet recruiting (last update at trial registry 31 Aug. 2020)
Number of Patients, Disease severity*	Unclear, 1'200 for both cohorts defined by mild/moderate versus severe COVID-19**	N= 3170 Not reported	N=60; moderate to severe

	Severe		
Setting (hospital, ambulatory,..)	Hospital	Hospital	Hospital
Intervention (generic drug name and dosage)**	Aspirin: 150 mg daily for 28 days or until hospital discharge (whichever is sooner)	• Aspirin 75mg once daily unless contraindicated • Clopidogrel 75mg, once daily unless contraindicated • Rivaroxaban 2.5 mg twice daily unless contraindicated. If patient on DOAC then change to rivaroxaban 2.5mg unless contraindicated • Atorvastatin 40mg once daily unless contraindicated • Omeprazole, if patient not on a proton pump inhibitor, add omeprazole 20mg once daily	Aspirin: Low dose aspirin (75 mg OD) for 10 days along with standard of care
Comparator (standard care or generic drug name and dosage)	Non identical placebo; doses as per above	• No intervention (supportive care)	Standard of care: standard practice of the institute at that time
Primary Outcome(s)	• Cohort 1 index case: Percentage of patients with COVID-19 associated mild disease/moderate pneumonia progressing to severe pneumonia [Time frame 14 days] • Cohort 1, Household contacts: Percentage of HH members that get infected with SARS-CoV-2 [Time frame 14 days] • Cohort 2: Percentage of COVID-19 associated severe pneumonia patients worsening their condition [Time frame at discharge or day 28]	All-cause mortality at 30 days after admission	SpO2/ FiO2 ratio in day 1- 7 post randomization
Sponsor/ lead institution, country (also country of recruitment if different)	London School of Hygiene and Tropical Medicine, Great Britain; Recruitment in Gambia	Imperial College London, UK	All India Institute of Medical Sciences, New Delhi, India

*Mixed COVID-19, Mild, Moderate, Severe, Critical COVID-19
** RCT with two cohorts, descriptions only apply to cohort 2, cohort 1 is described in EUNETHTA RCR 22 on Ivermectin[16].
Abbreviations: see list of abbreviation on page 5.

Table 4-6 Ongoing trials of single agent: Aspirin, continued

Trial Identifier/registry ID(s)/contact	**IRCT20180205038626N7 zahra ahmadnia; gums.icrc@gmail.com**	**PACTR202006473370201 CRASH-19 Ian Roberts; crash19@lshtm.ac.uk**	**NCT04554433 Ragab; +201099323347; Dr.ezz2712@gmail.com**
Study design, study phase	RCT. Single center two-arm trial with parallel group assignment Permutation block randomisation (block size 6); Concealment: sealed envelopes; Masking: outcome assessor	RCT. Multinational open label trial with factorial group assignment Permuted block randomisation Concealment: central randomisation by phone/fax	RCT. Open label trial with parallel group assignment
Recruitment status	Recruitment complete (last update at trial registry 4 April. 2021)	Not yet recruiting (last update at trial registry 17 June 2020)	Not yet recruiting (last update at trial registry 28 October 2020)
Number of Patients, Disease severity*	N=36; non-critical	N=10'000, non-critical	N=80, COVID-19 with mild to severe ARDS
Setting (hospital, ambulatory,..)	Hospital	Hospital	Hospital
Intervention (generic drug name and dosage)**	Aspirin 80 mg for three months.	• Aspirin: 150mg once daily, up to 28 days (n=1250) • Losartan: 100mg once daily, up to 28 days (n=1250) • Simvastatin: 80mg once daily, up to 28 days (n=1250) • Aspirin & Losartan, up to 28 days (n=1250) • Aspirin and Simvastatin, up to 28 days (n=1250) • Losartan and Simvastatin, up to 28 days (n=1250) • Aspirin & Losartan & Simvastatin, up to 28 days (n=1250)	combination of Asprin in anti - inflammatory dose and controlled ethanol vapor inhalation in concentrations and technique according to their medical condition
Comparator (standard care or generic drug name and dosage)	Standard treatment for three months, not further described	• Usual standard of care at the study hospital, up to 28 days (n=1250)	standard protocol
Primary Outcome(s)	Thromboembolic events at the beginning of the study and 3 and 6 months later	In-hospital death up to 28 days	Disinfection of COVID-19 in human respiratory tract. [Time Frame: Negative PCR test within 7 days from starting the protocol]
Sponsor/ lead institution, country (also country of recruitment if different)	Rasht University of Medical Sciences, Rasht, Iran	London School of Hygiene and Tropical Medicine, UK Recruitment in Nigeria and Pakistan	Ragab, Resident of anesthesia and surgical ICU, Mansoura University, Egypt

*Mixed COVID-19, Mild, Moderate, Severe, Critical COVID-19
Abbreviations: see list of abbreviation on page 5.

