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Ongoing Clinical Trials for the Management of the COVID-19 Pandemic

Mark P. Lythgoe[1,3,*] and Paul Middleton[2,3]

COVID-19 has rapidly developed into a worldwide pandemic with a significant health and economic burden. There are currently no approved treatments or preventative therapeutic strategies. Hundreds of clinical studies have been registered with the intention of discovering effective treatments. Here, we review currently registered interventional clinical trials for the treatment and prevention of COVID-19 to provide an overall summary and insight into the global response.

Race towards a Successful Intervention for Covid-19

Over the past two decades, three novel pathogenic human coronaviruses have emerged from animal reservoirs [1]. These are Middle East respiratory syndrome-related coronavirus (MERS-CoV), severe acute respiratory syndrome coronavirus (SARS-CoV), and, most recently, severe acute respiratory syndrome coronavirus 2 (referred to as COVID-19, SARS-CoV-2, or 2019-nCoV). All three have led to global health emergencies, with significant morbidity and mortality [2]. Before 2020, the largest outbreak was of SARS-CoV in 2003, which affected over 8000 individuals globally and was associated with 774 deaths (case fatality rate of 9.6%)[i] [3]. The overall cost to the global economy of SARS-CoV was estimated to be between US$30 billion and US$100 billion [4].

Following the first identification in patients with severe pneumonia in Wuhan province, China in November 2019, COVID-19 has spread rapidly and now affects all permanently inhabited continents. This is the greatest pandemic of modern times and has been declared a Public Health Emergency of International Concern by the WHO Director-General[ii]. As of 27 March 2020 (date of submission), COVID-19 was affecting 199 countries and territories, with >510 000 confirmed cases globally[iii]. It is associated with an estimated mortality of between 1% and 5%[iii]. Furthermore, human-to-human transmission has continued apace, despite escalating public health measures. Current estimates of the impact on the worldwide economy are US$1 trillion and rising[iv].

Currently, there are no approved therapies for either the treatment or prevention of COVID-19. With the predicted number of cases set to rise significantly, this represents a prodigious acute unmet medical need. Several national and international research groups are working collaboratively on a variety of preventative and therapeutic interventions. Potential avenues being explored include vaccine development, convalescent plasma, interferon-based therapies, small-molecule drugs, cell-based therapies, and monoclonal antibodies (mAbs) [5]. However, drug therapy development is a costly and timely process with a high attrition rate [6]. The speed of the normal drug development pathway is unacceptable in the context of the current global emergency. Therefore, there has been considerable interest in repurposing existing drugs and expediting developmental antiviral treatments, such as those for influenza, hepatitis B (HBV), hepatitis C (HCV), and filoviruses, to allow more rapid development [5]. The swift genomic sequencing of COVID-19 has facilitated this process, allowing comparison with MERS-CoV, SARS-CoV, and other morbific viruses [7]. This strategy has identified several genomic regions of interest

Glossary

Adalimumab: mAb targeted against TNF-α; an immunosuppressant commonly used in inflammatory conditions.
Anti-PD-1 antibody: antibody against Programmed Cell Death Protein 1 (PD-1); inhibition of PD-1 can reverse immune exhaustion; used in oncology treatment (e.g., melanoma).
ASC09: HIV protease inhibitor; under development by Ascletis Pharmaceuticals.
Aviptadil: a vasodilator and short-acting alpha-adrenoreceptor antagonist.
Azvudine: nucleoside reverse transcriptase inhibitor with efficacy against HCV and HIV.
Baloxavir marboxil: polymerase acidic endonuclease inhibitor approved for influenza.
Bevacizumab: mAb targeting vascular endothelial growth factor (VEGF).
Bismuth: oral medication used in treatment of *Helicobacter pylori*; some evidence of inhibition of SARS coronavirus helicase ATPase.
Blinding: experimental procedure in which the participant, investigator, care provider, or outcome assessor in a clinical trial are unaware of which treatment arm the participant is receiving. Studies can be described as the number of roles that are blinded (i.e., single, double or quadruple-blinded study). Blinding reduces the risk of bias in the outcome of a trial.
Carrimycin: macrolide antibiotic.
Cytokine-induced killer cells (CIK cell): $CD8^+$ T cells expanded from *ex vivo* stimulation of lymphocytes; used in experimental immunotherapy.
Cobicistat: CYP3A inhibitor licensed for use in HIV; potentiates action of other antiviral medication.
Danoprevir: NS3/4A protease inhibitor used in treatment of HCV.
Darunavir: HIV protease inhibitor.
Dexmedetomidine: sedative α2-adrenergic receptor agonist.
Dihydroartemisinin/piperaquine: combination antimalarial medication.
Dipyridamole: antiplatelet medication that is a phosphodiesterase inhibitor; exerts antiviral effects via inhibition of nucleoside uptake.
Double-blind: where two groups within a study, typically the participant and the outcome assessor, are blinded to the treatment received by the participant.
Ebastine: H_1 receptor antagonist.
Eculizumab: mAb that inhibits activation of complement protein C5; used in thrombotic microangiopathy.
Emtricitabine/tenofovir: combination nucleoside reverse transcriptase inhibitor used in the treatment of HIV-1.
Enoxaparin: low-molecular-weight heparin, an anticoagulant.
Favipiravir: RNA-dependent RNA polymerase inhibitor, investigated against RNA viruses, such as Influenza, Ebola and Marburg viruses.

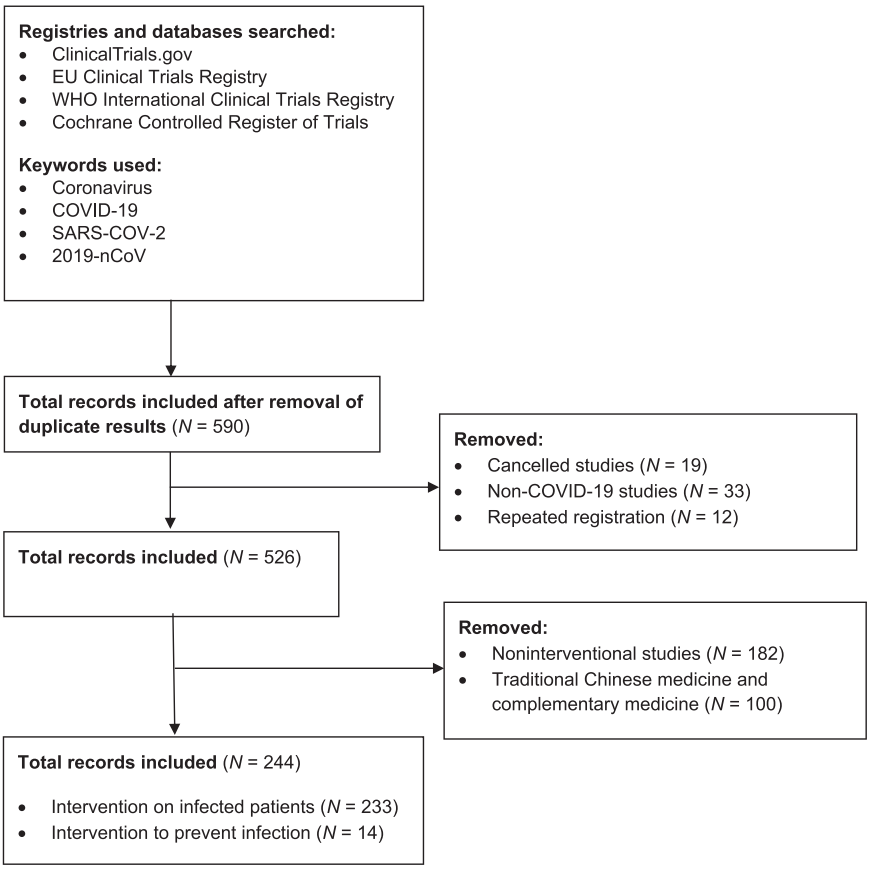

Figure 1. Flow Diagram Showing the Study Selection Process of Clinical Trials Discussed in This Article and Listed in Table 1 in the Main Text. Data in the WHO International Clinical Trials Registry were incorporated from various national registries, including those from Australia, New Zealand, China, The Netherlands, Brazil, India, Cuba, Republic of Korea, Germany, Iran, Japan, Sri Lanka, Thailand, and Peru, and also ClinicalTrials.gov, EU Clinical Trials registry, International Standard Randomised Controlled Trial Number (ISRCTN)[xi], and the Pan-African registries. Three studies included treatment for patients with COVID-19 and an intervention to prevention infection in uninfected patients.

for therapeutic modulation, specifically the identification of highly conserved regions involving viral enzymes between different pathogenic coronaviruses.

Exploring Current Clinical Trials for Covid-19

Since 2005, it has been recommended by the International Committee of Medical Journal Editors (ICMJE) that all clinical trials should be registered in publicly available domains before they may be considered for publication [8]. The introduction of this requirement and other initiatives to increase clinical trial transparency has contributed to an increasing number of trials being recorded in online registries, such as ClinicalTrials.gov[v] and the International Clinical Trials Registry Platform (ICTRP)[vi] of the WHO. The logging of trials on registries has vastly facilitated the dissemination of information across several domains, including intervention, methodology, patient group, and outcome measures. Furthermore, in the event of the nonpublication of results, it means that trial information remains freely available for analysis.

