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%) [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 [1]. As of 27 March 2020 (date of submission), COVID-19 was affecting 199 countries and territories, with >510,000 confirmed cases globally [1]. It is associated with an estimated mortality of between 1% and 5% [11]. 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 [6].

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 development of 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 morbilliviruses [7]. This strategy has identified several genomic regions of interest for in silico drug development, such as the spike protein region.
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® and the International Clinical Trials Registry Platform (ICTRP)™ 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®, WHO

Registries and databases searched:
- ClinicalTrials.gov®
- EU Clinical Trials Registry
- WHO International Clinical Trials Registry
- Cochrane Controlled Register of Trials

Total records included after removal of duplicate results (N = 590)

Total records included (N = 526)

Total records included (N = 244)

• Intervention on infected patients (N = 233)
• Intervention to prevent infection (N = 14)

Removed:
• Cancelled studies (N = 19)
• Non-COVID-19 studies (N = 33)
• Repeated registration (N = 12)

• Noninterventional studies (N = 182)
• Traditional Chinese medicine and complementary medicine (N = 100)

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)®, 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.
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ICTRP\textsuperscript{iv}, EU Clinical Trials Register\textsuperscript{ix}, and Cochrane Central Register of Controlled Trials\textsuperscript{vii}, 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 \cite{9}. However, lopinavir has insufficient oral bioavailability for significant therapeutic activity, due to rapid catabolism by the cytochrome P450 enzyme system (specifically 3A4 isoenzyme) \cite{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 \cite{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 \cite{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 \cite{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 \cite{12,14}. There has been much interest in this molecule, following treatment of the first COVID-19 case, and subsequent recovery, in the USA \cite{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).

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 \textit{in vitro} \cite{12}. An early report of clinical experience in 100 patients with COVID-19 reported both beneficial clinical and virological outcomes with chloroquine treatment \cite{16}. More recently, a nonrandomised open-label study examining the effect of hydroxychloroquine (EU Clinical Trial Number\textsuperscript{vi}: 2020-000890-25; recruitment target stated as 25 participants in the registry) reported on a cohort of 36 patients \cite{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 \cite{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)

| 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: ronivir 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
Arm B: standard treatment | 20 | Yes | No | Recruiting | China |
| ChiCTR2000029853 (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 + trisazavir
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\(^a\) | Size\(^a\) | Randomised | Blinded | Status          | Country of origin (pharma sponsor) |
|-----------------------------|-------------------|-----------|------------|---------|-----------------|------------------------------------|
| 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 (Novoferon)  
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 | | 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 | 30 | Yes | No | Recruiting | Iran |
| IRCT20100228003449N28 (ICTPR) | Arm A: hydroxychloroquine, lopinavir/ritonavir, and interferon beta 1a | 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 |
| JPRIJRCTs041190120 (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 |

(continued on next page)
### Table 1. (continued)

