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**Clinical trials for the prevention and treatment of Coronavirus Disease 2019 (COVID-19): The current state of play**

Joshua S Davis
Principal Research Fellow
Menzies School of Health Research
Global and Tropical Health Division
Casuarina, Northern Territory
Australia

Infectious Diseases Physician
John Hunter Hospital
Department of Infectious Diseases
Newcastle, New South Wales
Australia

David Ferreira
Cardiology Registrar
John Hunter Hospital
Department of Cardiology
Newcastle, New South Wales
Australia

Justin T Denholm
Medical Director
Royal Melbourne Hospital
Victorian Tuberculosis Program
Peter Doherty Institute
Parkville, Victoria
Australia

Principal Research Fellow
University of Melbourne
Department of Microbiology and Immunology
Parkville, Victoria
Australia

Steven YC Tong
Senior Research Fellow
The Peter Doherty Institute for Infection and Immunity
Clinical Research
Melbourne, Victoria
Australia

## Summary

- In the three months since COVID-19 emerged from Wuhan, China and spread around the world, over 1,100 clinical studies have been registered globally on clinical trials registries, including over 500 randomised controlled trials.
- Such rapid development and launch of clinical trials is impressive but presents challenges, including the potential for duplication and competition.
- There is currently no known effective treatment for COVID-19.
- In order to focus on those studies most likely to influence clinical practice, we summarise currently registered randomised trials with a target sample size of at least 1000 participants (n=31).
- We have broken these trials into 4 categories: 1) Prophylaxis; 2) Treatment of outpatients with mild COVID-19; 3) Treatment of hospitalised patients with moderate COVID-19; and 4) Treatment of critically ill patients with COVID-19.
- The most common therapeutic agent being trialled currently is hydroxychloroquine (24 trials with potential sample size of over 25,000 participants), followed by lopinavir/ritonavir (7 trials) and remdesevir (5 trials)
- There are many current candidate drugs in pre-clinical and early phase development and these form a pipeline for future large clinical trials if current candidate therapies prove ineffective or unsafe.


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## Introduction

Since Coronavirus Disease 2019 (COVID-19) emerged from Wuhan, China in December 2019, the pace of scientific progress has been breathtaking. The COVID-19 pandemic is unprecedented in our lifetimes in many ways: the speed and scale of the global spread of disease, the impact on national and global economies, and in parallel the spread of information, misinformation (inadvertently incorrect) and disinformation (maliciously incorrect).

In this context, we have seen a fundamental change in the way that clinical trials are designed, implemented and reported. Rather than the usual timeline of at least 12 to 24 months from clinical trial concept to first patient enrolled, in the three months since COVID-19 disease was widely recognised, over 1,100 clinical studies have been registered, of which more than 500 are randomised trials. Let us pause for a moment to reflect on how remarkable this is: in December 2019, no one had heard of Severe Acute Respiratory Syndrome Coronavirus-2 (SARS CoV-2) or the disease it causes, COVID-19. Within weeks of the first cases presenting in Wuhan, China, the causative pathogen had been identified and sequenced and diagnostic tests were developed. Within one to two months, multiple clinical trials had been launched, including securing funding and investigational product supply, writing of protocols, ethics and site approvals, design of database, data capture and randomisation schedules, statistical analysis plans and safety monitoring. All of this was achieved in the midst of an evolving pandemic that was overwhelming hospitals and health services, and later on during government-sanctioned social distancing, when face to face meetings were not possible.

In part, this unbelievable speed was assisted by what we have learned from similar recent pandemics: Severe Acute Respiratory Syndrome (SARS) in 2003 (1), Middle East Respiratory Syndrome (MERS) in 2012 (2) and H1N1 influenza in 2009 (3). SARS and MERS are caused by coronaviruses which are closely related to SARS-CoV-2, and several candidate drugs for their treatment were identified by *in-vitro* assays followed by animal studies and limited clinical trials (4, 5). These drugs were the first that were

repurposed for clinical trials in COVID-19. Most of the drugs being tested in larger trials have either been shown to have an in-vitro antiviral effect against SARS, MERS or SARS-CoV-2 (6) (7), or to have an immunomodulatory effect which would be expected to reduce the uncontrolled lung inflammation in late COVID-19 disease (8) **table 1.**

Following the H1N1 influenza pandemic in 2019, international observational studies and research platforms were designed and sat ready to activate for the next pandemic. These include ISARIC (the International Severe Acute Respiratory and emerging Infection Consortium), whose data collection tools have been used for many of the current COVID-19 trials (9). Finally, the WHO rapidly developed and made publicly available a master protocol in early March, in an attempt to guide and harmonise COVID-19 clinical trials.