In the context of the current global COVID-19 pandemic, we performed an analysis of online registries (ClinicalTrials.gov[v], WHO

GD31: described within the trial report as novel nucleoside analogue.
Interferon alpha: cytokine used in the treatment of chronic viral infections, such as HBV and HCV.
Interferon beta 1b: cytokine used in the treatment of multiple sclerosis.
Leflunomide: immunosuppressive used in the treatment of rheumatoid arthritis.
Lipoic acid: antioxidant.
Losartan: angiotensin-II receptor antagonist.
Novaferon: recombinant interferon-like protein; *in vitro* and *in vivo* model evidence of more potent activity compared with interferon.
Open-label: a study in which the treatment received by the participant is known to both the participant and investigators.
Oseltamivir: neuraminidase inhibitor; licenced for influenza A and B treatment.
Pegasys: pegylated interferon alpha 2a.
Polyinosinic-polycytidylic acid: immunostimulant; TLR3 agonist.
PUL-042: immunostimulant; TLR2/6/9 agonist.
Randomised study: a trial in which the treatment or intervention is randomly allocated to a participant. Randomisation reduces the risk of bias in a trial outcome.
Recombinant IL-2: cytokine used in cancer immunotherapy treatment (e.g., melanoma).
Ribavirin: guanosine analogue; antiviral agent used against a range of morbific viral infections (e.g., HCV, human respiratory syncytial virus, and Lassa virus).
Ruxolitinib: selective inhibitor of Janus Kinase type 1 and 2; used within haematology against polycythaemia vera and myelofibrosis.
Sildenafil: phosphodiesterase type 5 inhibitor; vasodilator used commonly for erectile dysfunction and pulmonary arterial hypertension.
Sodium aescinate: saponin extract of *Aesculus hippocastanum* seeds; investigated for use in lung injury.
Sofosbuvir/daclatasvir: combination mediation used in treatment of HCV. Sofosbuvir is a nucleotide prodrug and acts as an inhibitor of HCV NS5B RNA-dependant RNA polymerase. Daclatasvir is an HCV NS5A inhibitor.
Sofosbuvir/ledipasvir: combination mediation used in treatment of HCV; Ledipasvir is an inhibitor of HCV NS5A protein.
Stem cell educator therapy: circulation of patient blood through a cell separator followed by brief co-culture of immune cells with cord-blood stem cells and return of the educated immune cells to the patient's circulation.
Suramin: antitrypanosomal drug used in treatment of African trypanosomiasis.
Tetrandrine: bisbenzylisoquinoline alkaloid; a calcium channel blocker with anti-inflammatory and immunosuppressant properties.
Thalidomide: antiangiogenic and immunomodulator used against a range of haematological malignancies, including multiple myeloma. Teratogenic antiemetic causing range of birth defects, such as phocomelia.

ICTRP[vi], EU Clinical Trials Register[vii], and Cochrane Central Register of Controlled Trials[viii]; Figure 1) to collate all registered therapeutic and preventative interventions under clinical investigation. We hope that this will clarify current investigational advances and guide potential future strategies. We identified 344 interventional studies focusing on both preventative strategies and the treatment of patients with COVID-19 (Figure 1) as of 20 March 2020. This search identified 100 studies that focused on forms of traditional Chinese medicine (TCM), including herbal medicines, acupuncture and other forms of complementary medicine. These have not been further analysed due to a lack of scientific rationale, inadequate provision of information regarding active ingredients, and limited applicability to mainstream medical practice. Table 1 (Key Table) shows interventional treatments (Table 1A) and preventative strategies (Table 1B) under clinical investigation for COVID-19.

Treatment Strategies

Antiviral Treatments

As briefly mentioned earlier, many studies have focused on repurposing established antiviral therapies, especially those that showed prior efficacy against SARS-CoV and MERS-CoV. The combination of lopinavir/ritonavir is the most common exploratory antiviral, appearing in 34 investigational studies (Table 1A: Antivirals). Both drugs function as protease inhibitors and are used extensively in the management of HIV-1 [9]. However, lopinavir has insufficient oral bioavailability for significant therapeutic activity, due to rapid catabolism by the cytochrome P450 enzyme system (specifically 3A4 isoenzyme) [9]. Thus, ritonavir is given concomitantly to inhibit this, significantly boosting the half-life of lopinavir. Lopinavir/ritonavir was investigated for efficacy against SARS-CoV in 2004 and found to be effective compared with a historical control [10]. However, efficacy was not seen in a **randomised open-label study** (see Glossary) (lopinavir/ritonavir versus standard care) in 199 patients with COVID-19 (Clinical Trial Number: ChiCTR2000029308, recruitment target stated as 160 participants in the registry; Table 1). No significant benefit was seen in either overall mortality or reduction in viral load [11]. The authors highlighted several limitations, including a lack of treatment **blinding**, with study participants and investigators being aware of treatment assignments, thus reducing study objectivity. While there are multiple other ongoing studies exploring lopinavir/ritonavir in COVID-19, none utilises a **double-blind** methodology to address this limitation.

Remdesivir is a novel nucleotide analogue antiviral, initially developed for the management of the Ebola and Marburg viruses [12,13]. However, it has efficacy against a range of pathogenic viruses, including both SARS-CoV and MERS-CoV in *in vitro* and *in vivo* models [12,14]. There has been much interest in this molecule, following treatment of the first COVID-19 case, and subsequent recovery, in the USA [15]. There are currently ten registered trials taking place globally to investigate efficacy for COVID-19 (Table 1A: Antivirals).

Several other antiviral drugs are being investigated, predominately those with activity against various influenza subtypes and other RNA viruses. These include **favipiravir** (T-705, Avigan), **umifenovir** (Arbidol), **triazavirin** (TZV), and **baloxavir marboxil** (Xofluza). Many trials are focusing on drugs typically used in the management of RNA viruses, such as HCV and HIV. These include **danoprevir**/ritonavir, **azvudine**, **sofosbuvir/ledipasvir**, **sofosbuvir/daclatasvir**, **darunavir**/**cobicistat,** and **emtricitabine/tenofovir** (Table 1A: Antivirals). Additionally, there are 26 studies investigating the utility of antiviral interferon-based treatments, interestingly also looking at various different routes of administration (e.g., nasal).

Thymosin: thymus hormones that stimulate development of T cells.
Tranilast: antiallergic analogue of a tryptophan metabolite; NLRP3 inflammasome inhibitor.
Triazavirin: guanine nucleotide analogue with broad-spectrum antiviral effects.
Umifenovir (Arbidol): non-nucleoside antiviral membrane fusion inhibitor; licensed in Russia for the treatment of influenza.

Antimalarial Treatments

Thirty-five trials are now investigating the use of the antimalarial drugs chloroquine and hydroxychloroquine against COVID-19 (Table 1A: Antimalarials). Chloroquine was found to have significant inhibitory effects on viral cell entry and replication *in vitro* [12]. An early report of clinical experience in 100 patients with COVID-19 reported both beneficial clinical and virological outcomes with chloroquine treatment [16]. More recently, a nonrandomised open-label study examining the effect of hydroxychloroquine (EU Clinical Trial Number[vii]: 2020-000890-25; recruitment target stated as 25 participants in the registry) reported on a cohort of 36 patients [17]. It reported a significant reduction in nasopharyngeal swab viral positivity 6 days after inclusion in the hydroxychloroquine group compared with control. However, in a deviation from their registry-described protocol, 16 patients were designated as controls and six patients received concurrent treatment with azithromycin to prevent bacterial superinfection. Selection of patients receiving azithromycin was based on clinical judgement. The subgroup receiving azithromycin all had negative viral swabs after 6 days compared with 57% (8/14) of hydroxychloroquine alone and 12.5% (2/16) of control [17]. This study is limited by its lack of randomisation and blinding, and small sample size. There is much interest in chloroquine or hydroxychloroquine for the treatment of COVID-19, with a further 34 studies registered (Table 1A: Antimalarials); however, only four report using a robust

Key Table

Table 1. Ongoing Clinical Trials for the (A) Treatment and (B) Prevention of COVID-19 (Current as of 20 March, 2020)[a]

Clinical trial ID (Registry)	Intervention[b]	Size[c]	Randomised	Blinded	Status	Country of origin (pharma sponsor)
(A) Ongoing clinical trials for treatment of COVID-19						
Antiviral						
ChiCTR2000029609 (ICTPR)	**Arm A** (mild–moderate): chloroquine **Arm B** (mild–moderate): lopinavir/ritonavir **Arm C** (mild–moderate): lopinavir/ritonavir + chloroquine **Arm D** (severe): lopinavir/ritonavir **Arm E** (severe): chloroquine	205	No	No	Recruiting	China
ChiCTR2000029600 (ICTPR)	**Arm A:** interferon alpha atomisation **Arm B** lopinavir/ritonavir and interferon alpha atomisation **Arm C:** favipiravir and interferon alpha atomisation	90	No	No	Recruiting	China
NCT04261270 (ClinicalTrials.gov)	**Arm A: ASC09** and **oseltamivir** **Arm B:** ritonavir and oseltamivir **Arm C:** oseltamivir	60	Yes	Single	Recruiting	China
NCT04261907 (ClinicalTrials.gov)	**Arm A:** ASC09/ritonavir **Arm B:** lopinavir/ritonavir	160	Yes	No	Recruiting	China (Ascletis Pharm)
ChiCTR2000030487 (ICTPR)	**Arm A:** azvudine	10	No	No	Recruiting	China
ChiCTR2000030424 (ICTPR)	**Arm A:** azvudine	30	No	No	Not recruiting	China
ChiCTR2000030041 (ICTPR)	**Arm A:** azvudine	40	No	No	Not recruiting	China
ChiCTR2000029853 (ICTPR)	**Arm A:** azvudine **Arm B:** standard treatment	20	Yes	No	Recruiting	China
ChiCTR2000029544 (ICTPR)	**Arm A:** baloxavir marboxil **Arm B:** favipiravir **Arm C:** standard treatment	30	Yes	Unspecified	Not recruiting	China
ChiCTR2000029548 (ICTPR)	**Arm A:** baloxavir marboxil **Arm B:** favipiravir **Arm C:** lopinavir/ritonavir	30	Yes	No	Not recruiting	China
ChiCTR2000030001 (ICTPR)	**Arm A:** basic treatment + triazavirin **Arm B:** basic treatment	240	Yes	Yes	Recruiting	China
NCT04273763 (ClinicalTrials.gov)	**Arm A:** bromhexine (mucolytic), umifenovir, interferon a2b, and favipiravir **Arm B:** umifenovir and interferon a2b	60	Yes	No	Recruiting	China (WanBangDe Pharm. Group)
ChiCTR2000030002 (ICTPR)	**Arm A:** conventional treatment **Arm B:** conventional treatment + **tranilast**	60	Yes	No	Recruiting	China
ChiCTR2000030472 (ICTPR)	**Arm A:** danoprevir/ritonavir **Arm B:** standard treatment	20	Unspecified	No	Recruiting	China
ChiCTR2000030259 (ICTPR)	**Arm A:** danoprevir/ritonavir **Arm B:** standard treatment	60	Yes	Unspecified	Recruiting	China
ChiCTR2000030000 (ICTPR)	**Arm A:** danoprevir/ritonavir **Arm B: Pegasys** **Arm C: Novaferon** **Arm D:** Coriolus	50	Unspecified	No	Recruiting	China