Table 4-7 Ongoing trials of single agent: Aspirin, continued

Trial Identifier/registry ID(s)/contact	**ClinicalTrials.gov Identifier: NCT04808895 / Eudract ID 2020-006130-12-IT (new)** **ASPERUM** **Pietro Minuz;+39 045-8124414; pietro.minuz@univr.it**	
Study design, study phase	Phase 3 RCT: multicentre national two arm double blind placebo controlled trial with parallel group assignment Masking: Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor)	
Recruitment status	Not yet recruiting (last update at trial registry at 22 March 2021)	
Number of Patients, Disease severity*	N=204 Moderate COVID-19 with pneumonia	
Setting (hospital, ambulatory,..)	hospital	
Intervention (generic drug name and dosage)**	Aspiring: tablets of 100 mg acetylsalicylic acid. Loading dose of 300 mg on day 1 followed by 100mg once daily on day 2 to 15	
Comparator (standard care or generic drug name and dosage)	Placebo: tablets of placebo, identical to active comparator (one tablet daily dose. On the first day 3 tablets will be administered)	
Primary Outcome(s)	Occurrence of the first of the following events: • Prevention of clinical worsening, defined as transfer to ICU [Time Frame: day 15] • Prevention of lung function worsening, defined as PaO2/FiO2 lower than 150 mm Hg [Time Frame: day 15] • Prevention of death, defined as death of any cause [Time Frame: day 15]	
Sponsor/ lead institution, country (also country of recruitment if different)	Azienda Ospedaliera Universitaria Integrata Verona, Italy	

*Mixed COVID-19, Mild, Moderate, Severe, Critical COVID-19
Abbreviations: see list of abbreviation on page 5.

Table 4-8 Ongoing trials of combination therapies including Aspirin

Trial Identifier/registry ID(s)/contact	**NCT04410328** **ATTAC-19** **Amit Singla; 3195123558;** **as3321@njms.rutgers.edu**	**CTRI/2020/09/028088** **CAM-Covid-19** **Vivek Chauhan;** **drvivekshimla@yahoo.com**	**NCT04768179** **IVCOM** **Jackson Mukonzo; 256758113468;** **mukojack@yahoo.co.uk**
Study design, study phase	RCT. Single center open label two arm pilot trial with parallel group assignment	RCT. Single center open label two arm pilot trial with parallel group assignment Computer generated randomization Concealment: central randomisation	RCT. Single center open label three arm pilot trial with parallel group assignment
Recruitment status	Recruiting (last update at trial registry 23 Oct. 2020)	Not yet recruiting (last update at trial registry 25 Sept. 2020)	Not yet recruiting (last update at trial registry 24 Feb. 2021)
Number of Patients, Disease severity*	N=132 Not reported	N=34 Severe	N=490 moderate
Setting (hospital, ambulatory,..)	Hospital	Hospital	Hospital
Intervention (generic drug name and dosage)	Dipyridamole and Aspirin (Aggrenox): • Dipyridamole ER 200mg/ Aspirin 25mg orally/enterally 2 times daily plus standard care starting on the day of enrollment for a total of 2 weeks.	Colchicine, Aspirin and Montelukast: • Colchicine - 0.6 mg per oral, 12 hourly till discharge Aspirin - 325 mg per oral 6 hourly till discharge Montelukast - 10 mg per oral once a day till discharge	low dose aspirin and ivermectin combination therapy • Trial arm: 3-day ivermectin (IVM) 200 mcg/kg/day plus 14-day of 75mg ASA/day + standard of care (intervention 1) • Trial arm: 3-day IVM 600 mcg/kg/day plus 14-day of 75mg ASA/day + standard of care (Intervention 2)
Comparator (standard care or generic drug name and dosage)	Standard of care: standard care starting on the day of enrolment for a total of 2 weeks.	Standard of care	Standard of care
Primary Outcome(s)	Covid Ordinal Scale: Change in composite COVID ordinal scale at day 15. Ordinal scale Ranging from 1) not hospitalized with resumption of normal activities to 8) death. [Time Frame: 15 days]	Change in the marker of Adult Multi-system Inflammatory Syndrome i.e. C-reactive Protein up to 4 months	• SARS COV 2 Viral clearance [Time Frame: Day 14] • World Health Organization COVID-19 ordinal improvement score [Time Frame: Day 14]. Minimum score is 0 (un infected, no clinical or virological evidence of infection) Maximum sore is 8 (death) Higher scores mean a worse outcome, low scores mean a better outcome
Sponsor/ lead institution, country (also country of recruitment if different)	Rutgers, The State University of New Jersey, USA	Indira Gandhi Medical College, Shimla, India	Makerere University, Uganda