| Clinical trial ID (Registry) | Interventionš | Size | Randomised | Blinded | Status | Country of origin (pharma sponsor) |
|-----------------------------|----------------|------|-------------|---------|--------|-----------------------------------|
| (ICTPR)                     | Arm B: placebo eye drops |      |             |         | recruiting |                                   |
| NCT04293887 (ClinicalTrials.gov) | Arm A: interferon α1b nebulised | 328  | Yes | No | Not recruiting China |
| NCT04310793 (ClinicalTrials.gov) | Arm A: interferon alpha 2a and ribavirin | 30   | Yes | Unspecified | Recruiting China |
| NCT04310793 (ClinicalTrials.gov) | Arm B: umifenovir and ribavirin |      |             |         |                                   |
| ChiCTR2000030187 (ICTPR) | Arm A: lopinavir/ritonavir | 160  | Yes | No | Recruiting China |
| Arm B: standard of care | Arm C: no intervention |      |             |         |                                   |
| 2020-001113-21 (EU-CTR) | Arm A: lopinavir/ritonavir | 2000 | Yes | No | Recruiting UK |
| Arm B: interferon beta 1a | Arm C: remdesivir |      |             |         |                                   |
| ChiCTR2000029468 (ICTPR) | Arm A: lopinavir/ritonavir and emtricitabine/tenofovir | 120  | Unspecified | Unspecified | Not recruiting China |
| Arm B: lopinavir/ritonavir | Arm C: lopinavir/ritonavir and interferon alpha inhalation |      |             |         |                                   |
| JP8N-JCTRt031190227 (ICTPR) | Arm A: lopinavir/ritonavir and hydroxychloroquine | 50   | Unspecified | Unspecified | Not recruiting Japan |
| Arm B: lopinavir/ritonavir and traditional Chinese medicine | Arm C: lopinavir/ritonavir and interferon alpha 2b and Qing-Wen Bai-Du-Yin granules |      |             |         |                                   |
| 2018-001441-23 (EU-CTR) | Arm A: lopinavir/ritonavir and Xiyanping injection | 80   | Unspecified | Unspecified | Recruiting China |
| Arm B: ritonavir | Arm B: ritonavir |      |             |         |                                   |
| NCT04252885 (ClinicalTrials.gov) | Arm A: lopinavir/ritonavir + basic treatment (unspecified) | 125  | Yes | No | Recruiting China |
| Arm B: umifenovir + basic treatment (unspecified) | Arm C: basic treatment (unspecified) |      |             |         |                                   |
| NCT04276688 (ClinicalTrials.gov) | Arm A: lopinavir/ritonavir + ribavirin + interferon beta 1b | 70   | Yes | No | Recruiting Hong Kong |
| Arm B: lopinavir/ritonavir | Arm C: lopinavir/ritonavir |      |             |         |                                   |
| ChiCTR2000029539 (ICTPR) | Arm A: lopinavir/ritonavir | 328  | Yes | No | Recruiting China |
| Arm B: standard treatment | Arm C: standard treatment |      |             |         |                                   |
| ChiCTR2000029996 (ICTPR) | Arm A: low-dose favipiravir | 60   | Yes | No | Recruiting China |
| Arm B: medium-dose favipiravir | Arm C: high-dose favipiravir |      |             |         |                                   |
| ChiCTR2000029638 (ICTPR) | Arm A: nebulised rSiFN-co | 100  | Yes | Yes | Recruiting China |
| Arm B: nebulised interferon alpha | Arm B: nebulised interferon alpha |      |             |         |                                   |
| Clinical trial ID (Registry) | Intervention* | Size | 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  
Arm B: unspecified  
Arm C: unspecified  
Arm D: available | 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                              |
Table 1. (continued)

| Clinical trial ID (Registry) | Intervention | Size | 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 | Not recruiting | China |
| NCT04275388 (ClinicalTrials.gov) | Arm A: Xyamping injection, lopinavir/ritonavir and interferon alpha nebulisation  
Arm B: lopinavir/ritonavir and interferon alpha nebulisation | 348 | Yes | No | Not recruiting | China (Jiangxi Qingfeng Pharmaceutical) |

**Antimalarial**

| Clinical trial ID (Registry) | Intervention | Size | Randomised | Blinded | Status         | Country of origin (pharma sponsor) |
|------------------------------|--------------|------|------------|---------|----------------|-----------------------------------|
| ChiCTR2000030031 (ICTPR)    | Arm A: chloroquine  
Arm B: placebo | 120 | Yes | Double | Recruiting | China |
| ChiCTR2000029888 (ICTPR)    | Arm A: chloroquine  
Arm B: standard treatment | 80 | Unspecified | Unspecified | Recruiting | China |
| ChiCTR2000029975 (ICTPR)    | Arm A: chloroquine | 10 | No | Unspecified | Not recruiting | China |
| ChiCTR2000029909 (ICTPR)    | Arm A: chloroquine  
Arm B: standard treatment | 100 | Yes | Single | Recruiting | China |
| ChiCTR2000029905 (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 |
| Clinical trial ID (Registry) | Intervention(s) | Size | 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**