Table 1. (continued)

Clinical trial ID (Registry)	Intervention[b]	Size[c]	Randomised	Blinded	Status	Country of origin (pharma sponsor)
	Arm E: standard treatment					
NCT04252274 (ClinicalTrials.gov)	**Arm A:** darunavir and cobicistat **Arm B:** standard treatment	30	Yes	No	Recruiting	China
NCT04304053 (ClinicalTrials.gov)	**Arm A:** darunavir/cobicistat **Arm B:** isolation	3040	Yes	No	Recruiting	Spain
ChiCTR2000029541 (ICTPR)	**Arm A:** darunavir/cobicistat and **thymosin** **Arm B:** lopinavir/ritonavir and thymosin **Arm C:** thymosin	100	Yes	No	Not recruiting	China
NCT04291729 (ClinicalTrials.gov)	**Arm A:** darunavir/ritonavir and atomised interferon **Arm B:** peginterferon a2 **Arm C:** interferon alpha (Novaferon) **Arm D:** lopinavir/ritonavir **Arm E:** atomised interferon + Chinese medicine (unspecified)	50	No	No	Recruiting	China (Ascletis Pharmaceutical)
ChiCTR2000030535 (ICTPR)	**Arm A: ebastine** and **interferon** alpha inhalation and lopinavir **Arm B:** interferon alpha inhalation and lopinavir	100	Yes	Single	Recruiting	China
ChiCTR2000030113 (ICTPR)	**Arm A:** favipiravir **Arm B:** ritonavir	20	Yes	No	Recruiting	China
ChiCTR2000030254 (ICTPR)	**Arm A:** favipiravir **Arm B:** umifenovir	240	Yes	No	Recruiting	China
ChiCTR2000030987 (ICTPR)	**Arm A:** favipiravir and chloroquine **Arm B:** favipiravir **Arm C:** placebo	150	Yes	Unspecified	Recruiting	China
NCT04310228 (ClinicalTrials.gov)	**Arm A:** favipiravir and tocilizumab **Arm B:** favipiravir **Arm C:** tocilizumab	150	Yes	No	Recruiting	China
ChiCTR2000029895 (ICTPR)	**Arm A: GD31**	160	No	Unspecified	Recruiting	China
IRCT20100228003449N27 (ICTPR)	**Arm A:** hydroxychloroquine, lopinavir/ritonavir, and **interferon beta** 1b **Arm B:** hydroxychloroquine and lopinavir/ritonavir	30	Yes	No	Recruiting	Iran
IRCT20100228003449N28 (ICTPR)	**Arm A:** hydroxychloroquine, lopinavir/ritonavir, and interferon beta 1a **Arm B:** hydroxychloroquine and lopinavir/ritonavir	30	Yes	No	Recruiting	Iran
IRCT20100228003449N29 (ICTPR)	**Arm A:** hydroxychloroquine, lopinavir/ritonavir, and sofosbuvir/ledipasvir **Arm B:** hydroxychloroquine and lopinavir/ritonavir	50	Yes	No	Recruiting	Iran
JPRN-jRCTs041190120 (ICTPR)	**Arm A:** immediate favipiravir (Day 1–10) **Arm B:** delayed favipiravir (Day 6–15)	86	Yes	No	Recruiting	Japan
2020-001023-14 (EU-CTR)	**Arm A:** inhaled interferon alpha 1b **Arm B:** placebo	400	Yes	Double	Recruiting	UK (Synairgen Ltd)
ChiCTR2000029989	**Arm A:** interferon a1b eye drops	300	Yes	Unspecified	Not	China

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Table 1. (continued)

Clinical trial ID (Registry)	Intervention[b]	Size[c]	Randomised	Blinded	Status	Country of origin (pharma sponsor)
(ICTPR)	**Arm B:** placebo eye drops				recruiting	
NCT04293887 (ClinicalTrials.gov)	**Arm A:** interferon a1b nebulised **Arm B:** standard treatment	328	Yes	No	Not recruiting	China
ChiCTR2000030922 (ICTPR)	**Arm A:** interferon alpha 2a and **ribavirin** **Arm B:** umifenovir and ribavirin	30	Yes	Unspecified	Recruiting	China
ChiCTR2000029308 (ICTPR) [11]	**Arm A:** lopinavir/ritonavir **Arm B** standard treatment	160	Yes	No	Recruiting	China
NCT04307693 (ClinicalTrials.gov)	**Arm A:** lopinavir/ritonavir **Arm B:** hydroxychloroquine **Arm C:** no intervention	150	Yes	No	Recruiting	South Korea
ChiCTR2000030187 (ICTPR)	**Arm A:** lopinavir/ritonavir **Arm B:** standard of care	60	Yes	Unspecified	Recruiting	China
2020-001113-21 (EU-CTR)	**Arm A:** lopinavir/ritonavir **Arm B:** dexamethasone **Arm C:** interferon beta 1a **Arm D:** placebo	2000	Yes	No	Recruiting	UK
2020-000936-23 (EU-CTR)	**Arm A:** lopinavir/ritonavir **Arm B:** interferon beta 1a **Arm C:** remdesivir	3000	Yes	No	Recruiting	France
NCT04251871 (ClinicalTrials.gov)	**Arm A:** lopinavir/ritonavir and interferon alpha inhalation and traditional Chinese medicine **Arm B:** lopinavir/ritonavir and interferon alpha inhalation	150	Yes	No	Recruiting	China
ChiCTR2000029468 (ICTPR)	**Arm A:** lopinavir/ritonavir and emtricitabine/tenofovir **Arm B:** lopinavir/ritonavir	120	Unspecified	Unspecified	Not recruiting	China
JPRN-jRCTs031190227 (ICTPR)	**Arm A:** lopinavir/ritonavir and hydroxychloroquine	50	Unspecified	Unspecified	Not recruiting	Japan
ChiCTR2000030166 (ICTPR)	**Arm A:** lopinavir/ritonavir and interferon alpha 2b and Qing-Wen Bai-Du-Yin granules **Arm B:** lopinavir/ritonavir and interferon alpha 2b	20	Yes	No	Not recruiting	China
ChiCTR2000030218 (ICTPR)	**Arm A:** lopinavir/ritonavir and Xiyanping injection **Arm B:** ritonavir	80	Unspecified	Unspecified	Recruiting	China
NCT04252885 (ClinicalTrials.gov)	**Arm A:** lopinavir/ritonavir + basic treatment (unspecified) **Arm B:** umifenovir + basic treatment (unspecified) **Arm C:** basic treatment (unspecified)	125	Yes	No	Recruiting	China
NCT04276688 (ClinicalTrials.gov)	**Arm A:** lopinavir/ritonavir + ribavirin + interferon beta 1b **Arm B:** lopinavir/ritonavir	70	Yes	No	Recruiting	Hong Kong
ChiCTR2000029539 (ICTPR)	**Arm A:** lopinavir/ritonavir **Arm B:** standard treatment	328	Yes	No	Recruiting	China
ChiCTR2000029996 (ICTPR)	**Arm A:** low-dose favipiravir **Arm B:** medium-dose favipiravir **Arm C:** high-dose favipiravir	60	Yes	No	Recruiting	China
ChiCTR2000029638 (ICTPR)	**Arm A:** nebulised rSIFN-co **Arm B:** nebulised interferon alpha	100	Yes	Yes	Recruiting	China

Table 1. (continued)

Clinical trial ID (Registry)	Intervention[b]	Size[c]	Randomised	Blinded	Status	Country of origin (pharma sponsor)
ChiCTR2000029496 (ICTPR)	**Arm A:** Novaferon atomisation inhalation **Arm B:** lopinavir/ritonavir **Arm C:** Novaferon and lopinavir/ritonavir	90	Yes	No	Recruiting	China
NCT04303299 (ClinicalTrials.gov)	**Arm A:** oseltamivir and chloroquine **Arm B:** lopinavir/ritonavir and favipiravir **Arm C:** lopinavir/ritonavir and oseltamivir **Arm D:** lopinavir/ritonavir and oseltamivir **Arm E:** favipiravir and lopinavir/ritonavir **Arm F:** darunavir/ritonavir, oseltamivir, and chloroquine **Arm G:** standard treatment	80	Yes	No	Not recruiting	Thailand
NCT04302766 (ClinicalTrials.gov)	**Arm A:** remdesivir	Unspecified	Unspecified	Unspecified	Available	USA
NCT04292899 (ClinicalTrials.gov)	**Arm A:** remdesivir **Arm B:** standard treatment	400	Yes	No	Recruiting	USA and Asia (Gilead)
NCT04292730 (ClinicalTrials.gov)	**Arm A:** remdesivir **Arm B:** standard treatment	600	Yes	No	Recruiting	USA and Asia (Gilead)
NCT04280705 (ClinicalTrials.gov)	**Arm A:** remdesivir **Arm B:** placebo	394	Yes	Double	Recruiting	USA and South Korea
2020-000841-15 (EU-CTR)	**Arm A:** remdesivir **Arm B:** standard treatment	400	Yes	No	Recruiting	Worldwide (Gilead)
2020-000842-32 (EU-CTR)	**Arm A:** remdesivir **Arm B:** standard treatment	600	Yes	No	Recruiting	Worldwide (Gilead)
NCT04252664 (ClinicalTrials.gov)	**Arm A:** remdesivir **Arm B:** placebo	308	Yes	Quadruple	Recruiting	China
NCT04257656 (ClinicalTrials.gov)	**Arm A:** remdesivir **Arm B:** placebo	453	Yes	Quadruple	Recruiting	China
NCT04315948 (ClinicalTrials.gov)	**Arm A:** remdesivir **Arm B:** lopinavir/ritonavir **Arm C:** lopinavir/ritonavir and interferon beta 1a **Arm D:** hydroxychloroquine **Arm E:** standard treatment	3100	Yes	No	Recruiting	France
ChiCTR2000029387 (ICTPR)	**Arm A:** ribavirin and interferon alpha-1b **Arm B:** lopinavir/ritonavir, and interferon alpha-1b **Arm C:** ribavirin, lopinavir/ritonavir, and interferon alpha-1b	108	Unspecified	Unspecified	Recruiting	China
IRCT20200128046294N2 (ICTPR)	**Arm A: sofosbuvir/daclatasvir** **Arm B:** standard treatment	70	Yes	Single	Recruiting	Iran
ChiCTR2000029400 (ICTPR)	**Arm A:** traditional Chinese medicine **Arm B:** lopinavir/ritonavir **Arm C:** traditional Chinese medicine and lopinavir/ritonavir	60	Unspecified	Unspecified	Recruiting	China
ChiCTR2000030262 (ICTPR)	**Arm A:** type 1 interferon and TFF2 dose 1 **Arm B:** type 1 interferon and TFF2 dose 2 **Arm C:** standard treatment	30	Yes	Unspecified	Recruiting	China