*Mixed COVID-19, Mild, Moderate, Severe, Critical COVID-19;
Abbreviations: see list of abbreviation on page 5

Table 4-9 Ongoing observational studies evaluating the effect of aspirin

Trial Identifier/registry ID(s)/contact	**NCT04466670**
Study design, study phase	Phase 3 Non-randomised controlled study with adaptive design and parallel group assignment¨ Masking: none
Recruitment status	Recruiting (last update at trial registry at 10 July 2020)
Number of Patients, Disease severity*	N=310 Not described
Setting (hospital, ambulatory,..)	Hospital
Intervention (generic drug name and dosage)	• Trial arm Unfractionated heparin • Trial arm acetylsalicylic acid: Aspirin (ASA) 100 mg daily PO during at least 5 days • Trial arm Enoxaparin In all intervention arms: AND arterial oxygen saturation greater than or equal to 92% or PaO2 to FiO2 ratio greater than 200 for 2 consecutive days associated to thromboprophylaxis institutional protocol
Comparator (standard care or generic drug name and dosage)	Standard of care
Primary Outcome(s)	Hospital discharge - alive / death: number of COVID-19 positive patients who are alive within 30 days of symptoms onset
Sponsor/ lead institution, country (also country of recruitment if different)	University of Sao Paulo General Hospital, Brazil

*Mixed COVID-19, Mild, Moderate, Severe, Critical COVID-19
Abbreviations: see list of abbreviation on page 5.

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6 APPENDIX

6.1 Search strategy to identify randomised controlled trials

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

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

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

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

Table 6-1 Search strategy to identify randomised controlled studies

Database	URL	Search line / Search terms	Date of search
Pubmed	pubmed.ncbi.nlm.nih.gov	1. (((((((("Coronavirus"[Mesh]) OR (coronavirus*[Title/Abstract] OR coronovirus*[Title/Abstract] OR coronavirinae*[Title/Abstract] OR Coronavirus*[Title/Abstract] OR Coronovirus*[Title/Abstract] OR Wuhan*[Title/Abstract] OR Hubei*[Title/Abstract] OR Huanan[Title/Abstract] OR "2019-nCoV"[Title/Abstract] OR 2019nCoV[Title/Abstract] OR nCoV2019[Title/Abstract] OR "nCoV-2019"[Title/Abstract] OR "COVID-19"[Title/Abstract] OR COVID19[Title/Abstract] OR "CORVID-19"[Title/Abstract] OR CORVID19[Title/Abstract] OR "WN-CoV"[Title/Abstract] OR WNCoV[Title/Abstract] OR "HCoV-19"[Title/Abstract] OR HCoV19[Title/Abstract] OR CoV[Title/Abstract] OR "2019 novel*"[Title/Abstract] OR Ncov[Title/Abstract] OR "n-cov"[Title/Abstract] OR "SARS-CoV-2"[Title/Abstract] OR "SARSCoV-2"[Title/Abstract] OR "SARSCoV2"[Title/Abstract] OR "SARS-CoV2"[Title/Abstract] OR SARSCov19[Title/Abstract] OR "SARS-Cov19"[Title/Abstract] OR "SARSCov-19"[Title/Abstract] OR "SARS-Cov-19"[Title/Abstract] OR Ncovor[Title/Abstract] OR Ncorona*[Title/Abstract] OR Ncorono*[Title/Abstract] OR NcovWuhan*[Title/Abstract] OR NcovHubei*[Title/Abstract] OR NcovChina*[Title/Abstract] OR NcovChinese*[Title/Abstract])) OR ((((respiratory*[Title/Abstract] AND (symptom*[Title/Abstract] OR disease*[Title/Abstract] OR illness*[Title/Abstract] OR condition*))[Title/Abstract] OR "seafood market*"[Title/Abstract] OR "food market*")[Title/Abstract] AND (Wuhan*[Title/Abstract] OR Hubei*[Title/Abstract] OR China*[Title/Abstract] OR Chinese*[Title/Abstract] OR Huanan*))[Title/Abstract])) OR ("severe acute respiratory syndrome*")) OR ((corona*[Title/Abstract] OR corono*)[Title/Abstract] AND (virus*[Title/Abstract] OR viral*[Title/Abstract] OR virinae*)[Title/Abstract])) AND (((((((randomized controlled trial [pt]) OR (controlled clinical trial [pt])) OR (randomized [tiab])) OR (placebo [tiab])) OR (clinical trials as topic [mesh: noexp])) OR (randomly [tiab])) OR (trial [ti]))) NOT (animals [mh] NOT humans [mh]) AND (2019/10/01:2020[dp])	31/03/2021 3.582 records