| Clinical trial ID (Registry) | Intervention(s) | Size | Randomised | Blinded | Status | Country of origin (pharma sponsor) |
|-----------------------------|-----------------|------|-------------|---------|--------|-----------------------------------|
| 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 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 |
| NCT042680588 (ClinicalTrials.gov) | Arm A: fingolimod Arm B: standard treatment | 30 | No | No | Recruiting | China |
| ChiCTR2000030703 (ICTPR) | Arm A: beclomethasone and antiviral therapy Arm B: antiviral therapy | 40 | Yes | Single | Recruiting | China |
| NCT04275245 (ClinicalTrials.gov) | 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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| Clinical trial ID (Registry) | Intervention | Size | Randomised | Blinded | Status | Country of origin (pharma sponsor) |
|-----------------------------|--------------|------|------------|---------|--------|----------------------------------|
| ChiCTR2000029386 (ICTRP)    | 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 (ICTRP)    | Arm A: standard treatment + leflunomide  
Arm B: standard treatment + placebo | 200 | Yes        | Yes       | Not yet recruiting | China |
| ChiCTR2000030196 (ICTRP)    | Arm A: tocilizumab | 60  | No         | No       | Not recruiting | China |
| NCT04315480 (ClinicalTrials.gov) | Arm A: tocilizumab  
Arm B: standard treatment  
Arm C: placebo | 400 | Yes        | Quadruple | Recruiting | USA (Regeneron Pharmaceuticals) |
| NCT04317092 (ClinicalTrials.gov) | Arm A: tocilizumab | 330 | No         | No       | Recruiting | Italy |
| ChiCTR2000030442 (ICTRP)    | Arm A: tocilizumab, IVIG, and CCRT | 100 | No         | Unspecified | Not recruiting | China |
| ChiCTR2000030580 (ICTRP)    | Arm A: tozumab and adalimumab  
Arm B: standard treatment | 60  | Yes        | Unspecified | Recruiting | China |
| NCT04317040 (ClinicalTrials.gov) | Arm A: CD24Fc  
Arm B: placebo | 230 | Yes        | Quadruple | Not recruiting | USA (OncoImmune) |
| ChiCTR2000029776 (ICTRP)    | Arm A: conventional treatment + polynosin-polycytidylic acid  
Arm B: conventional treatment | 40  | Yes        | No        | Recruiting | China |
| NCT04299724 (ICTRP)         | Arm A: Covid-19/aAPC vaccine | 100 | No         | No       | Recruiting | China |
| ChiCTR2000030939 (ICTRP)    | Arm A: CSA0001 | 10  | Yes        | Unspecified | Recruiting | China |
| ChiCTR2000030016 (ICTRP)    | Arm A: inhaled inactive Mycobacterium vaccine  
Arm B: inhaled physiological saline | 60  | Yes        | Yes       | Recruiting | China |
| ChiCTR2000030167 (ICTRP)    | 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 |
| NCT04268969 (ClinicalTrials.gov) | 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 (ICTRP)    | 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 (ICTRP)    | Arm A: recombinant chimeric DC vaccine  
Arm B: normal saline | 120 | Yes        | Unspecified | Not recruiting | China |
| ChiCTR2000030007 (ICTRP)    | Arm A: standard treatment + rhG-CSF  
Arm B: standard treatment | 200 | Yes        | No        | Not yet recruiting | China |
| 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 (Guangzhou 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                         |
| ChiCTR2000029900 (ICTPR)   | 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                         |

(continued on next page)
Table 1. (continued)

| Clinical trial ID (Registry) | Interventiona | Sizel | Randomised | Blinded | Status | Country of origin (pharma sponsor) |
|-----------------------------|--------------|-------|------------|---------|--------|-----------------------------------|
| NCT04280224 (ClinicalTrials.gov) | Arm A: NK cells  
Arm B: standard treatment | 30 | Yes | No | Recruiting | China  
(pharma sponsor) |
| ChiCTR2000030509 (ICTRP) | 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<sup>a</sup> | Size<sup>b</sup> | 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  
Arm B: standard treatment | 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<sup>a</sup>  
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                              |
| NCT04306933 (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                              |