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Table 1. (continued)

Clinical trial ID (Registry)	Intervention[b]	Size[c]	Randomised	Blinded	Status	Country of origin (pharma sponsor)
ChiCTR2000029573 (ICTPR)	**Arm A:** umifenovir **Arm B:** Novaferon and umifenovir **Arm C:** lopinavir/ritonavir **Arm D:** umifenovir **Arm E:** novaferon and lopinavir/ritonavir **Arm F:** novaferon and umifenovir	480	Yes	No	Not recruiting	China
ChiCTR2000029621 (ICTPR)	**Arm A:** umifenovir **Arm B:** standard treatment	380	Yes	No	Recruiting	China
NCT04254874 (ClinicalTrials.gov)	**Arm A:** umifenovir **Arm B:** umifenovir and pegylated interferon alpha 2b	100	Yes	Single	Recruiting	China
NCT04255017 (ClinicalTrials.gov)	**Arm A:** umifenovir **Arm B:** oseltamivir **Arm C:** lopinavir/ritonavir	400	Yes	Single	Recruiting	China
ChiCTR2000029993 (ICTPR)	**Arm A:** umifenovir and Liushen capsule **Arm B:** standard treatment	40	Yes	No	Recruiting	China
NCT04275388 (ClinicalTrials.gov)	**Arm A:** Xiyanping injection, lopinavir/ritonavir and interferon alpha nebulisation **Arm B:** lopinavir/ritonavir and interfer n alpha nebulisation	348	Yes	No	Not recruiting	China (Jiangxi Qingfeng Pharmaceutical)
Antimalarial						
ChiCTR2000030031 (ICTPR)	**Arm A:** chloroquine **Arm B:** placebo	120	Yes	Double	Recruiting	China
ChiCTR2000029988 (ICTPR)	**Arm A:** chloroquine **Arm B:** standard treatment	80	Unspecified	Unspecified	Recruiting	China
ChiCTR2000029975 (ICTPR)	**Arm A:** chloroquine	10	No	Unspecified	Not recruiting	China
ChiCTR2000029939 (ICTPR)	**Arm A:** chloroquine **Arm B:** standard treatment	100	Yes	Single	Recruiting	China
ChiCTR2000029935 (ICTPR)	**Arm A:** chloroquine	100	No	Unspecified	Recruiting	China
ChiCTR2000029837 (ICTPR)	**Arm A:** chloroquine **Arm B:** placebo	120	Yes	Double	Not recruiting	China
ChiCTR2000029826 (ICTPR)	**Arm A:** chloroquine **Arm B:** placebo	45	Yes	Double	Not recruiting	China
ChiCTR2000029542 (ICTPR)	**Arm A:** chloroquine **Arm B:** standard treatment	20	Unspecified	Unspecified	Recruiting	China
ChiCTR2000029741 (ICTPR)	**Arm A:** chloroquine **Arm B:** lopinavir/ritonavir	112	Yes	No	Recruiting	China
ChiCTR2000030718 (ICTPR)	**Arm A:** chloroquine **Arm B:** standard treatment	80	Yes	No	Recruiting	China
ChiCTR2000029992 (ICTPR)	**Arm A:** chloroquine and hydroxychloroquine **Arm B:** standard treatment	100	Yes	No	Not recruiting	China
ChiCTR2000030417 (ICTPR)	**Arm A:** chloroquine aerosol inhalation **Arm B** water aerosol inhalation	30	Unspecified	Unspecified	Not recruiting	China
ChiCTR2000030082 (ICTPR)	**Arm A:** **dihydroartemisinin/piperaquine** tablets combined with antiviral	40	Yes	No	Suspended	China

Table 1. (continued)

Clinical trial ID (Registry)	Intervention[b]	Size[c]	Randomised	Blinded	Status	Country of origin (pharma sponsor)
	treatment (presumed alpha-interferon + umifenovir) **Arm B:** alpha-interferon + umifenovir					
ChiCTR2000029898 (ICTPR)	**Arm A:** hydroxychloroquine **Arm B:** chloroquine	100	Yes	No	Recruiting	China
NCT04261517 (ClinicalTrials.gov)	**Arm A:** hydroxychloroquine **Arm B:** standard of care	30	Yes	No	Recruiting	China
ChiCTR2000030054 (ICTPR)	**Arm A:** hydroxychloroquine **Arm B:** standard treatment	100	Yes	No	Not recruiting	China
ChiCTR2000029868 (ICTPR)	**Arm A:** hydroxychloroquine **Arm B:** standard treatment	200	Yes	Unspecified.	Recruiting	China
ChiCTR2000029740 (ICTPR)	**Arm A:** hydroxychloroquine **Arm B:** standard treatment	78	Yes	No	Recruiting	China
ChiCTR2000029559 (ICTPR)	**Arm A:** hydroxychloroquine **Arm B:** hydroxychloroquine **Arm C:** placebo	300	Unspecified	Unspecified	Recruiting	China
2020-000890-25 (EU-CTR) [17]	**Arm A:** hydroxychloroquine	25	No	No	Recruiting	France
ChiCTR2000029899 (ICTPR)	**Arm A:** hydroxychloroquine **Arm B:** chloroquine	100	Yes	No	Recruiting	China
NCT04315896 (ClinicalTrials.gov)	**Arm A:** hydroxychloroquine **Arm B:** placebo	500	Yes	Quadruple	Not recruiting	Mexico
NCT04316377 (ClinicalTrials.gov)	**Arm A:** hydroxychloroquine **Arm B:** standard treatment	202	Yes	No	Not recruiting	Norway
Immunosuppressants						
NCT04263402 (ClinicalTrials.gov)	**Arm A:** methylprednisolone (<40 mg/day) **Arm B:** methylprednisolone (40–80 mg/day)	100	Yes	Single	Recruiting	China
ChiCTR2000030089 (ICTPR)	**Arm A:** conventional treatment + adalimumab **Arm B:** conventional treatment	60	Yes	No	Not yet recruiting	China
ChiCTR2000030481 (ICTPR)	**Arm A:** early corticosteroid intervention **Arm B:** middle–late corticosteroid intervention **Arm C:** standard care	200	Yes	No	Recruiting	China
NCT04288713 (ClinicalTrials.gov)	**Arm A:** eculizumab	Unspecified	Unspecified	Unspecified	Available	USA
NCT04280588 (ClinicalTrials.gov)	**Arm A:** fingolimod **Arm B:** standard treatment	30	No	No	Recruiting	China
ChiCTR2000030703 (ICTPR)	**Arm A:** ixekizumab and antiviral therapy **Arm B:** antiviral therapy	40	Yes	Single	Recruiting	China
NCT04275245 (ClinicalTrials.gov) [20]	**Arm A:** meplazumab	20	No	No	Recruiting	China
NCT04273321 (ClinicalTrials.gov)	**Arm A:** methylprednisolone **Arm B:** standard treatment	400	Yes	No	Recruiting	China
NCT04244591 (ClinicalTrials.gov)	**Arm A:** methylprednisolone **Arm B:** standard treatment	80	Yes	No	Recruiting	China
ChiCTR2000029656 (ICTPR)	**Arm A:** methylprednisolone **Arm B:** standard treatment	100	Yes	No	Not recruiting	China

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Table 1. (continued)

Clinical trial ID (Registry)	Intervention[b]	Size[c]	Randomised	Blinded	Status	Country of origin (pharma sponsor)
ChiCTR2000029386 (ICTPR)	**Arm A:** methylprednisolone **Arm B:** standard treatment	48	Yes	Unspecified	Recruiting	China
NCT04315298 (ClinicalTrials.gov)	**Arm A:** sarilumab high dose **Arm B:** sarilumab low dose **Arm C:** placebo	400	Yes	Quadruple	Recruiting	USA (Regeneron Pharmaceuticals)
ChiCTR2000030058 (ICTPR)	**Arm A:** standard treatment + **leflunomide** **Arm B:** standard treatment + placebo	200	Yes	Yes	Not yet recruiting	China
ChiCTR2000030196 (ICTPR)	**Arm A:** tocilizumab	60	No	No	Not recruiting	China
ChiCTR2000029765 (ICTPR)	**Arm A:** tocilizumab **Arm B:** standard treatment	188	Yes	Unspecified	Recruiting	China
NCT04315480 (ClinicalTrials.gov)	**Arm A:** tocilizumab	30	No	No	Not recruiting	France
NCT04317092 (ClinicalTrials.gov)	**Arm A:** tocilizumab	330	No	No	Recruiting	Italy
ChiCTR2000030442 (ICTPR)	**Arm A:** tocilizumab, IVIG, and CCRT	100	No	Unspecified	Not recruiting	China
ChiCTR2000030580 (ICTPR)	**Arm A:** tozumab[d] and adalimumab **Arm B:** standard treatment	60	Yes	Unspecified	Recruiting	China
Immune modulators						
NCT04317040 (ClinicalTrials.gov)	**Arm A:** CD24Fc **Arm B:** placebo	230	Yes	Quadruple	Not recruiting	USA (OncoImmune)
ChiCTR2000029776 (ICTPR)	**Arm A:** conventional treatment + **polyinosinic-polycytidylic acid** **Arm B:** conventional treatment	40	Yes	No	Recruiting	China
NCT04299724 (ICTPR)	**Arm A:** Covid-19/aAPC vaccine	100	No	No	Recruiting	China
ChiCTR2000030939 (ICTPR)	**Arm A:** CSA0001	10	Yes	Unspecified	Recruiting	China
ChiCTR2000030016 (ICTPR)	**Arm A:** inhaled inactive *Mycobacterium* vaccine **Arm B:** inhaled physiological saline	60	Yes	Yes	Recruiting	China
ChiCTR2000030167 (ICTPR)	**Arm A:** interleukin-2 **Arm B:** standard treatment	80	Yes	Unspecified	Not recruiting	China
NCT04261426 (ClinicalTrials.gov)	**Arm A:** IVIG **Arm B:** standard treatment	80	Yes	No	Not recruiting	China
NCT04276896 (ICTPR)	**Arm A:** LV-SMENP-DC vaccine and antigen specific cytotoxic T cells	100	No	No	Recruiting	China
NCT04268537 (ClinicalTrials.gov)	**Arm A:** PD-1-blocking Ab **Arm B:** thymosin **Arm C:** standard treatment	120	Yes	Single	Not recruiting	China
ChiCTR2000030028 (ICTPR)	**Arm A:** PD-1 mAb + standard treatment **Arm B:** standard treatment	40	Yes	No	Not yet recruiting	China
NCT04312997 (ClinicalTrials.gov)	**Arm A: PUL-042** nebuliser **Arm B:** sterile saline inhaler	100	Yes	Quadruple	Not recruiting	USA (Pulmotect)
ChiCTR2000030750 (ICTPR)	**Arm A:** recombinant chimeric DC vaccine **Arm B:** normal saline	120	Yes	Unspecified	Not recruiting	China
ChiCTR2000030007 (ICTPR)	**Arm A:** standard treatment + rhG-CSF **Arm B:** standard treatment	200	Yes	No	Not yet recruiting	China