Database	URL	Search line / Search terms	Date of search
Ovid MEDLINE(R) ALL)	ovidsp.dc2.ovid.com	1. exp coronavirus/ 2. ((corona* or corono*) adj1 (virus* or viral* or virinae*)).ti,ab,kw. 3. (coronavirus* or coronovirus* or coronavirinae* or Coronavirus* or Coronovirus* or Wuhan* or Hubei* or Huanan or "2019-nCoV" or 2019nCoV or nCoV2019 or "nCoV-2019" or "COVID-19" or COVID19 or "CORVID-19" or CORVID19 or "WN-CoV" or WNCoV or "HCoV-19" or HCoV19 or CoV or "2019 novel*" or Ncov or "n-cov" or "SARS-CoV-2" or "SARSCoV-2" or "SARSCoV2" or "SARS-CoV2" or SARSCov19 or "SARS-Cov19" or "SARSCov-19" or "SARS-Cov-19" or Ncovor or Ncorona* or Ncorono* or NcovWuhan* or NcovHubei* or NcovChina* or NcovChinese*).ti,ab,kw. 4. (((respiratory* adj2 (symptom* or disease* or illness* or condition*)) or "seafood market*" or "food market*") adj10 (Wuhan* or Hubei* or China* or Chinese* or Huanan*)).ti,ab,kw. 5. ((outbreak* or wildlife* or pandemic* or epidemic*) adj1 (China* or Chinese* or Huanan*)).ti,ab,kw. 6. "severe acute respiratory syndrome*".ti,ab,kw. 7. or/1-6 8. randomized controlled trial.pt. 9. controlled clinical trial.pt. 10. random*.ab. 11. placebo.ab. 12. clinical trials as topic.sh. 13. random allocation.sh. 14. trial.ti. 15. or/8-14 16. exp animals/ not humans.sh. 17. 15 not 16 18. 7 and 17 19. limit 18 to yr="2019 -Current"	31/03/2021 3.666 records
OVID EMBASE	ovidsp.dc2.ovid.com	1. exp Coronavirinae/ or exp Coronavirus/ 2. exp Coronavirus infection/ 3. ((("Corona virinae" or "corona virus" or Coronavirinae or coronavirus or COVID or nCoV) adj4 ("19" or "2019" or novel or new)) or (("Corona virinae" or "corona virus" or Coronavirinae or coronavirus or COVID or nCoV) and (wuhan or china or chinese)) or "Corona virinae19" or "Corona virinae2019" or "corona virus19" or "corona virus2019" or Coronavirinae19 or Coronavirinae2019 or coronavirus19 or coronavirus2019 or COVID19 or COVID2019 or nCOV19 or nCOV2019 or "SARS Corona virus 2" or "SARS Coronavirus 2" or "SARS-COV-2" or "Severe Acute Respiratory Syndrome Corona virus 2" or "Severe Acute Respiratory Syndrome Coronavirus 2").ti,ab,kw. 4. or/1-3 5. Clinical-Trial/ or Randomized-Controlled-Trial/ or Randomization/ or Single-Blind-Procedure/ or Double-Blind-Procedure/ or Crossover-Procedure/ or Prospective-Study/ or Placebo/ 6. (((clinical or control or controlled) adj (study or trial)) or ((single or double or triple) adj (blind$3 or mask$3)) or (random$ adj (assign$ or allocat$ or group or grouped or patients or study or trial or distribut$)) or (crossover adj (design or study or trial)) or placebo or placebos).ti,ab. 7. 5 or 6 8. 4 and 7 9. limit 8 to yr="2019 -Current"	31/03/2021 4.582 records

6.2 Search strategy to identify observational studies

As of October 2020, NIPHNO is responsible for setting up the search strategy to identify observational studies.