How do we separate the wheat from the chaff and make some sense of all the noise we are hearing about clinical trials for COVID-19? To help with this, we wrote a narrative review, with the aim of summarising currently registered large clinical trials of therapeutic agents for COVID-19.

***Scope of this article***

We have only included:

i) Trials which have been registered in one or more national or international clinical trials registries.

ii) Trials including at least 2 arms, with interventions allocated by randomisation.

iii) Trials assessing therapeutic or prophylactic agents (including antiviral, immunomodulatory and miscellaneous drugs or blood products). We have excluded trials assessing devices (e.g. oxygen delivery devices), therapeutic strategies (e.g. higher versus lower PEEP, liberal versus restrictive fluid strategies), or other non-pharmacological interventions.

iv) Trials with a target total sample size of at least 1,000 participants. We chose this arbitrary threshold because such trials are the most likely to result in findings which influence clinical practice, and it filters out phase 1 and 2 trials of agents which may never enter clinical practice.

v) We excluded those trials assessing traditional Chinese medicines, because their results will be unlikely to be implementable internationally, as well as trials which have been suspended or abandoned.

We searched the following clinical trials registries: The U.S National Institutes of Health-hosted ClinicalTrials.gov (www.clinicaltrials.gov), The Australian New Zealand Clinical Trials Registry (www.anzctr.org.au), and the WHO International Clinical Trials Registry Platform (www.who.int/ictrp), which includes trials from all major national registries worldwide. In addition, we used two recently created COVID-19 meta-registries: 1) A European collaborative project called "living mapping and systematic review of COVID-19 studies" (www.covid-nma.com), and 2) A US-led global collaboration created by a commercial research organisation called Cytel Inc., "Review of active international clinical trials for COVID-19" (www.covid19-trials.com). We encourage readers to consult these sources since the field is changing so rapidly.

We found 31 currently registered trials which met our inclusion criteria. Their key characteristics are summarised in **table 1**.

## Prophylaxis trials

We found 12 trials assessing prophylactic agents for COVID-19 (table 2). Analyses of COVID-19 transmission in Shenzhen China demonstrated household and close contact secondary infection rates of 15% and 10% respectively (10). Trials assessing prophylactic agents can be divided into pre-exposure prophylaxis (PrEP – where the agent is taken continuously during a period of risk) and post-

exposure prophylaxis (PEP – where the agent is taken for a limited time, starting as soon as possible after exposure to a known case). PrEP has the theoretical advantage of preserving precious drug supplies; PEP strategies rely on entire at-risk populations taking prophylactic drugs, of whom only a small proportion will actually be exposed.

We found six registered trials assessing PrEP, all of which target health care workers and first responders, with a combined target sample size of over 110,000 participants. Four of these examine the benefit of the anti-malarial and immunomodulatory drug hydroxychloroquine/chloroquine (COPCOV, WHIP COVID-19 and CROWN CORONA) and one used the HIV drug emtricitabine/tenofovir (EPICOS). All have clinical endpoints of infection incidence and severity. One open-label trial, based in Australia, will randomise 4,000 HCW to Bacille Calmette-Guerin vaccine, used for its purported "off target" immunomodulatory effects of reducing the risk of common non-TB infections (11) or no intervention.

We also found six large PEP trials, including COVID-19 PEP, SHARP COVID-19, HCQ4COV19, CORIPREV-LR and two others. Hydroxychloroquine is the interventional agent in five of these trials while CORIPREV-LR is using the HIV protease inhibitor Lopinavir/ritonavir. Of note, secondary endpoints in CORIPREC-LR will include the short and long-term psychological impact of coronavirus exposure. Only two of these trials are actively recruiting at the time of writing, however follow-up will be short (14 to 28 days) and should allow results to be released soon.