Table 1. (continued)

Clinical trial ID (Registry)	Intervention[b]	Size[c]	Randomised	Blinded	Status	Country of origin (pharma sponsor)
ChiCTR2000029636 (ICTPR)	**Arm A:** standard treatment and vMIP atomised inhalation	40	No	No	Recruiting	China
ChiCTR2000029806 (ICTPR)	**Arm A:** subcutaneous thymosin **Arm B:** camrelizumab infusion **Arm C:** conventional treatment	120	Yes	No	Recruiting	China
ChiCTR2000030779 (ICTPR)	**Arm A: ulinastatin** (trypsin inhibitor) **Arm B:** standard treatment	100	Yes	No	Recruiting	China
Cytokine removal						
ChiCTR2000030475 (ICTPR)	**Arm A:** CytoSorb cytokine removal	19	No	No	Not recruiting	China
ChiCTR2000030477 (ICTPR)	**Arm A:** oXiris membrane	19	No	No	Not recruiting	China
ChiCTR2000030265 (ICTPR)	**Arm A:** oXiris membrane **Arm B:** standard treatment	30	Unspecified	Unspecified	Not recruiting	China
ChiCTR2000030835 (ICTPR)	**Arm A:** high-dose MSCs **Arm B:** low-dose MSCs	20	No	Unspecified	Recruiting	China
ChiCTR2000029817 (ICTPR)	**Arm A:** high-dose NK cells and MSCs **Arm B:** conventional-dose NK cells and MSCs **Arm C:** preventive-dose NK cells and MSCs	60	Unspecified	Unspecified	Not recruiting	China (Guangchou Reborn Health Management Co)
ChiCTR2000029606 (ICTPR)	**Arm A:** menstrual blood-derived stem cells **Arm B:** artificial liver therapy **Arm C:** artificial liver therapy and menstrual blood-derived stem cells **Arm D:** standard treatment	73	Unspecified	Unspecified	Recruiting	China
NCT04315987 (ClinicalTrials.gov)	**Arm A:** MSCs	24	No	No	Not recruiting	Brazil (Cellavita Pesquisa Cientifica Ltd)
NCT04276987 (ClinicalTrials.gov)	**Arm A:** MSC-derived exosomes	30	No	No	Not recruiting	China (Cellular Biomedicine Group)
NCT04288102 (ClinicalTrials.gov)	**Arm A:** MSCs **Arm B:** placebo	60	Yes	Quadruple	Recruiting	China
NCT04252118 (ClinicalTrials.gov)	**Arm A:** MSCs **Arm B:** standard treatment	20	No	No	Recruiting	China (IPM, Vcanbio Cell and Gene Engineering)
ChiCTR2000030300 (ICTPR)	**Arm A:** MSCs	9	No	Unspecified	Recruiting	China
ChiCTR2000030224 (ICTPR)	**Arm A:** MSCs **Arm B:** normal saline	32	Unspecified	Unspecified	Not recruiting	China
ChiCTR2000030173 (ICTPR)	**Arm A:** MSCs **Arm B:** standard treatment	60	Unspecified	Unspecified	Not recruiting	China (Hunan yuanpin Cell Biotech)
ChiCTR2000030020 (ICTPR)	**Arm A:** MSCs	20	No	No	Recruiting	China
ChiCTR2000029990 (ICTPR) [22]	**Arm A:** MSCs **Arm B:** saline	120	Yes	Unspecified	Recruiting	China
ChiCTR2000030261 (ICTPR)	**Arm A:** MSC-derived exosomes **Arm B:** standard treatment	26	Unspecified	Unspecified	Not recruiting	China

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Table 1. (continued)

Clinical trial ID (Registry)	Intervention[b]	Size[c]	Randomised	Blinded	Status	Country of origin (pharma sponsor)
NCT04280224 (ClinicalTrials.gov)	**Arm A:** NK cells **Arm B:** standard treatment	30	Yes	No	Recruiting	China
ChiCTR2000030509 (ICTPR)	**Arm A:** NK cells **Arm B:** electrolyte injection	40	Unspecified	Unspecified	Not recruiting	China
ChiCTR2000030944 (ICTPR)	**Arm A:** NK cells and MSC **Arm B:** standard treatment	20	Yes	No	Not recruiting	China
NCT04302519 (ClinicalTrials.gov)	**Arm A:** pulp MSCs	24	No	No	Not recruiting	China (CAR-T Biotechnology Co, Ltd)
ChiCTR2000029580 (ICTPR)	**Arm A: ruxolitinib** and MSCs **Arm B:** standard treatment	70	Yes	Single	Recruiting	China
NCT04299152 (ClinicalTrials.gov)	**Arm A: stem cell educator therapy** **Arm B:** standard treatment	20	Yes	Single	Not recruiting	USA (Tianhe Stem Cell Biotechnologies Inc)
ChiCTR2000030329 (ICTPR)	**Arm A:** umbilical cord blood **CIK** cells **Arm B** umbilical cord NK cells **Arm C:** standard treatment	90	Unspecified	Unspecified	Not recruiting	China
ChiCTR2000029812 (ICTPR)	**Arm A:** umbilical cord blood mononuclear cell preparations **Arm B:** standard treatment	60	Unspecified	Unspecified	Not recruiting	China (Guangzhou Reborn Health Management Consultation Co)
ChiCTR2000029572 (ICTPR)	**Arm A:** umbilical cord blood mononuclear cells **Arm B:** standard treatment	30	Yes	Unspecified	Recruiting	China
ChiCTR2000029818 (ICTPR)	**Arm A:** umbilical cord blood plasma preparations **Arm B:** standard treatment	60	Unspecified	Unspecified	Not recruiting	China (Guangzhou Reborn Health Management Consultation Co)
NCT04293692 (ClinicalTrials.gov)	**Arm A:** umbilical cord MSCs **Arm B:** placebo	48	Yes	Triple	Withdrawn	China (Wuhan Hamilton Biotechnology)
NCT04273646 (ClinicalTrials.gov)	**Arm A:** umbilical cord MSCs **Arm B:** placebo	48	Yes	No	Not recruiting	China (Wuhan Biotechnology)
NCT04269525 (ClinicalTrials.gov)	**Arm A:** umbilical cord MSCs	10	No	No	Recruiting	China (Tuohua Biological Technology Co)
ChiCTR2000030138 (ICTPR)	**Arm A:** umbilical cord MSCs **Arm B:** placebo	60	Yes	Double	Not recruiting	China
ChiCTR2000030484 (ICTPR)	**Arm A:** umbilical cord MSCs **Arm B:** umbilical cord MSCs and derived exosomes **Arm C:** placebo	120	Unspecified	Unspecified	Not recruiting	China
ChiCTR2000030116 (ICTPR)	**Arm A:** umbilical cord MSCs dose A **Arm B** umbilical cord MSCs dose B	16	Yes	Unspecified	Recruiting	China
ChiCTR2000029816 (ICTPR)	**Arm A:** umbilical cord MSCs **Arm B:** standard treatment	60	Yes	No	Not recruiting	China (Guangzhou Reborn Health Management)
NCT04313322 (ClinicalTrials.gov)	**Arm A:** Wharton jelly MSCs	5	No	No	Recruiting	Jordan (Stem Cells Arabia)
ChiCTR2000030088 (ICTPR)	**Arm A:** Wharton jelly MSCs **Arm B:** saline	20	Yes	Unspecified	Not recruiting	China

Table 1. (continued)