From September to December 2020, we received records that EPPI Centre has screened after searching weekly in Medline and Embase (until beginning of November 2020), from November onwards Microsoft Academics Graph (MAG). We supplemented these studies with a weekly search in Scopus (Elsevier). Detailed descriptions of the EPPI and NIPHNO searches are given at their websites [17, 18]. The retrieved hits were imported to a reference management tool, Endnote (Clarivate Analytics), for deduplication. We then searched the EndNote database using the generic names and synonyms for the included COVID-19 drugs.

From January onwards, an information specialist at NIPHNO has conducted searches in Medline (Ovid), Embase (Ovid) and Scopus (Elsevier) using the search strategy described in Table 6-2. To screen the references, two reviewers use a binary machine learning (ML) classifier. References that scored above the identified threshold of 30% certainty to be relevant were retained for screening; while those scoring below this threshold score were set aside.

Prior to using the binary ML classifier score to discard low scoring records, we screened 1028 references manually to train the classifier. The classifier is continuously being updated a long with new references being screened. References that have been set aside, can potentially be picked up in a later stage by a new classifier version. For drugs that have less than 5 publications included in the training batch, we combine the classifier with manual text word searches.

As a supplement we used Microsoft Academics Graph (MAG) to identify further relevant research. We used articles previously included in the EUnetHTA rolling collaborative review until last search and ran the Bring up-to-date function in EPPI Reviewer. Bring up-to-date uses the neural networks of MAG to identify publications similar to input articles, added to the MAG database.

Table 6-2 Search strategy to identify observational studies

Database	URL	Search terms / Search modality	Date of search
Embase 1974 to 2021 Ovid MEDLINE(R) ALL 1946 to 2021		Lines 1 and 2 are copies of Ovid's Expert searches for covid-19 in MEDLINE and Embase 1 ((((pneumonia or covid* or coronavirus* or corona virus* or ncov* or 2019-ncov or sars*).mp. or exp pneumonia/) and Wuhan.mp.) or (2019-ncov or ncov19 or ncov-19 or 2019-novel CoV or sars-cov2 or sars-cov-2 or sarscov2 or sarscov-2 or Sars-coronavirus2 or Sars-coronavirus-2 or SARS-like coronavirus* or coronavirus-19 or covid19 or covid-19 or covid 2019 or ((novel or new or nouveau) adj2 (CoV or nCoV or covid or coronavirus* or corona virus or pandemi*2)) or ((covid or covid19 or covid-19) and pandemic*2) or (coronavirus* and pneumonia)).mp. or COVID-19.rx,px,ox,sh. or severe acute respiratory syndrome coronavirus 2.os.) use medall [COVID-19 in MEDLINE] 2 ((((pneumonia or covid* or coronavirus* or corona virus* or ncov* or 2019-ncov or sars*).mp. or exp pneumonia/) and Wuhan.mp.) or (coronavirus disease 2019 or 2019-ncov or ncov19 or ncov-19 or 2019-novel CoV or severe acute respiratory syndrome coronavirus 2 or sars-cov2 or sars-cov-2 or sarscov2 or sarscov-2 or Sars-coronavirus2 or	From 26/2/2021 until 05/04/2021 1759 records

