Clinical trials for the prevention and treatment of COVID-19: current state of play

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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 12–24 months from clinical trial concept to first patient enrolled, since COVID-19 disease was widely recognised, over 1100 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, the causative pathogen had been identified and sequenced and diagnostic tests were developed. Within 1–2 months, multiple clinical trials had been launched, including securing funding and investigational product supply, writing of protocols, ethics and site approvals, database design, 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 during government-sanctioned social distancing, when face-to-face meetings were not possible.

In part, this extraordinary 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 to be 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] (Box 1).

Following the 2009 H1N1 influenza pandemic, international observational studies and research platforms were designed and sat ready to activate for the next pandemic. These include the International Severe Acute Respiratory and Emerging Infection Consortium (ISARIC), whose data collection tools have been used for many of the current COVID-19 trials.[9] Finally, the World Health Organization (WHO) rapidly developed and made publicly available a master protocol in early March, in an attempt to guide and harmonise COVID-19 clinical trials.

Summary

- Since coronavirus disease 2019 (COVID-19) emerged in Wuhan, China in December 2019 and spread around the world, over 1100 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 the 31 currently registered randomised trials with a target sample size of at least 1000 participants.
- We have grouped these trials into four categories: prophylaxis; treatment of outpatients with mild COVID-19; treatment of hospitalised patients with moderate COVID-19; and treatment of hospitalised patients with moderate or severe disease.
- 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 (seven trials) and remdesevir (five trials)
- There are many 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.

To help clarify which studies are most likely to influence clinical practice, this narrative review summarises currently registered large clinical trials of therapeutic agents for COVID-19.

Scope of this article

We have only included:

- trials registered in one or more national or international clinical trials registries;
- trials including at least two arms, with interventions allocated by randomisation;
- trials assessing therapeutic or prophylactic agents, including antiviral, immunomodulatory and miscellaneous drugs or blood products. We have excluded trials assessing devices (eg, oxygen delivery devices), therapeutic strategies (eg, higher versus lower positive end expiratory pressure, liberal versus restrictive fluid strategies), and other non-pharmacological interventions; and
- trials with a target total sample size of at least 1000 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.

We excluded 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.

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We searched the following clinical trials registries: the United States 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. We used a sensitive but non-specific search strategy, using the search terms "COVID", "SARS-CoV-2" and "Coronavirus". We then reviewed each hit against the inclusion criteria. The search was carried out on 7 April 2020 and repeated on 21 April 2020. In addition, we used two recently created COVID-19 metaregistries: a European collaborative project (www.covid-nma.com) and a US-led global collaboration created by a commercial research organisation (www.covid19-trials.com). We encourage readers to consult these sources as the field is changing so rapidly.

We found 31 currently registered trials which met our inclusion criteria. Their key characteristics are summarised in Box 1. We have grouped these trials into four categories: prophylaxis; treatment of outpatients with mild COVID-19; treatment of hospitalised patients with moderate COVID-19; and treatment of hospitalised patients with moderate through to severe disease caused by COVID-19.

1 Characteristics of included trials (*N* = 31)

	No. of trials	Comments
Patient setting		
Prophylaxis	12	6 pre exposure, 6 post exposure
Mild disease (outpatients)	7	
Moderate disease	4	
Moderate to severe disease	9	
Therapeutic agent		
Chloroquine or hydroxychloroquine	24	Directly antiviral, immunomodulatory Very variable dosing regimens
Antiretrovirals	8	Directly antiviral 7 lopinavir–ritonavir 1 emtricitabine–tenofovir
Remdesivir	5	Directly antiviral Only available intravenously
Interferon	5	Upregulates host antiviral 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	5	Aspirin, statin, colchicine, faviparavir, dexamethasone, BCG vaccine
Sponsor-type		
Investigator initiated	27	
Commercial	4	
Publicly available protocol		
Yes	3	
No	28	

Prophylaxis trials

We found 12 trials assessing prophylactic agents for COVID-19 (Box 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). PEP has the theoretical advantage of preserving precious drug supplies; PrEP strategies rely on entire at-risk populations taking prophylactic drugs, only a small proportion of whom will actually be exposed.

We found six registered trials assessing PrEP (Box 2), 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 antimalarial and immunomodulatory drug hydroxychloroquine/chloroquine (COPCOV, WHIP COVID-19 and CROWN CORONA) and one used the HIV drug emtricitabine–tenofovir (EPICOS). All have clinical end points of infection incidence and severity. One open label trial, based in Australia, will randomise 4000 health care workers to BCG vaccine, used for its purported off-target immunomodulatory effects of reducing the risk of common infections other than tuberculosis,[11] or no intervention.