(continued on next page)
| Clinical trial ID (Registry) | Interventiona  | Size  | Randomised | Blinded | Status | Country of origin (pharma sponsor) |
|-----------------------------|----------------|-------|------------|---------|--------|-----------------------------------|
| 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: carriymycin Arm B: lopinavir/ritonavir | 520 | Yes | No | Recruiting | China |
| NCT04286503 (ClinicalTrials.gov) | Arm A: carriymycin + 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) | Interventionb | Sizec | 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 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  
Arm B: standard treatment | 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 | Size | Randomised | Blinded | Status | Country of origin (pharma sponsor) |
|------------------------------|--------------|------|------------|---------|--------|-----------------------------------|
| Arm D (severe): lopinavir/ritonavir | Arm A: acetylcysteine inhalation (mucolytic effect) via tracheal tube | 60 | Yes | Unspecified | Not recruiting | China |
| Arm E (severe) normal treatment + sodium aescinate | Arm B: saline inhalation via tracheal tube | 340 | Yes | Double | Not recruiting | China |
| Arm A: acetylcysteine inhalation | Arm A: conventional treatment | 460 | Yes | No | Recruiting | China |
| Arm B: conventional treatment + dipyridamole | Arm B: placebo | 200 | No | No | Not recruiting | China |
| Arm A: conventional treatment | Arm A: bismuth | 60 | Yes | No | Not recruiting | China |
| Arm B: placebo | Arm B: saline inhalation via tracheal tube | 39 | Yes | Unspecified | Not recruiting | China |
| Arm A: intravenous aviptadil followed by nebulised in 48 h if required | Arm A: intravenous aviptadil followed by nebulised in 48 h if required | 20 | Yes | Single | Not recruiting | USA and Israel (NeuroRx) |
| Arm B: aviptadil nebuliser followed by intravenous in 48 h if required | Arm B: high-dose vitamin C | 39 | Yes | Unspecified | Not recruiting | China |
| Arm A: low-molecular-weight heparin | Arm A: low-dose Ad5-nCoV | 108 | No | No | Not recruiting | China |
| Arm B: mechanical prevention | Arm B: middle-dose Ad5-nCoV | 108 | No | No | Not recruiting | China |
| Arm C: high-dose Ad5-nCoV | Arm C: high-dose vitamin C | 108 | No | No | Not recruiting | China |
| Arm A: sildenafil | Arm A: mRNA-1273 (100 μg) | 45 | No | No | Recruiting | USA (ModernaTX) |
| Arm B: placebo | Arm B: mRNA-1273 (250 μg) | 45 | No | No | Recruiting | USA (ModernaTX) |
| Arm C: mRNA-1273 (25 μg) | Arm A: verapamil | 3040 | Yes | No | Recruiting | Spain |
| Arm B: no intervention | Arm B: verapamil | 450 | Unspecified | Unspecified | Not recruiting | China |
| Arm C: umifenovir | Arm C: verapamil | 1000 | Unspecified | No | Not recruiting | China |

(B) Ongoing clinical trials for prevention of COVID-19

#### Vaccine

| Clinical trial ID (Registry) | Intervention | Size | Randomised | Blinded | Status | Country of origin (pharma sponsor) |
|------------------------------|--------------|------|------------|---------|--------|-----------------------------------|
| NCT0312009 (ClinicalTrials.gov) | Arm A: mRNA-1273 (25 μg) | 45 | No | No | Recruiting | China |
| Arm B: mRNA-1273 (100 μg) | Arm C: mRNA-1273 (250 μg) | 45 | No | No | Recruiting | China |

#### Antiviral

| Clinical trial ID (Registry) | Intervention | Size | Randomised | Blinded | Status | Country of origin (pharma sponsor) |
|------------------------------|--------------|------|------------|---------|--------|-----------------------------------|
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 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...
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 202013. Subsequently, the incidence of COVID-19 has increased dramatically. The WHO has now declared that Europe has become the new disease epicentre, with 40% 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 Asiad, with the total number of participants since then exceeding 12000. Consequently, the median number of participants in European registered studies is 12000, 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

https://clinicaltrials.gov
https://www.who.int/ictrp/en/
https://www.clinicaltrialsregister.eu/
https://www.gov.uk/government/news/eu-boosts-funding-for-covid-19-epidemic-encourages-clinical-trial-cooperation
https://www.cochranelibrary.com/central/about-central
https://www.euro.who.int/en/health-topics/health-emergencies/coronavirus-covid-19/situation-reports
https://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
https://www.bioworld.com/articles/433824-eu-boosts-funding-for-covid-19-epidemic-encourages-clinical-trial-cooperation
https://www.isrctn.com/?gclid=Cj0KCQjwjoH0BRD6ArIsAEW0ISd1pp6xJmUyqab:04Qb1nnPvzStao:l39DIwI5aAa222gsxqAy21Nt8d3MxAjEIEALx_w_wcB
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7143607/
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**Spotlight**

**Structure-Based Virtual Screening Accelerates GPCR Drug Discovery**

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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 MT1 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 MT1 receptor template [5]. The authors aimed to identify new chemotypes for the MT1 receptor, a G<sub>q/11</sub> 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 MT2 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 in the transmembrane (TM)4 and Q181 ECL2 of the melatonin derivative 2-phénylmeratonin (2-PMT) in the binding pocket of MT1 crystal structure (Figure 1A).

In their work, Stein and colleagues set out to identify MT<sub>1</sub>-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<sub>1</sub>-selective 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