		Sars-coronavirus-2 or SARS-like coronavirus* or coronavirus-19 or covid19 or covid-19 or covid 2019 or ((novel or new or nouveau) adj2 (CoV or nCoV or covid or coronavirus* or corona virus or pandemi*2)) or ((covid or covid19 or covid-19) and pandemic*2) or (coronavirus* and pneumonia)).mp. or (coronavirus disease 2019 or severe acute respiratory syndrome coronavirus 2).sh,dj.) use oemezd [COVID-19 in Embase] 3 (COVID-19 serotherapy/ or Immunization, Passive/ or tocilizumab/ or camostat/ or nafamostat/ or AP301 peptide/ or Interleukin 1 Receptor Antagonist Protein/ or alunacedase alfa/ or darunavir/ or favipiravir/ or sarilumab/ or exp Interferons/ or gimsilumab/ or canakinumab/ or REGN-COV-2/ or bamlanivimab/ or baricitinib/ or molnupiravir/ or Aspirin/ or mavrilimumab/ or exp Vitamin D/dt or Vitamin D Deficiency/dt or Ivermectin/) use medall [MeSH-terms for drugs in MEDLINE] 4 (Hyperimmune globulin/dt or tocilizumab/ or camostat/ or camostat mesilate/ or nafamstat/ or solnatide/ or anakinra/ or darunavir/ or favipiravir/ or sarilumab/ or exp Interferon/ or gimsilumab/ or canakinumab/ or baricitinib/ or acetylsalicylic acid/ or mavrilimumab/ or exp Vitamin D/dt or Vitamin D Deficiency/dt or ivermectin/) use oemezd [Emtree-terms for drugs in Embase] 5 ((convalescent adj (plasma or sera or serum)) or serotherap* or ((atoxin or hyperimmunoglobulin or hyperimmune globulin or hyperimmune gammaglobulin) adj therap*) or passive immuni?ation or (tocilizumab or atlizumab or (MRA adj monoclonal antibod*) or MSB-11456 or MSB11456 or R-1569 or R1569 or RO-4788533 or RO4788533 or Actemra or Roactemra) or (camostat* or FOY-305 or FOY305 or FOY S 980) or (nafamostat or nafamstat or FUT-175 or FUT175) or (solnatide or AP301 or AP-301 or (TIP adj peptide)) or (anakinra or ((interleukin 1 or IL1 or IL-1) adj2 (antagonist or block* or inhibitor*)) or IL-1Ra or Kineret) or (alunacedase or APN01 or APN-01 or rhACE2 or recombinant human angiotensin converting enzyme 2 or GSK-2586881 or GSK2586881) or (darunavir or prezista or TMC-114 or TMC114 or UIC-94017 or UIC94017) or (favipi?avir or T-705 or T705 or Avigan or Olumiant) or (sarilumab or REGN-88 or REGN88 or SAR-153191 or SAR153191 or Kevzara) or (interferon* or (IFN adj1 (alpha* or beta* or gamma*)) or novaferon or CL-884 or CL884) or (gimsilumab or KIN-1901 or KIN1901 or morab-022 or morab022) or (canakinumab or ACZ-885 or ACZ885 or immunoglobulin G1 or Ilaris) or (REGN-CoV-2 or REGN-CoV2 or antibody cocktail or ((casirivimab or REGN-10933 or REGN10933) and (imdevimab or REGN-10987 or REGN10987))) or (bamlanivimab or LY-CoV555 or LYCoV555 or LY-3819253 or LY3819253) or (baricitinib or LY-3009104 or LY3009104 or INCB-028050 or INCB028050 or INCB-28050 or INCB28050 or Olumiant) or (molnupiravir or MK-4482 or MK4482 or EIDD-2801 or EIDD2801) or (aspirin or acetylsalicylic acid) or (mavrilimumab or	

		immunoglobulin G4 or CAM-3001 or CAM3001) or ((vitamin? D? or D?-vitamin?) adj4 (high-dose* or highdose* or supplement*)) or (ivermect* or MK-933 OR MK933)).mp,bt,ot,du,dy,tn,nm. [other terms (title, abstract, author keywords and more) in MEDLINE and Embase] 6 (202009* or 202010* or 202011 or 202012* or 202101* or 202102*).dt. use medall [time limits in MEDLINE] 7 (202009* or 202010* or 202011 or 202012* or 202101* or 202102*).dc. use oemezd [time limits in Embase] 8 (1 and (3 or 5) and 6) use medall 9 (2 and (4 or 5) and 7) use oemezd	