We also found six large PEP trials (Box 2). Hydroxychloroquine is the interventional agent in five of these trials, while CORIPREV-LR is using the HIV protease inhibitor lopinavir–ritonavir. Of note, secondary end points in CORIPREV-LR will include the short and long term psychological impact of coronavirus exposure.

Outpatients with mild COVID-19

Mild disease is variably defined, but is usually 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. About 80% of patients who contract COVID-19 have mild or trivial symptoms; this cohort is therefore large and important to include in clinical trials.[12] Therapeutic agents which prevent disease progression and thus the need for hospital admission would clearly be of great benefit both to individual patients and to the health care system as a whole. There are several randomised controlled trials currently investigating the management of these patients (Box 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 United States

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 or hydroxychloroquine 2. Placebo	Symptomatic infection and respiratory severity score at 100 days	No
EPICOS (NCT04334928)	Randomized Clinical Trial for the Prevention of SARS-CoV-2 Infection (COVID-19) in Healthcare Personnel	Spain	Investigator initiated	4000	1. Emtricitabine–tenofovir disoproxil and hydroxychloroquine 2. Emtricitabine–tenofovir disoproxil and placebo 3. Hydroxychloroquine and placebo 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	3000	1. Daily hydroxychloroquine 2. Weekly hydroxychloroquine 3. Placebo	Number of infections in health care workers at 8 weeks	No
CROWN CORONA (NCT04333732)	CROWN CORONATION: Chloroquine RepurpOsing to healthWorkers for Novel CORONAvirus mitigaTION	Australia, Canada, Ireland, South Africa, United Kingdom, US, Zambia	Investigator initiated	55 000	1. Low dose chloroquine or hydroxychloroquine 2. Mid dose chloroquine or hydroxychloroquine 3. High dose chloroquine or hydroxychloroquine 4. Placebo	Symptomatic infection and WHO 7-point ordinal scale at 3 months	No
BRACE (NCT04327206)	BCG Vaccination to Protect Healthcare Workers Against COVID-19	Australia	Investigator initiated	4170	1. BCG vaccine 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	2944	1. Low risk: recombinant human interferon-α1b 2. High risk: recombinant human interferon-α 1b and thymosin-α 1	New infection up to 6 weeks	No
Post-exposure prophylaxis							
COVID-19 PEP* (NCT04308668)	Post-exposure Prophylaxis / Preemptive Therapy for SARS-Coronavirus-2	Canada, US	Investigator initiated	3000	1. Hydroxychloroquine 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	US (New York City)	Investigator initiated	1600	1. Hydroxychloroquine 2. Placebo	Symptomatic laboratory 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 Among Adults Exposed to Coronavirus Disease	US	Investigator initiated	2000	1. Hydroxychloroquine 2. Vitamin C	Laboratory confirmed infection from day 1 to 14 and at day 28	No
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	3000	1. Hydroxychloroquine 2. Standard preventive measures	Laboratory confirmed infection until day 28	No
HCQ4COV19 (NCT04304053)	Treatment of COVID-19 Cases and Chemoprophylaxis of Contacts as Prevention	Spain	Investigator initiated	3040	1. Hydroxychloroquine and public health measures 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	1220	1. Lopinavir–ritonavir 2. Control	RNA confirmed infection at 14 days	No

* This trial is also listed in Box 3. ◆

trial comparing hydroxychloroquine to vitamin C (Box 3). All three investigate the efficacy of hydroxychloroquine or chloroquine; however, ACT COVID19 combines the antimalarial with the macrolide antibiotic azithromycin. Follow-up is from 2 to 6 weeks with clinical primary end points of infection severity, hospitalisation, mechanical ventilation and death. With