## Mild disease/outpatient trials

"Mild disease" is variably defined, but usually is taken to mean cough, fever, malaise and upper respiratory tract symptoms without dyspnoea or the need for supplemental oxygen therapy (12). This overlaps substantially with the ability to manage without hospital admission, and many clinical trials use outpatient management as a surrogate for mild disease. Approximately 80% of patients who contract COVID-19 have mild or trivial symptoms, so this cohort large and important to include in

clinical trials (12). Therapeutic agents which prevent disease progression and thus need for hospital admission would clearly be of great benefit both to individual patients and to the healthcare system as a whole. There are several randomised controlled trials currently investigating the management of these patients (**Table 3**). Broadly these trials can be classified based on target population: the general infected population and those at high risk of worsening disease.

Trials investigating treatment of the general infected population include ACT COVID19, COVID-19 PEP and a trial comparing hydroxychloroquine to vitamin C in the United States. All three investigate the efficacy of hydroxychloroquine/chloroquine, however ACT COVID19 combines the antimalarial with the macrolide antibiotic azithromycin. Follow-up is from 2 to 6 weeks with clinical primary endpoints of infection severity, hospitalisation, mechanical ventilation and death. With a combined sample size of more than 3,000, the studies should provide helpful guidance on the management those with mild disease.

Trials examining those at high risk of disease progression include COLCORONA, COVERAGE and a study based in Brazil comparing hydroxychloroquine to standard of care. These trials have sparked interest world-wide. There is a diversity of therapies in these studies, COLCORONA assessing the efficacy of the anti-metabolite colchicine while COVERAGE is using a multi-arm multi-stage (MAMS) design to compare hydroxychloroquine, imantinib, telmisartan and favipiravir. These trials are enrolling those older than 65 years of age, diabetics and those with respiratory and cardiovascular disease, and all have primary endpoints at timepoints ranging from 14 to 30 days.

## Moderate disease trials

Moderate disease is defined as patients requiring hospitalisation but not requiring advanced respiratory support (meaning invasive or non-invasive ventilation) or intensive care unit admission at the time of enrolment. The moderate patient group is important and amenable to study as there is expected to be a reasonably frequent rate of clinically important events (e.g., 20% of hospitalised

patients may progress to requiring advanced respiratory support) compared to mild disease where the low event rate makes powering of studies more difficult. The lower event rate may also mean that concerns of drug toxicities and expense are harder to justify if the benefit is likely to be marginal. On the other hand, in comparison to severe disease trials, commencing antiviral treatment prior to a patient requiring advanced respiratory support may have the benefit of reducing viral replication at an earlier stage. Immunomodulation may also be more effective if commenced when immune dysregulation is just beginning rather than well established.

We identified only four trials that were restricted to this moderate patient group (noting that some trials include both moderate and severe patients and are discussed in the moderate / severe section; **table 4**). The primary endpoint for these studies is either: 1) death or need for advanced respiratory support; or 2) the WHO's seven-point ordinal scale (ranging from 1 for outpatients with no limitations on activity through to 7 for death). The investigational agents were hydroxychloroquine, lopinavir/ritonavir, and remdesivir. Only one trial is placebo controlled with blinding of participants and investigators.

## Moderate/Severe disease trials

We identified 8 trials of moderate to severe COVID-19 patients, with plans to enrol over 15,000 participants **(table 5).** All trials will allocate participants hospitalised with confirmed SARS-CoV-2 to receive an agent with potential antiviral activity, with several also enrolling participants for an immunomodulatory therapy. Antiviral therapies studied in this population are most commonly hydroxychloroquine/chloroquine (7/8) and/or lovinavir/ritanavir (5/8), with remdesivir evaluated in 3 studies. The dose of hydroxychloroquine used for trials varied notably, with doses ranging from a total of 4g to 6g of hydroxychloroquine over 7-14 days of treatment. All studies included an arm for participants receiving standard of care, underscoring the lack of treatments with established efficacy in even these high-risk cohorts. In addition to antiviral arms, 4 studies included immunomodulatory

arms, with studies considering the impact of corticosteroids, interferon-beta 1A, and interleukin blockers such as anakinra and tocilizumab.