6.3 Search strategy to identify ongoing studies

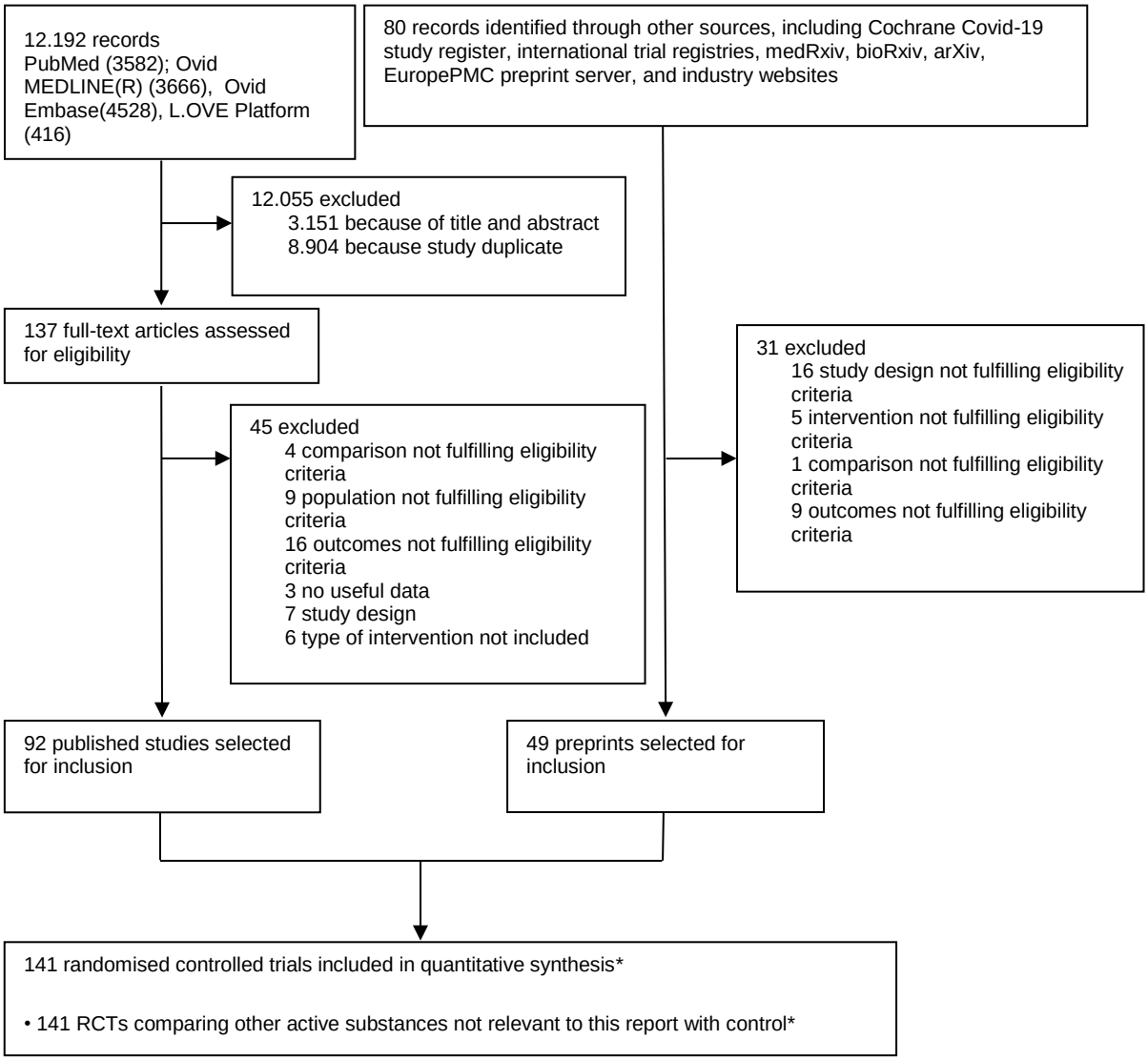
SNHTA is responsible for searching in trial registries to identify ongoing and unpublished studies. The combination of search terms related to COVID-19 and Aspirin are described in Appendix Table 6-3.

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*" [adapt if you used "Advanced search mode"] Terms used at Condition or disease: • covid-19 Terms used at "other terms": • aspirin clinicaltrials.gov automatically searches relevant synonyms of aspirin and COVID-19	20/04/2021	21 1 new
ISRCTN	https://www.isrctn.com/	Basic search mode [adapt if you used "Advanced search mode"] Search terms: 1. covid-19 and aspirin 2. covid-19 and Acetylsalicylic Acid 3. covid-19 and ASA 4. SARS-CoV-2 and aspirin 5. SARS-CoV-2 and Acetylsalicylic Acid 6. SARS-CoV-2 and ASA	20/04/2021	5 1 new
European Clinical Trials Registry	https://www.clinicaltrialsregister.eu/	Basic search mode [adapt if you used "Advanced search mode"] Search terms: 1. covid-19 and aspirin 2. covid-19 and Acetylsalicylic Acid 3. covid-19 and ASA 4. SARS-CoV-2 and aspirin 5. SARS-CoV-2 and Acetylsalicylic Acid 6. SARS-CoV-2 and ASA	20/04/2021	6 2 new
ICTRP COVID-19 collection accessed through search platform of clincaltrials.gov	https://clinicaltrials.gov/ct2/who_table	Basic search mode Terms used: aspirin acetylsalicylic acid	20/04/2021	24 4 new
COVID-NMA	https://covid-nma.com/dataviz/	Basic search mode Terms used: aspirin	20/04/2021	13 0 new
Cochrane COVID-19 register	https://covid-19.cochrane.org/	Filtered by aspirin	20.04.2021	17 0 new
Google Scholar / Google/ PubMed	Google.com Scholar.google.com Pubmed.org	Basic search mode Terms used: trial acronyms and clinical trial registration numbers of included ongoing studies (both randomized and non-randomized studies)	12/02/2021	3