Clinical trial ID (Registry)	Intervention[b]	Size[c]	Randomised	Blinded	Status	Country of origin (pharma sponsor)
Plasma-based therapy						
ChiCTR2000030702 (ICTPR)	**Arm A:** convalescent plasma therapy **Arm B:** standard treatment	50	Yes	No	Recruiting	China
ChiCTR2000030046 (ICTPR)	**Arm A:** anti-2019-nCoV virus inactivated plasma	10	No	No	Recruiting	China
ChiCTR2000030381 (ICTPR)	**Arm A:** anti-SARS-CoV-2 inactivated convalescent plasma **Arm B:** ordinary plasma	40	Yes	No	Not recruiting	China
ChiCTR2000030010 (ICTPR)	**Arm A:** anti-SARS-CoV-2 virus inactivated plasma **Arm B:** ordinary plasma	100	Yes	Double	Not recruiting	China
ChiCTR2000030841 (ICTPR)	**Arm A:** convalescent immunoglobulin **Arm B:** gamma-globulin	10	No	No	Recruiting	China
NCT04264858 (ClinicalTrials.gov)	**Arm A:** convalescent immunoglobulin **Arm B:** gamma globulin	10	No	No	Not recruiting	China
ChiCTR2000030039 (ICTPR)	**Arm A:** convalescent plasma **Arm B:** standard treatment	90	No	No	Recruiting	China
ChiCTR2000029850 (ICTPR)	**Arm A:** convalescent plasma **Arm B:** standard treatment	20	No	Unspecified	Recruiting	China
ChiCTR2000030627 (ICTPR)	**Arm A:** convalescent plasma therapy **Arm B:** standard treatment	30	Yes	Unspecified	Recruiting	China
ChiCTR2000029757 (ICTPR)	**Arm A:** convalescent plasma therapy **Arm B:** standard treatment	200	Yes	No	Recruiting	China
ChiCTR2000030929 (ICTPR)	**Arm A:** convalescent plasma therapy **Arm B:** control plasma	60	Yes	Double	Not recruiting	China
ChiCTR2000030179 (ICTPR)	**Arm A:** plasma treatment **Arm B:** standard treatment	100	Yes	Unspecified	Recruiting	China
Inhaled gas						
ChiCTR2000030258 (ICTPR)	**Arm A:** hydrogen inhalation[e] **Arm B:** standard treatment	60	Yes	No	Not recruiting	China
ChiCTR2000029739 (ICTPR)	**Arm A:** hydrogen–oxygen nebuliser **Arm B:** oxygen	440	Yes	Unspecified	Recruiting	China
NCT04290871 (ClinicalTrials.gov)	**Arm A:** inhaled nitric oxide **Arm B:** no intervention	104	Yes	Yes	Not yet recruiting	China
NCT04306393 (ClinicalTrials.gov)	**Arm A:** inhaled nitric oxide **Arm B:** no intervention	200	Yes	Yes	Not yet recruiting	USA
NCT04305457 (ClinicalTrials.gov)	**Arm A:** inhaled nitric oxide **Arm B:** no intervention	240	Yes	No	Not yet recruiting	USA
NCT04290858 (ClinicalTrials.gov)	**Arm A:** inhaled nitric oxide **Arm B:** no intervention	240	Yes	No	Not yet recruiting	China
Antifibrotic						
NCT04282902 (ClinicalTrials.gov)	**Arm A:** pirfenidone **Arm B:** standard treatment	294	Yes	No	Recruiting	China
ChiCTR2000030892 (ICTPR)	**Arm A:** pirfenidone **Arm B:** standard treatment	20	Yes	No	Recruiting	China
ChiCTR2000030333 (ICTPR)	**Arm A:** pirfenidone **Arm B:** standard treatment	292	Yes	No	Recruiting	China
Antiangiogenic						
NCT04275414	**Arm A:** bevacizumab	20	No	No	Recruiting	China

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Table 1. (continued)

Clinical trial ID (Registry)	Intervention[b]	Size[c]	Randomised	Blinded	Status	Country of origin (pharma sponsor)
(ClinicalTrials.gov)						
NCT04305106 (ClinicalTrials.gov)	**Arm A:** bevacizumab **Arm B:** standard treatment	118	Yes	Triple	Recruiting	China
NCT04273581 (ClinicalTrials.gov)	**Arm A:** thalidomide **Arm B:** placebo	40	Yes	Quadruple	Not recruiting	China
NCT04273529 (ClinicalTrials.gov)	**Arm A:** thalidomide **Arm B:** placebo	100	Yes	Quadruple	Not recruiting	China
Antimicrobial						
ChiCTR2000030539 (ICTPR)	**Arm A:** 3% hydrogen peroxide gargle **Arm B:** standard treatment	40	Unspecified	Unspecified	Not recruiting	China
ChiCTR2000029867 (ICTPR)	**Arm A: carrimycin** **Arm B:** lopinavir/ritonavir	520	Yes	No	Recruiting	China
NCT04286503 (ClinicalTrials.gov)	**Arm A:** carrimycin + basic treatment (unspecified) **Arm B:** lopinavir/ritonavir or umifenovir or chloroquine phosphate + basic treatment (unspecified)	520	Yes	No	Recruiting	China (Shenyang Tonglian Group)
ChiCTR2000030029 (ICTPR)	**Arm A: suramin**	20	No	No	Not yet recruiting	China
Antioxidants						
ChiCTR2000029851 (ICTPR)	**Arm A:** alpha **lipoic acid** **Arm B:** placebo	68	Yes	Unspecified	Recruiting	China
ChiCTR2000030471 (ICTPR)	**Arm A:** lipoic acid injection **Arm B:** standard treatment	384	Yes	Single	Recruiting	China
Microbiome						
ChiCTR2000030897 (ICTPR)	**Arm A:** Newgen beta-gluten probiotic **Arm B:** standard treatment	20	Yes	Unspecified	Recruiting	China
ChiCTR2000029999 (ICTPR)	**Arm A:** probiotics **Arm B:** probiotics	60	No	No	Not recruiting	China
ChiCTR2000029974 (ICTPR)	**Arm A:** probiotics **Arm B:** standard treatment	300	Yes	No	Recruiting	China (Qingdao East Sea Pham.)
ChiCTR2000029849 (ICTPR)	**Arm A:** Unspecified intestinal flora intervention **Arm B:** standard treatment	60	Yes	Unspecified	Recruiting	China
NCT04251767 (ClinicalTrials.gov)	**Arm A:** washed microbiota transplant **Arm B:** placebo	40	Yes	Quadruple	Enrolling by invitation	China
Organ support						
ChiCTR2000030503 (ICTPR)	**Arm A:** artificial liver system **Arm B:** standard treatment	60	No	No	Recruiting	China
ChiCTR2000030540 (ICTPR)	**Arm A:** CRRT **Arm B:** CRRT only for emergency indication	152	Unspecified	Unspecified	Not recruiting	China
ChiCTR2000030761 (ICTPR)	**Arm A:** CRRT	20	No	No	Not recruiting	China
ChiCTR2000030744 (ICTPR)	**Arm A:** ECMO **Arm B:** standard treatment	30	No	No	Recruiting	China
ChiCTR2000030855 (ICTPR)	**Arm A:** external diaphragmatic pacing	200	No	No	Not recruiting	China
ChiCTR2000030773 (ICTPR)	**Arm A:** Unspecified blood purification	20	No	No	Recruiting	China

Table 1. (continued)

Clinical trial ID (Registry)	Intervention[b]	Size[c]	Randomised	Blinded	Status	Country of origin (pharma sponsor)
Therapy interventions						
ChiCTR2000030260 (ICTPR)	**Arm A:** enteral nutrition emulsion **Arm B:** standard treatment	20	Yes	No	Not recruiting	China
ChiCTR2000030198 (ICTPR)	**Arm A:** health education and pulmonary rehabilitation **Arm B:** health education	60	Unspecified	Unspecified	Not recruiting	China
ChiCTR2000030418 (ICTPR)	**Arm A:** lung rehabilitation **Arm B:** usual activity	80	Unspecified	Unspecified	Recruiting	China
ChiCTR2000030578 (ICTPR)	**Arm A:** lung rehabilitation training **Arm B:** standard treatment	40	Unspecified	Unspecified	Not recruiting	China
NCT04283825 (ClinicalTrials.gov)	**Arm A:** psychological and physical rehabilitation **Arm B:** standard treatment	100	No	No	Not recruiting	China
ChiCTR2000030084 (ICTPR)	**Arm A:** psychological intervention **Arm B:** standard treatment	180	Unspecified	Unspecified	Recruiting	China
ChiCTR2000030467 (ICTPR)	**Arm A:** psychological intervention and traditional Chinese medicine **Arm B:** psychological intervention, traditional Chinese medicine, and traditional Chinese medicine psychological intervention	60	Unspecified	Unspecified	Not recruiting	China
ChiCTR2000029459 (ICTPR)	**Arm A:** pulmonary rehabilitation **Arm B:** standard treatment	50	Unspecified	Unspecified	Not recruiting	China
ChiCTR2000030433 (ICTPR)	**Arm A:** rehabilitation and lung eight-segment exercise[f]	80	No	No	Not recruiting	China
ChiCTR2000029460 (ICTPR)	**Arm A:** shadowboxing rehabilitation **Arm B:** standard treatment	100	Yes	No	Not recruiting	China
Ozonated autohemotherapy						
ChiCTR2000030165 (ICTPR)	**Arm A:** conventional treatment **Arm B** (mild): conventional treatment + ozonated autohemotherapy **Arm C** (severe): conventional treatment + ozonated autohemotherapy	60	No	No	Recruiting	China
ChiCTR2000030102 (ICTPR)	**Arm A:** conventional treatment **Arm B:** conventional treatment + ozone therapy **Arm C** (severe): conventional treatment + ozone therapy **Arm D** (severe): conventional treatment **Arm E** (critical): conventional treatment + ozone therapy **Arm F** (critical): conventional treatment	180	Yes	No	Recruiting	China
ChiCTR2000030006 (ICTPR)	**Arm A:** ozonated autohemotherapy **Arm B:** standard medical treatment	60	Yes	No	Recruiting	China
Other						
ChiCTR2000029742 (ICTPR)	**Arm A:** (general): normal treatment **Arm B** (general): normal treatment + **sodium aescinate** **Arm C** (severe): normal treatment + hormonotherapy (presumed glucocorticoids)	90	Yes	No	Recruiting	China

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Table 1. (continued)