The primary outcome measure in most of these trials is a clinically assessed ordinal scale, ranging from fully recovered to death. While assessment generally uses the World Health Organisation 7-point scale at 15 days post-enrolment, several groups have modified the scale or are using alternative time points. There are, however, no patient-reported outcomes amongst primary endpoints. Several trials do include patient-reported outcomes as secondary endpoints, particularly quality of life assessment, typically 3 months post-enrolment.

Trials exclusively are exclusively enrolling adult participants, and pregnancy and severe renal disease are generally exclusion criteria. While global experience to date continues to indicate that children are unlikely to develop severe COVID-19, the systematic exclusion of pregnant women and those with chronic renal failure is likely to mean that safety and efficacy of potential therapies will be largely unaddressed in these risk groups with severe disease.

One way of coping with the rapidly changing landscape of COVID-19 epidemiology and emergent treatment data is to use adaptive trial designs. Adaptive platform trials can study multiple interventions, across several domains (e.g. antiviral and immunomodulatory) for one disease, using a single master protocol (13). Moreover, key elements of the trial can change over time, according to strict pre-specified rules. These include changing the sample size, adding or dropping interventions (or "arms"), and altering the ratio of randomisation following frequent interim analyses so that a patient enrolled in the platform is statistically more likely to receive a more effective drug. REMAP-CAP **(table 5)** is an example of such a trial design, and was an existing platform trial examining multiple domains in patients with severe community acquired pneumonia admitted to ICU (14). It has added two new "pandemic" domains for COVID-19 patients, one antiviral and one immunomodulatory.

## Discussion

The thirty one large randomised trials described in this article share several common themes. First, nearly all of them are investigator-initiated. Why are pharmaceutical companies and commercial research organisations not running trials? They are, but most of their candidate drugs are not sufficiently advanced to run large phase 3 or 4 trials. There are over 300 registered randomised trials of smaller sample size or earlier phase. Many of the drugs tested in these smaller trials never proceed to larger studies die to toxicity, a lack of efficacy, or for commercial reasons, and they are beyond the scope of this article. However it is important to note that this drug development pipeline is crucial in our response to COVID-19. There is a reasonable chance that none of the therapies currently being tested will prove beneficial, or that a few will but with a small effect size. We urgently need candidate drugs joining the queue to be tested in large trials. Second, most of the trials are testing hydroxychloroquine or chloroquine and all of the antiviral drugs are being "repurposed" from an existing approved indication. Remdesevir is an exception – it is a broadly acting antiviral with activity against viral RNA-dependant RNA polymerase. It has been tested against other coronaviruses (SARS and MERS) and Ebola, but without sufficient data to allow registration (15-17). While it is possible (or even likely) that there are currently running large trials we have inadvertently not included in this review, their omission is not likely to change to overall pattern of findings as described above. We are also aware of several planned large trials which are not yet registered, including newer treatments such as convalescent plasma, angiotensin 2 receptor blockers and non-steroidal anti-inflammatory drugs.

The rapid creation and roll out of clinical trials for COVID-19 means we are likely to find accurate answers relatively quickly about candidate therapeutic agents, but also presents challenges. Foremost among these is the potential for competition between trials for participants, sites and funding. To avoid this it is crucial that, before planning a clinical trial, investigators determine if one already exists that could serve their patients. It is hoped that the current article will help with this, along with the

WHO meta-registry and COVID-19 trial summary websites mentioned in the introduction to this paper. Trialists should openly communicate with each other and the public about their trial protocols, their data collection plan, and their drug supply. Unfortunately, only a few of the 31 large trials described in this article have made their trial protocol publically available (table 1). Even if joining an existing trial is not possible, harmonisation of trial design (for example by using the same endpoints and data collection) is easy to achieve and will allow planned prospective individual patient meta-analyses to increase the overall power of all of these trials. Co-ordination at national and international levels is needed to avoid deleterious trial competition, as well as to prevent unnecessary duplicate trials from proceeding. The United Kingdom has taken an effective approach to this problem, by only endorsing three key trials, and encouraging all sites and investigators to focus their efforts on these three: one in the pre-hospital space (PRINCIPLE), one in non-severe hospital patients (RECOVERY) and one in ICU patients (REMAP-CAP). Partly as a result of this policy (as well as the unfortunate explosion of COVID-19 case numbers in the UK), the RECOVERY trial (**table 5**) has already randomised over 5,000 patients, within weeks of opening.