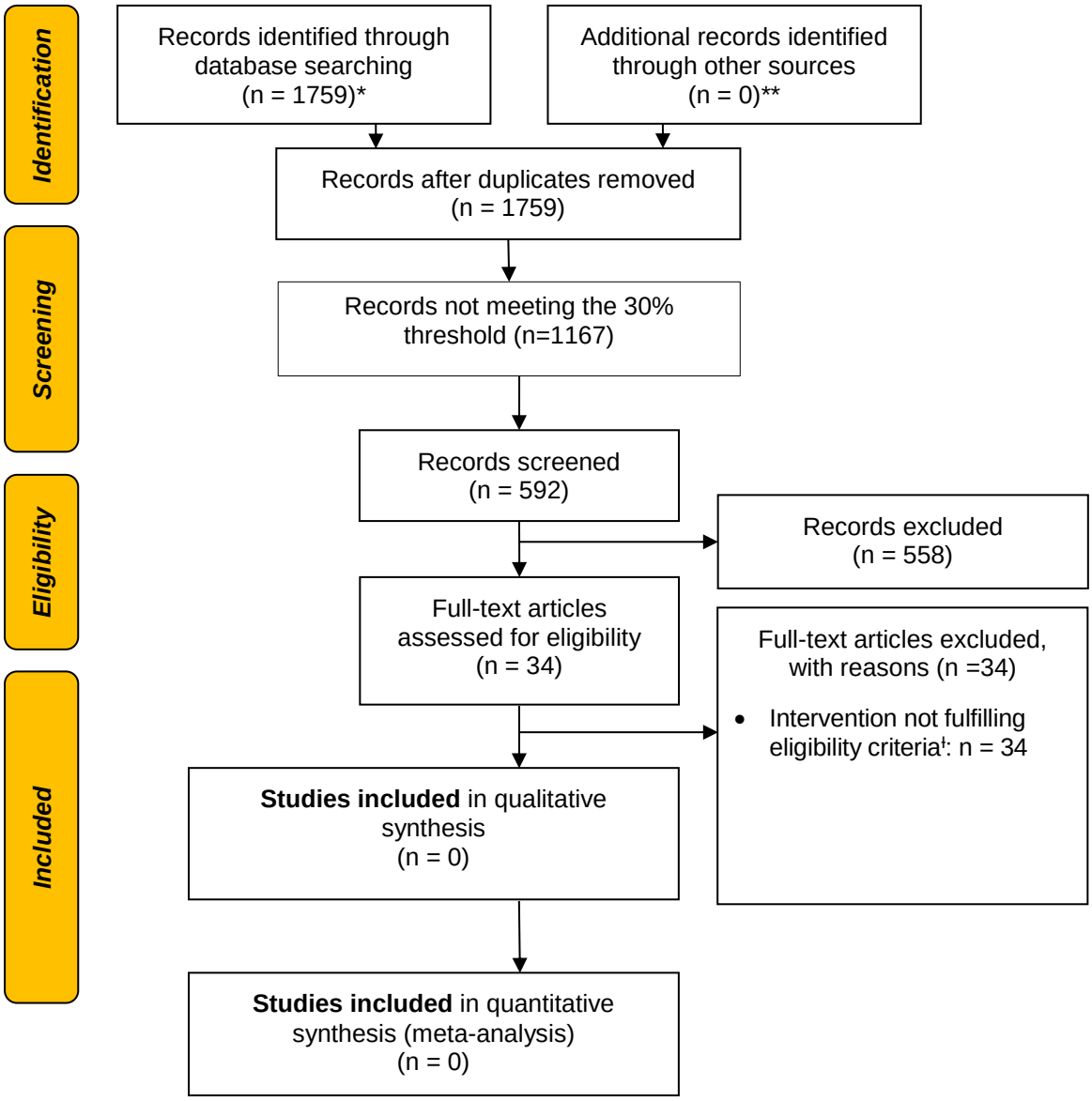
***** In Basic Search mode, one term was added to the field "condition or disease" and one term in the field "other terms".

6.4 Flow diagrams



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

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



Appendix Figure 6-2. Flow diagram depicting the selection process of observational studies

* Identified by NIPHNO through searches described in Table 6-2 for the period 26 February 2021 to 5 April 2021.
** identified by SNHTA through searches described in Table 6-3 for the period 15 March 2021 to 20 April 2021.
ł studies evaluating active substances relevant to other EUnetHTA rolling collaborative reviews