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	1500	1. Chloroquine plus azithromycin 2. Standard of care	Hospitalisation or death at 6 weeks post enrolment	No
COVID-19 PEP† (NCT04308668)	Post-exposure Prophylaxis / Preemptive Therapy for SARS-Coronavirus-2	Canada, United States	Investigator initiated	3000	1. Hydroxychloroquine 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	US	Investigator initiated	1250	1. Hydroxychloroquine 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	1057	1. Hydroxychloroquine 2. Imatinib 3. Favipiravir 4. Telmisartan	Hospitalisation or death at 14 days post enrolment	No
COLCORONA (NCT04322682)	Colchicine Coronavirus SARS-CoV2 Trial	Canada	Investigator initiated	6000	1. Colchicine 2. Placebo	Hospitalisation or death at 30 days post enrolment	No
A27736297878	Randomized, pragmatic, open study evaluating Hydroxychloroquine for prevention of Hospitalization and Respiratory Complications in outpatients with confirmed or presumptive diagnosis of Infection by COVID-19	Brazil	Commercial	1300	1. Hydroxychloroquine 2. Standard of care	Hospitalisation or uncontrolled asthma within 30 days	No
PRINCIPLE (ISRC TN86534580)	Platform Randomised trial of interventions against COVID-19 in older peoPLE	United Kingdom	Investigator initiated	3000	1. Hydroxychloroquine 2. Standard of care	Hospitalisation or death	No

* This trial is also listed in Box 4. † This trial is also listed in Box 2. ◆

a combined sample size of more than 3000, the studies should provide helpful guidance on the management of those with mild disease.

Trials examining patients at high risk of disease progression include COLCORONA, COVERAGE and a study based in Brazil comparing hydroxychloroquine to standard of care (Box 3). These trials have sparked interest globally. There is a diversity of therapies in these studies: COLCORONA is assessing the efficacy of the antimetabolite colchicine, while COVERAGE is using a multi-arm multi-stage design to compare hydroxychloroquine, imantinib, telmisartan and favipiravir. These trials are enrolling patients aged > 65 years, patients with diabetes, and those with respiratory and cardiovascular disease, and all have primary end points ranging from 14 to 30 days.

Hospitalised patients with moderate COVID-19

Moderate disease is defined as patients requiring hospitalisation but not requiring advanced respiratory support (invasive or non-invasive ventilation) or intensive care unit admission at the time of enrolment. The moderate COVID-19 group is important and amenable to study, as there is expected to be a reasonably frequent rate of clinically important events (eg, 20% of hospitalised patients may progress to requiring advanced respiratory support) compared with 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 before a patient requires 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 (Box 4), noting that some trials include both moderate and severe patients and are discussed below. The primary end point for these studies is either death or need for advanced respiratory support; or the WHO 7-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

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	2400	1. Lopinavir–ritonavir 2. Hydroxychloroquine 3. Lopinavir–ritonavir plus hydroxychloroquine 4. Standard of care	Advanced respiratory support or death at 15 days post enrolment	Yes
NCT04292730	Study to Evaluate the Safety and Antiviral Activity of Remdesivir (GS-5734™) in Participants With Moderate COVID-19 Compared to Standard of Care Treatment	United States, Europe	Commercial	1600	1. Remdesivir 5 days 2. Remdesivir 10 days 3. Standard of care	WHO 7-point ordinal scale at 11 days post enrolment	No
ACT COVID19* (NCT04324463)	Anti-Coronavirus Therapies to Prevent Progression of COVID-19 Trial	Canada	Investigator initiated	1500	1. Hydroxychloroquine plus azithromycin 2. Standard of care	Mechanical ventilation or death at 6 weeks post enrolment	No
HYCOVID (NCT04325893)	Hydroxychloroquine Versus Placebo in COVID-19 Patients at Risk for Severe Disease	France	Investigator initiated	1300	1. 1.Hydroxychloroquine 2. Placebo	Mechanical ventilation or death at 14 days post enrolment	No

* This trial is also listed in Box 4. ◆

one trial is placebo-controlled with blinding of participants and investigators.

Hospitalised patients with moderate to severe COVID-19

We identified eight trials of patients with moderate to severe COVID-19 with plans to enrol over 15 000 participants (Box 5). Severe disease is defined as patients requiring advanced respiratory support (non-invasive or invasive mechanical ventilation) or intensive care unit admission. All trials will allocate participants hospitalised with confirmed COVID-19 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 or chloroquine (seven trials) and/or lovinavir–ritanavir (five trials), with remdesivir evaluated in three trials. The dose of hydroxychloroquine used for trials varies notably, with doses ranging from a total of 4 g to 6 g 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, four trials included immunomodulatory arms, with studies considering the impact of corticosteroids, interferon-β 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 WHO 7-point scale at 15 days after enrolment, several groups have modified the scale or are using alternative time points. There are, however, no patient-reported outcomes among primary end points. Several trials include patient-reported outcomes as secondary end points, particularly quality-of-life assessment, typically 3 months after enrolment.