While several trials have already published their results (e.g. (18)), generating intense media interest, none of them have been sufficiently powered to change practice, and all enrolled well under 1000 patients and so have not been described in this article. Ongoing key trials described here to which Australians have access include BRACE (table 1), ASCOT (table 4) and REMAP-CAP (table 5).

The near-instant dissemination of information and opinion that is prevalent in today's world makes properly designed clinical trials more important than ever. United States President Donald Trump's promotion of hydroxychloroquine (based on information from a preprint of a small and poorly designed study (19)) led to a huge surge in the use of the drug, with a consequent depletion of supply in many countries, well in advance of any definitive data from clinical trials. The fact that many scientists and clinical trialists have "dropped everything" to work on vaccines, therapeutics and clinical

trials for COVID-19 augurs well that we will have access to safe and effective prevention and treatment strategies for COVID-19 within months, rather than the usual time scale of decades.

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**Table 1 - Characteristics of included trials (n=31)**

| | | n | | Comments |
|---|---|---|---|---|
| **Patient setting** | | | | |
| | Prophylaxis | 12 | | 6 Pre-exposure, 6 post-exposure |
| | Mild disease (outpatients) | 6 | | |
| | Moderate disease | 4 | | |
| | Moderate to severe disease | 9 | | |
| **Therapeutic agent** | | | | |
| | (Hydroxy)chloroquine | 24 | Directly antiviral, immunomodulatory | Very variable dosing regimens |
| | Antiretrovirals | 8 | Directly antiviral | 7=Lopinavir/ritonavir<br>1=Emtricitabine/tenofovir |
| | Remdesivir | 5 | Directly antiviral | Only available intravenously |
| | Interferon | 5 | Upregulates host anti-viral immune responses | |
| | Angiotensin 2 receptor blockers | 3 | Attenuates angiotensin 2-induced lung injury | |
| | Cytokine blocking monoclonal antibodies | 3 | Attenuates “cytokine storm” induced lung damage | Anakinra (IL-1), Tocilizumab (IL-6), Sarilumab (IL-6) |
| | Small molecule kinase inhibitors | 2 | Inhibits viral endocytosis | Imatininb, baricitinib |
| | Vitamin C | 2 | Immunomodulatory | |
| | Azithromycin | 2 | Immunomodulatory | |
| | Other | | | Aspirin, Statin, Colchicine, Faviparavir, Dexamethasone, BCG vaccine, |
| **Sponsor-type** | | | | |
| | Investigator-initiated | 27 | | |
| | Commercial | 4 | | |
| **Protocol publicly available?** | | | | |
| | Yes | 3 | | |
| | No | 28 | | |