Clinical trial ID (Registry)	Intervention[b]	Size[c]	Randomised	Blinded	Status	Country of origin (pharma sponsor)
	Arm D (severe): lopinavir/ritonavir **Arm E** (severe)**:** normal treatment + sodium aescinate					
ChiCTR2000030328 (ICTPR)	**Arm A:** acetylcysteine inhalation (mucolytic effect) via tracheal tube **Arm B:** saline inhalation via tracheal tube	60	Yes	Unspecified	Not recruiting	China
ChiCTR2000030398 (ICTPR)	**Arm A: bismuth** **Arm B:** placebo	340	Yes	Double	Not recruiting	China
ChiCTR2000030055 (ICTPR)	**Arm A:** conventional treatment **Arm B:** conventional treatment + **dipyridamole**	460	Yes	No	Recruiting	China
ChiCTR2000030853 (ICTPR)	**Arm A: dexmedetomidine**	200	No	No	Not recruiting	China
ChiCTR2000030700 (ICTPR)	**Arm A: enoxaparin** sodium **Arm B:** standard treatment	60	Yes	No	Not recruiting	China
ChiCTR2000030135 (ICTPR)	**Arm A:** high-dose vitamin C **Arm B:** standard treatment	39	Yes	Unspecified	Not recruiting	China
NCT04311697 (ClinicalTrials.gov)	**Arm A:** intravenous **aviptadil** followed by nebulised in 48 h if required **Arm B:** aviptadil nebuliser followed by intravenous in 48 h if required	20	Yes	Single	Not recruiting	USA and Israel (NeuroRx)
ChiCTR2000030170 (ICTPR)	**Arm A:** jakotinib[g]	8	Unspecified	Unspecified	Recruiting	China
NCT04312009 (ClinicalTrials.gov)	**Arm A: losartan** **Arm B:** placebo	200	Yes	Quadruple	Not recruiting	USA
NCT04311177 (ClinicalTrials.gov)	**Arm A:** losartan **Arm B:** placebo	478	Yes	Quadruple	Not recruiting	USA
ChiCTR2000030946 (ICTPR)	**Arm A:** low-molecular-weight heparin **Arm B:** mechanical prevention	120	Yes	Unspecified	Recruiting	China
NCT04304313 (ClinicalTrials.gov)	**Arm A: sildenafil**	10	No	No	Recruiting	China
NCT04308317 (ClinicalTrials.gov)	**Arm A: tetrandrine** **Arm B:** standard treatment	60	Yes	No	Enrolling by invitation	China
NCT04264533 (ClinicalTrials.gov)	**Arm A:** vitamin C **Arm B:** sterile water for injection	140	Yes	Triple	Recruiting	China
(B) Ongoing clinical trials for prevention of COVID-19						
Vaccine						
NCT04299724 (ClinicalTrials.gov)	**Arm A:** Covid-19/aAPC vaccine	100	No	No	Recruiting	China
NCT04313127 (ClinicalTrials.gov)	**Arm A:** low-dose Ad5-nCoV **Arm B:** middle-dose Ad5-nCoV **Arm C:** high-dose Ad5-nCoV	108	No	No	Not recruiting	China (CanSino Biologics)
NCT04283461 (ClinicalTrials.gov)	**Arm A:** mRNA-1273 (25 μg) **Arm B:** mRNA-1273 (100 μg) **Arm C:** mRNA-1273 (250 μg)	45	No	No	Recruiting	USA (ModernaTX)
Antiviral						
NCT04304053 (ClinicalTrials.gov)	**Arm A:** darunavir/cobicistat **Arm B:** isolation	3040	Yes	No	Recruiting	Spain
ChiCTR2000030013 (ICTPR)	**Arm A:** interferon a1b **Arm B:** no intervention	450	Unspecified	Unspecified	Not recruiting	China
ChiCTR2000029592	**Arm A:** umifenovir	1000	Unspecified	No	Not	China

Table 1. (continued)

Clinical trial ID (Registry)	Intervention[b]	Size[c]	Randomised	Blinded	Status	Country of origin (pharma sponsor)
(ICTPR)	**Arm B:** without umifenovir				recruiting	
Antimalarial						
NCT04303507 (ClinicalTrials.gov)	**Arm A:** chloroquine **Arm B:** placebo	10000	Yes	Double	Not recruiting	UK
NCT04308668 (ClinicalTrials.gov)	**Arm A:** hydroxychloroquine **Arm B:** placebo	1500	Yes	Quadruple	Recruiting	USA
ChiCTR2000029803 (ICTPR)	**Arm A:** hydroxychloroquine (low dose) **Arm B:** hydroxychloroquine – high dose **Arm C:** umifenovir – low dose **Arm D:** umifenovir – high dose	320	Yes	No	Not recruiting	China
Personal protective equipment						
ChiCTR2000030317 (ICTPR)	**Arm A:** gastroscope mask **Arm B:** without mask	300	Yes	No	Not recruiting	China
NCT04296643 (ClinicalTrials.gov)	**Arm A:** medical masks **Arm B:** N95 respirators	676	Yes	Single	Not recruiting	USA
Other						
NCT04312243 (ClinicalTrials.gov)	**Arm A:** nitric oxide **Arm B:** no treatment	460	No	No	Not recruiting	USA
NCT04313023 (ClinicalTrials.gov)	**Arm A:** PUL-042 **Arm B:** normal saline	200	Yes	Quadruple	Not yet recruiting	USA (Pulmotect)
ChiCTR2000030432 (ICTPR)	**Arm A:** rehabilitation and lung eight-segment exercises **Arm B:** normal activity	80	Yes	No	Not recruiting	China

[a]Abbreviations: Ad5, adenovirus type 5; APC, antigen-presenting cells; CIK cells, **cytokine-induced killer cells**; CRRT, continuous renal replacement therapy; DC, dendritic cell; ECMO, extracorporeal membrane oxygenation; IVIG, intravenous immunoglobulin; MSCs, mesenchymal stem cells; NK cells, natural killer cells; rhG-CSF, recombinant human granulocyte colony-stimulating factor; rSFIN-co, recombinant supercompound interferon; TFF2, Trefoil factor 2; vMIP, viral macrophage inflammatory protein.
[b]For part (B), this column indicates the intervention to prevent infection.
[c]Participant size as stated in registry entry.
[d]No literature outside trial protocol; likely tocilizumab.
[e]Hydrogen inhalation has shown evidence of antioxidant and anti-inflammatory effects in ischaemia–reperfusion injury.
[f]No literature outside trial protocol; likely a form of lung rehabilitation.
[g]No literature outside trial protocol; possible Janus kinase inhibitor.

double-blind randomised controlled protocol to investigate efficacy.

Immunosuppressants/ Immunomodulators

There is evidence that a hyperinflammatory response significantly contributes to mortality in COVID-19 infections [18]. Corticosteroids were previously trialled in SARS-CoV; however, the results were inconclusive and adverse effects were associated [19]. Seven registered studies are evaluating the effect of corticosteroids in COVID-19 (Table 1A: Immunosuppressants). There is also interest in the anti-IL-6 drug, tocilizumab (used in the treatment of rheumatoid arthritis), with seven registered trials. Other immunosuppressants being investigated include **adalimumab** (anti-TNF), **eculizumab** (anti-C5), sarilumab (anti-IL-6), ixekizumab (anti-17A), and fingolimod (sphingosine-1-phosphate receptor modulator, used against multiple sclerosis). Meplazumab (anti-CD147) inhibits not only T cell chemotaxis, but also virus cell entry [20]. A preprint of a study of 17 patients compared with 11 controls (NCT04275245, original recruitment target 20) reported improved clinical and virological outcomes [20].

Conversely, several studies are investigating immune stimulation. These include the **anti-PD-1** antibody camrelizumab, **recombinant IL-2**, CSA0001 (LL-37 antiviral peptide with immunomodulatory functions), CD24FC [fusion protein that prevents Toll-like receptor (TLR) activation and activates immunosuppressive Siglec signalling] and recombinant human granulocyte colony-stimulating factor (rhG-CSF) (Table 1A: Immune Modulators). Three studies (NCT04299724, NCT04276896, and ChiCTR2000030750) examine the efficacy of experimental vaccines in infected patients. Three further studies are

investigating nonpharmaceutical interventions to modulate the immune system using cytokine filtration devices, such as oXiris and CytoSorb, to reduce circulating cytokines and inflammatory mediators (Table 1A: Cytokine Removal).

Cell and Plasma-Based Therapy

Twenty-four registered studies plan to investigate the role of mesenchymal stem cells (MSCs) (Table 1A: Cell-Based Therapies). MSCs have immunomodulatory and tissue repair effects through the secretion of cytokines and growth factors. They have previously been examined in a Phase I trial in Adult Respiratory Distress Syndrome (ARDS) [21]. Given that most of the deaths in COVID-19 are from respiratory failure, MSCs are postulated to have a beneficial effect. So far, one study of MSCs (ChiCTR2000029990, recruitment target stated as 120 participants in the registry) has reported results in seven patients with COVID-19, showing improvement in both clinical and inflammatory outcome compared with three control patients treated with saline [22]. This study plans to recruit 120 participants with 60 patients in each of the treatment (MSC) and control (saline) arms.

Use of plasma from patients who have recovered from COVID-19 has the potential benefit of providing disease-specific neutralising antibodies, before targeted therapies can be developed. During the Ebola outbreak in 2014, the WHO advised the use of convalescent plasma or whole-blood therapies. However, a nonrandomised comparative study in 84 patients with Ebola found no associated improvement in survival [23]. There are currently 12 registered trials to investigate convalescent plasma or immunoglobulins in COVID-19 (Table 1A: Plasma-Based Therapies).

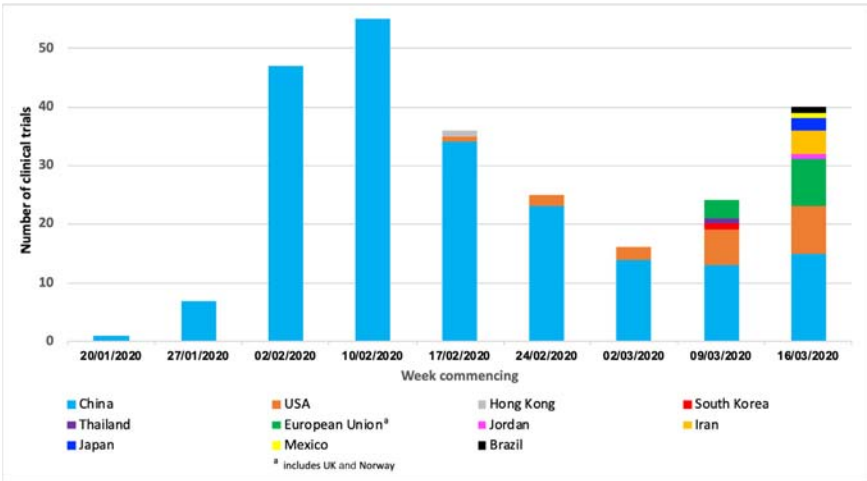
Alternative Treatment Strategies

Various other treatment strategies are currently under investigation, including the antifibrotic/inflammatory agent pirfenidone (used in treatment of idiopathic pulmonary fibrosis), and the antiangiogenic agents: **bevacizumab** (anti-VEGF) and **thalidomide** (Table 1A: Antifibrotics and Antiangiogenics). A further five studies aim to assess the therapeutic utility of modifying the gut microbiome (Table 1A: Microbiome), although the mechanisms by which this is performed are not explicit in the trial registers. Ten other studies are investigating holistic approaches, including physiotherapy, psychology, and nutritional intervention, on disease outcome (Table 1A: Therapy Interventions).