Trials 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.

A 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 (eg, 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 (Box 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 intensive care.[14] It has added two new pandemic domains for COVID-19 patients: one antiviral and one immunomodulatory.

Discussion

The 31 large randomised trials described in this article share several common themes. First, nearly all of them are investigator initiated. While pharmaceutical companies and commercial

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 and New Zealand, United States, Europe	Investigator initiated	7100 (a subset will have COVID-19)	Antiviral domain 1. Lopinavir–ritonavir 2. Hydroxychloroquine 3. Lopinavir–ritonavir plus hydroxychloroquine 4. Standard of care Immunomodulatory domain 1. Interferon-β 1a 2. Anakinra 3. Tocilizumab 4. Sarilumab 5. Standard of care	1. All-cause mortality (90 days)2. Days alive and out of intensive care unit (21 days)	Yes
SOLIDARITY (ISRCTN83971151)	Public health emergency SOLIDARITY trial of treatments for COVID-19 infection in hospitalized patients	Europe, Asia, Canada, South America, South Africa	Investigator initiated	Not given	1. Remdesivir 2. Lopinavir/ ritonavir 3. Lopinavir/ ritonavir plus interferon-β 4. Hydroxychloroquine or chloroquine 5. Standard of care	All-cause mortality	No
RECOVERY (ISRCTN50189673)	A randomised trial of treatments to prevent death in patients hospitalised with COVID-19	United Kingdom	Investigator initiated	5000	1. Lopinavir–ritonavir 2. Hydroxychloroquine 3. Interferon-β 1b (inhaled) 4. Dexamethasone (6 mg daily) 5. Standard of care	All-cause mortality (28 days)	Yes
DISCOVERY (NCT04315948)	Trial of Treatments for COVID-19 in Hospitalised Adults	Europe	Investigator initiated	3100	1. Remdesivir 2. Lopinavir–ritonavir 3. Lopinavir–ritonavir plus interferon-β 1a 4. Hydroxychloroquine 5. Standard of care	WHO 7-point ordinal scale at 15 days post enrolment	No
NOR Solidarity (NCT04321616)	The NOR Solidarity Multicenter Trial on the Efficacy of Different Anti-viral Drugs in SARS-CoV-2 Infected Patients	Europe	Investigator initiated	1218	1. 1.Remdesivir 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 (75 mg daily) 2. Losartan 3. Simvastatin 4. Low dose aspirin and losartan 5. Aspirin and simvastatin 6. Aspirin, losartan and simvastatin 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	US, Europe, Asia	Commercial	6000	1. Remdesivir 5 days 2. Remdesivir 10 days	WHO 7-point ordinal scale at 14 days post enrolment	No
COVIDMED (NCT04328012)	Comparison Of Therapeutics for Hospitalized Patients Infected With SARS-CoV-2	US	Commercial	3111	1. Lopinavir–ritonavir 2. Hydroxychloroquine 3. Losartan 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	1000	1. Lopinavir–ritonavir 2. Hydroxychloroquine 3. Baricitinib 4. Sarilumab 5. Standard of care		No

research organisations are also running trials, 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 owing to toxicity, lack of efficacy, or 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 broad-acting antiviral with activity against viral RNA-dependent RNA polymerase. It has been tested against other coronaviruses (SARS and MERS) and Ebola virus, but without sufficient data to allow registration.[15–17] While it is possible (or even likely) that there are current large trials that we have inadvertently omitted from this review, this is not likely to change the overall pattern of findings 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 it 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 that could serve their patients already exists. It is hoped that this article will help in this regard, along with the WHO metaregistry and COVID-19 trial summary websites mentioned above. 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 publicly available (Box 1). Even if joining an existing trial is not possible, harmonisation of trial design (eg, by using the same end points 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. Coordination 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: one in the pre-hospital space (PRINCIPLE; Box 3), one in non-severe hospital patients (RECOVERY; Box 5) and one in intensive care unit patients (REMAP-CAP; Box 5). Partly as a result of this policy (as well as the unfortunate explosion of COVID-19 case numbers in the UK), the RECOVERY trial randomised over 5000 patients within weeks of opening.

While some trials have already published their results,[18] generating intense media interest, none have been sufficiently powered to change practice, and all enrolled well under 1000 patients and have therefore not been described in this article. Ongoing key trials described here to which Australians have access include BRACE (Box 2), ASCOT (Box 4) and REMAP-CAP (Box 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. US 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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