**Table 2 – Randomised Trials of Prophylactic Therapies for COVID-19**

| Trial acronym/ number | Trial name | Country/region | Sponsor type | Target sample size | Trial Domains/Arms | Primary outcome | Publicly available protocol |
|---|---|---|---|---|---|---|---|
| Pre-Exposure Prophylaxis | | | | | | | |
| COPCOV (NCT04303507) | Chloroquine/ Hydroxychloroquine Prevention of Coronavirus Disease (COVID-19) in the Healthcare Setting | Europe, Asia | Investigator-initiated | 40,000 | 1. Chloroquine/Hydroxychloroquine<br>2. Placebo | Symptomatic infection and respiratory severity score at 100 days | No |
| EPICOS (NCT04334928) | Prevention of SARS-CoV-2 (COVID-19) Through Pre-Exposure Prophylaxis with Tenofovir Disoproxil Fumarate/Emtricitabine and Hydroxychloroquine in Healthcare Personnel | Spain | Investigator-initiated | 4,000 | 1. Emtricitabine/tenofovir disoproxil and hydroxychloroquine<br>2. Emtricitabine/tenofovir disoproxil and placebo<br>3. Hydroxychloroquine and placebo<br>4. Placebo and placebo | Confirmed symptomatic infection at 12 weeks | No |
| WHIP COVID-19 (NCT04341441) | Will Hydroxychloroquine Impede or Prevent COVID-19 | United States | Investigator-initiated | 3,000 | 1. Daily hydroxychloroquine<br>2. Weekly hydroxychloroquine<br>3. Placebo | Number of infections in healthcare workers at 8 weeks | No |
| CROWN CORONA (NCT04333732) | International, Multi-site, Bayesian Platform Adaptive, Randomised, Double-blind, Placebo-controlled Trial Assessing the Effectiveness of Varied Doses of Oral Chloroquine in Preventing or Reducing the Severity of COVID-19 | Australia, Canada, Ireland, South Africa, United Kingdom, United States, Zambia | Investigator-initiated | 55,000 | 1. Low-dose chloroquine/hydroxychloroquine<br>2. Mid-dose chloroquine/hydroxychloroquine<br>3. High-dose chloroquine/hydroxychloroquine<br>4. Placebo | Symptomatic infection and WHO 7-point ordinal scale at 3 months | No |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | Disease in Healthcare Workers | | | | | | |
| BRACE (NCT04327206) | BCG Vaccination to Protect Healthcare Workers Against COVID-19 | Australia | Investigator-initiated | 4,170 | 1. BCG vaccine<br>2. No intervention | Incidence of infection and severe infection at 6 months | No |
| NCT04320238 | Experimental Trial of rhIFNα Nasal Drops to Prevent 2019-nCOV in Medical Staff | China | Investigator-initiated | 2,944 | 1. Low risk: recombinant human interferon Alpha-1b<br>2. High risk: recombinant human interferon Alpha-1b and thymosin alpha 1 | New infection up to 6 weeks | No |
| Post-Exposure Prophylaxis | | | | | | | |
| COVID-19 PEP (NCT04308668) | Post-exposure Prophylaxis or Pre-emptive Therapy for SARS-Coronavirus-2 | Canada, United States | Investigator-initiated | 3,000 | 1. Hydroxychloroquine<br>2. Placebo | Incidence of infection and 3-point ordinal scale at 14 days post-enrolment | No |
| NCT04318444 | Hydroxychloroquine Post Exposure Prophylaxis for Household Contacts of COVID-19 Patients | United States (New York City) | Investigator-initiated | 1,600 | 1. Hydroxychloroquine<br>2. Placebo | Symptomatic lab confirmed infection at 14 days post-enrolment | No |
| NCT04328961 | Efficacy of Hydroxychloroquine for Post-exposure Prophylaxis to Prevent Severe Acute Respiratory Syndrome Coronavirus 2 Infection | United States | Investigator-initiated | 2,000 | 1. Hydroxychloroquine<br>2. Vitamin C | Laboratory confirmed infection from day 1 to 14 and at day 28 | No |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | Among Adults Exposed to Coronavirus Disease | | | | | | |
| SHARP COVID-19 (NCT04342156) | Safety and Efficacy of Hydroxychloroquine As COVID-19 Prophylaxis for At-Risk Population: A Cluster Randomized Controlled Trial | Singapore | Investigator-initiated | 3,000 | 1. Hydroxychloroquine<br>2. Standard preventative measures | Laboratory confirmed infection until day 28 | No |
| HCQ4COV19 (NCT04304053) | Treatment of COVID-19 Cases and Chemoprophylaxis of Contacts as Prevention | Spain | Investigator-initiated | 3,040 | 1. Hydroxychloroquine and public health measures<br>2. Public health measures | Incidence of secondary infection among contacts at 14 days | No |
| CORIPREV-LR (NCT04321174) | COVID-19 Ring-based Prevention Trial with Lopinavir/Ritonavir | Canada | Investigator-initiated | 1,220 | 1. Lopinavir/ritonavir<br>2. Control | RNA confirmed infection at 14 days | No |