Preventative Strategies

No effective vaccine or antiviral therapeutic agent for postexposure prophylaxis has been approved for preventing COVID-19 infection or any other human coronavirus. The development of vaccines is a complex, time-consuming process with a high attrition rate. Success in generating a vaccine in the recent 2009 flu pandemic (H1N1/09) has fuelled optimism towards one for COVID-19 [24]. Furthermore, both the rapid genomic sequencing of COVID-19 and insights gleaned during vaccine exploration for both MERS-CoV and SARS-CoV (both terminated due to successful disease containment) has allowed preclinical and animal work to advance rapidly [7].

Over 50 novel vaccines are estimated to be in development; however, only three vaccine studies are registered for Phase I evaluation (Table 1B: Vaccines). Two studies are actively recruiting in the USA and China, and a further study is newly registered (initial set-up). A modified mRNA vaccine (mRNA-1273) that encodes the COVID-19 viral spike protein has progressed rapidly through preclinical development to human testing (42 days from sequence identification), developed by Moderna, Inc and the National Institute of Allergy and Infectious Diseases (NIAID). However, such rapid development has prompted safety concerns from some experienced virologists [25]. Other current investigational vaccines being tested in humans include a replicative-defective adenovirus type 5 (Ad5)-nCoV that expresses COVID-19 viral proteins and a



Trends in Pharmacological Sciences

Figure 2. First Recording (Week Commencing) of Clinical Trials for COVID-19 in Registry by Country (Primary Sponsor/Principal Investigator Origin). Data are from registries in Australia, New Zealand, China, The Netherlands, Brazil, India, Cuba, Republic of Korea, Germany, Iran, Japan, Sri Lanka, Thailand, and Peru, and also ClinicalTrials.gov, EU Clinical Trials registry, International Standard Randomised Controlled Trial Number (ISRCTN), and the Pan-Africa registries.

lentiviral vector system to express viral proteins and immunomodulatory genes to modify antigen-presenting cells (aAPC) (Table 1B: Vaccines).

Furthermore, postexposure prophylaxis is an attractive strategy for both healthcare workers and household contacts exposed to COVID-19. Currently, six studies are looking at the use of antivirals, such as umifenovir, antimalarials, such as hydroxychloroquine and chloroquine, and the use of recombinant human **interferon alpha** (a)1b spray for the prevention of infection (Table 1B: Antiviral and Antimalarial).

Global Response

Over 85% of the clinical trials (excluding TCM) for either the prevention and/or treatment of COVID-19 have been registered in China, which is not surprising given that the country saw the outbreak of the disease first. The first clinical trials were registered within 1 month of COVID-19 identification and rapidly expanded after that (Figure 2). Public health initiatives have thus far successfully curtailed the previously exponential growth of COVID-19 cases in China. This has reduced the number of potential participants for clinical trials in China and the registration of new clinical trials has since declined. Furthermore, several studies have also been withdrawn or suspended (e.g., NCT04293692 and ChiCTR2000030082).

The wider global community has been slower to react. The first case of COVID-19 outside of Asia was reported in late January 2020[iii]. Subsequently, the incidence of COVID-19 has increased dramatically. The WHO has now declared that Europe has become the new disease epicentre, with 40% and rising of the total number of cases[ix]. However, until recently, <5% of clinical trials for COVID-19 were registered in Europe (Figure 2). The rapid escalation of trial registrations in response to increasing disease incidence seen in China has unfortunately not occurred in Europe. Despite this, there are now encouraging signs. Initiatives focused on pan-European collaboration are being championed by the European Union with a priority on larger patient studies compared with the smaller studies registered in China[x]. Consequently, the median number of participants in European registered studies is 1200 participants, compared with 60 and 394 in China and USA, respectively. An example is NCT04303507 (chloroquine postexposure prophylaxis), which plans to recruit 10 000 participants (Table 1B). However, this may in part reflect a higher proportion of preventative studies currently being carried out that include large numbers of participants. Hopefully, larger studies will provide higher quality evidence, although may take longer to generate results in the context of this escalating public health crisis.

With an increasing number of COVID-19 cases reported in North America, there has also been an increase in clinical trial registrations in the USA. The NIAID registered the first USA-led global trial in mid-February 2020, utilising 50 sites across Asia and USA (Figure 2). Studies registered in the USA have generally placed an emphasis on larger participant numbers than China (Table 1) and on an adaptive trial design for both the treatment and prevention of COVID-19.

Concluding Remarks

The COVID-19 pandemic represents the gravest global public health threat seen since the 1918 influenza outbreak and has rapidly become a global healthcare emergency. Clinical trials need to produce high-quality data that can be used to objectively assess potentials therapies for both the treatment and prevention of this global emergency. It is imperative to plough international resources into high-quality design clinical trials with robust scientific rationale and vigorous statistical rigor. Increasing international collaboration and the globalisation of clinical trials with large patient numbers should be the way forward to provide significant and definitive results.

Disclaimer Statement

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Resources

[i]www.who.int/csr/sars/country/table2004_04_21/en/
[ii]www.euro.who.int/en/health-topics/health-emergencies/coronavirus-covid-19
[iii]www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports
[iv]https://unctad.org/en/pages/newsdetails.aspx?OriginalVersionID=2300
[v]https://clinicaltrials.gov
[vi]www.who.int/ictrp/en/
[vii]www.clinicaltrialsregister.eu/
[viii]www.cochranelibrary.com/central/about-central
[ix]www.euro.who.int/en/health-topics/health-emergencies/coronavirus-covid-19/news/news/2020/3/global-solidarity-across-countries-and-continents-needed-to-fight-covid-19
[x]www.bioworld.com/articles/433824-eu-boosts-funding-for-covid-19-epidemic-encourages-clinical-trial-cooperation
[xi]www.isrctn.com/?gclid=Cj0KCQjwjoH0BRD6ARIsAEWO9Dt7ppl5xmcUMgabefiiRnPVSbsoH3CtwieB5maS2z4gzAyZ1nNjd8MaAjEREALw_wcB

[1]Department of Surgery and Cancer, Imperial College London, Hammersmith Hospital, Du Cane Road, London, W12 0HS, UK
[2]Department of Metabolism, Digestion and Reproduction, Imperial College London, St Marys Hospital, Praed Street, London, W21, NY, UK
[3]These authors contributed equally

*Correspondence:
M.Lythgoe@imperial.ac.uk (M.P. Lythgoe).

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Spotlight

Structure-Based Virtual Screening Accelerates GPCR Drug Discovery

Lei Liu[1,2] and Ralf Jockers[2,*]

Virtual ligand screening (VLS) against high-resolution structures of G-protein-coupled receptors (GPCRs) is likely to become the next-generation drug design approach of choice. Stein and colleagues recently demonstrated the feasibility of such an approach by discovering novel chemical scaffolds for the melatonin MT_1 receptor and compounds with unique *in vivo* activities.

One of the main motivations to solve the structures of GPCRs is the promise to accelerate the drug development process to eventually design more potent and selective medications targeting such receptors. GPCRs are proven drug targets with ~30% of currently marketed drugs targeting these transmembrane proteins [1]. However, many of the 400 potentially druggable GPCRs remain therapeutically unexplored and, for those already explored, the selectivity profile and potency of drugs can be further improved [2]. Most of the currently marketed drugs have been identified in ligand-screening campaigns with large-scale libraries of synthetic compounds, but this approach is expensive, time-consuming, and highly assay dependent. Computational docking of large virtual ligand libraries into orthosteric ligand-binding sites has emerged as an attractive alternative [3]. The recent explosion of GPCR structures now provides reliable templates for such studies, as already explored for several receptors [4].

In this context, we highlight here the article by Stein and colleagues based on the melatonin MT_1 receptor template [5].The authors aimed to identify new chemotypes for the MT_1 receptor, a $G_{i/o}$ protein-coupled GPCR regulating several important physiological functions, including circadian and seasonal rhythms, sleep, retinal physiology, and glucose homeostasis [6]. Drugs acting on melatonin receptors are currently prescribed for circadian disorders (jet lag, shift work, etc.), insomnia, and major depression [7]. This receptor appeared to represent a textbook case for VLS: (i) its crystal structure [8] and that of the highly homologous melatonin MT_2 receptor [9] were recently solved [10,11]; (ii) its pharmacology is poorly developed with few chemical scaffolds, few type-selective compounds, and few ligands with neutral antagonistic, inverse agonistic or pathway-biased activities [12]; and (iii) its orthosteric ligand-binding pocket is small with three well-defined ligand–receptor contacts: $N162^{4.60}$ in transmembrane (TM)4 and $Q181^{ECL2}$ of the extracellular loop (ECL)2 form hydrogen bonds with the methoxy and alkylamide side chains, respectively; and $F179^{ECL2}$ forms hydrophobic contacts with the indole ring of the melatonin derivative 2-phenylmelatonin (2-PMT) in the binding pocket of MT_1 crystal structure (Figure 1A).

In their work, Stein and colleagues set out to identify MT_1-selective ligands by computational docking of a virtual library of more than 150 million molecules, and went all the way down to chemical lead optimization and *in vitro* and *in vivo* validation to come up with two new MT_1-seletive inverse agonists [5]. Several aspects of this study merit to be mentioned: (i) the high success rate of 39% of biologically active compounds out of all experimentally tested candidate compounds with some primary hits showing low nanomolar affinities; and (ii) a remarkable number of