**Table 3 – Randomised Trials of Therapies for Mild, Outpatient COVID-19**

| Trial acronym/ number | Trial name | Country/region | Sponsor type | Target sample size | Trial Domains/Arms | Primary outcome | Publicly available protocol |
|---|---|---|---|---|---|---|---|
| ACT COVID19 (NCT04324463) | Anti-Coronavirus Therapies to Prevent Progression of COVID-19 Trial | Canada | Investigator-initiated | 1,500 | 1. Chloroquine plus Azithromycin<br>2. Standard of Care | Hospitalisation or death at 6 weeks post-enrolment | No |
| COVID-19 PEP* (NCT04308668) | Post-exposure Prophylaxis or Pre-emptive Therapy for SARS-Coronavirus-2 | Canada, United States | Investigator-initiated | 3,000 | 1. Hydroxychloroquine<br>2. Placebo | Incidence of infection and 3-point ordinal scale at 14 days post-enrolment | No |
| NCT04334967 | Hydroxychloroquine in Patients with Newly Diagnosed COVID-19 Compared to Standard of Care | United States | Investigator-initiated | 1,250 | 1. Hydroxychloroquine<br>2. Vitamin C | Hospitalisation or mechanical ventilation at 14 days post-enrolment | No |
| COVERAGE (2020-001435-27) | Home treatment of elderly patients with symptomatic SARS-CoV-2 infection | France | Investigator-initiated | 1,057 | 1. Hydroxychloroquine<br>2. Imatinib<br>3. Favipiravir<br>4. Telmisartan | Hospitalisation or death at 14 days post-enrolment | No |
| COLCORONA (NCT04322682) | Colchicine Coronavirus SARS-CoV2 Trial | Canada | Investigator-initiated | 6,000 | 1. Colchicine<br>2. Placebo | Hospitalisation or death at 30 days post-enrolment | No |
| A27736297878 | Randomized, pragmatic, open study evaluating Hydroxychloroquine for prevention of Hospitalization and | Brazil | Commercial | 1,300 | 1. Hydroxychloroquine<br>2. Standard of Care | Hospitalisation or uncontrolled asthma within 30 days | No |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | Respiratory Complications in outpatients with confirmed or presumptive diagnosis of Infection by COVID-19 | | | | | | |
| PRINCIPLE (ISRC TN86534580) | Platform Randomised trial of interventions against COVID-19 in older peoPLE | UK | Investigator-initiated | 3,000 | 1. Hydroxychloroquine<br>2. Standard of Care | Hospitalisation or death | No |

*This trial is also listed in table 1

**Table 4 - Randomised Trials of Therapies for Moderate COVID-19**

| Trial acronym/ number | Trial name | Country/region | Sponsor type | Target sample size | Trial Domains/Arms | Primary outcome | Publicly available protocol |
|---|---|---|---|---|---|---|---|
| ASCOT (ACTRN12620000445976) | Australasian COVID-19 Trial | Australia and New Zealand | Investigator-initiated | 2,400 | 1. Lopinavir/ritonavir<br>2. Hydroxychloroquine<br>3. Lopinavir / ritonavir plus hydroxychloroquine<br>4. Standard of care | Advanced respiratory support or death at 15 days post enrolment | Yes |
| NCT04292730 | A Phase 3 Randomized Study to Evaluate the Safety and Antiviral Activity of Remdesivir (GS-5734™) in Participants With Moderate COVID-19 Compared to Standard of Care Treatment | USA, Europe | Commercial | 1,600 | 1. Remdesivir 5 days<br>2. Remdesivir 10 days<br>3. Standard of care | WHO 7-point ordinal scale at 11 days post-enrolment | No |
| ACT COVID19 | Anti-Coronavirus Therapies to Prevent Progression of COVID-19 Trial | Canada | Investigator-initiated | 1,500 | 1.Hydroxychloroquine/Azithromycin<br>2. Standard of Care | Mechanical ventilation or death at 6 weeks post-enrolment | No |
| HYCOVID (NCT04325893) | Hydroxychloroquine Versus Placebo in COVID-19 Patients | France | Investigator-initiated | 1,300 | 1.Hydroxychloroquine<br>2. Placebo | Mechanical ventilation or death at 14 days | No |

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|---|---|---|---|---|---|---|---|
| | at Risk for Severe Disease | | | | | post-enrolment | |

**Table 5 – Randomised Trials of Therapies for Moderate and Severe COVID-19**

| Trial acronym/ number | Trial name | Country/region | Sponsor type | Target sample size | Trial Domains/Arms | Primary outcome | Publicly available protocol |
|---|---|---|---|---|---|---|---|
| REMAP CAP (NCT02735707) | Randomized, Embedded Multifactorial Adaptive Platform Trial for Community-Acquired Pneumonia | Australia/NZ, USA, Europe | Investigator-initiated | 7,100 (A subset will have COVID-19) | *Antiviral Domain*<br>1. Lopinavir/ritonavir<br>2. Hydroxychloroquine<br>3. Lopinavir/ritonavir plus hydroxychloroquine<br>4. Standard of care<br>*Immunomodulatory Domain*<br>1.Interferon Beta-1a<br>2. Anakinra<br>3. Tocilizumab<br>4. Sarilumab<br>5. Standard of care | 1. All-cause mortality (90 days)<br>2. Days alive and out of ICU (21 days) | Yes |
| SOLIDARITY (ISRCTN83971151) | An international randomized trial of additional treatments for COVID-19 in hospitalized patients who are all receiving the local standard of care | Europe, Asia, Canada, Sth America, Sth Africa | Investigator-initiated | Not given | 1. Remdesivir<br>2. Lopinavir/ ritonavir<br>3. Lopinavir/ ritonavir plus interferon-beta<br>4. Hydroxychloroquine/chloroquine<br>5. Standard of care | All-cause mortality | No |
| RECOVERY (ISRCTN50189673) | A randomised trial of treatments to prevent death in patients hospitalised with COVID-19 | UK | Investigator-initiated | 5,000 | 1.Lopinavir/r<br>2.Hydroxychloroquine<br>3. Interferon Beta-1b (inhaled)<br>4. Dexamethasone (6mg daily)<br>5. Standard of care | All-cause mortality (28 days) | Yes |
| DISCOVERY (NCT04315948) | Trial of Treatments for COVID-19 in Hospitalised Adults | Europe | Investigator-initiated | 3,100 | 1. Remdesivir<br>2. Lopinavir/ ritonavir<br>3. Lopinavir/ ritonavir plusInterferon Beta-1a | WHO 7-point ordinal scale at 15 days | No |

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| | | | | | 4. Hydroxychloroquine<br>5. Standard of care | post-enrolment | |
| NOR Solidarity (NCT04321616) | The NOR Solidarity multicenter trial on the efficacy of different anti-viral drugs in SARS-CoV-2 infected patients (COVID-19). | Europe | Investigator-initiated | 1,218 | 1.Remdesivir<br>2. Hydroxychloroquine | All-cause in-hospital mortality (21 days) | No |
| CRASH-19 (NCT04343001) | Coronavirus Response – Active Support for Hospitalised COVID-19 Patients | Nigeria, Pakistan | Investigator-initiated | 10,000 | 1. Aspirin (75mg daily)<br>2. Losartan<br>3. Simvastatin<br>4. Low-dose aspirin and losartan<br>5. Aspirin and simvastatin<br>6. Aspirin, losartan and simvastatin<br>6. Standard of care | All-cause mortality (28 days) | No |
| NCT04292899 | A Phase 3 Randomized Study to Evaluate the Safety and Antiviral Activity of Remdesivir (GS-5734™) in Participants With Severe COVID-19 | USA, Europe, Asia | Commercial | 6,000 | 1. Remdesivir 5 days<br>2. Remdesivir 10 days | WHO 7-point ordinal scale at 14 days post-enrolment | No |
| COVID MED (NCT04328012) | Comparison Of Therapeutics for Hospitalized Patients Infected With SARS-CoV-2 | USA | Commercial | 3,111 | 1. Lopinavir/ritonavir<br>2. Hydroxychloroquine<br>3. Losartan<br>3. Placebo | 8-point ordinal scale at 60 days post-enrolment | No |
| NCT04321993 | Treatment of Moderate to Severe Coronavirus Disease (COVID-19) in Hospitalized Patients | Canada | Investigator-initiated | 1,000 | 1. Lopinavir/ritonavir<br>2. Hydroxychloroquine<br>3. Baricitinib<br>4. Sarilumab<br>5. Standard of care | | No |