Systematic Review of the Registered Clinical Trials of Coronavirus Diseases
2019 (COVID-19)

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Abstract

Background: Since the outbreak of coronavirus diseases 2019 (COVID-19), many researchers in China have immediately carried out clinical research scheme of the COVID-19. But, there is still a lack of systematic review of registered clinical trials. Therefore, we made the first systematic review of the clinical trials of COVID-19 in order to provide evidence for the control of the COVID-19. Methods: The database from the Chinese Clinical Registration Center and the ClinicalTrials.gov were searched to collect the registered clinical trials of COVID-19. The retrieval inception date is February 9, 2020. Two evaluators independently selected literature, extracted data and evaluated the risk of bias. This study is based on the recommendations of PRISMA in Cochrane handbook. Results: A total of 75 COVID-19 registered clinical trials (63 interventional studies and 12 observational studies) were obtained. 97.3% of clinical trials were initiated by Chinese organizations. Only 11 trials have begun to recruit patients, and all registered clinical trials have not been completed. Most of the trials are early clinical exploratory trials or in pre-experiment stage (only two trials of Remdesivir in III stage), and the sample size of subjects recruited is small. The main intervention methods include traditional Chinese medicine treatment, western medicine treatment and integrated Chinese and Western medicine treatment. The subjects were mainly non severe adult patients (≥ 18 years old). The main outcomes were clinical observation and examination. The duration of most trials was more than 5 months, and the median of the intervention study was 180 d (95% CI: 146.3 - 328.9 d); the median of the observation period was 334 d (95% CI: 166.6 - 363.4 d). Overall, both the methodology quality of intervention register trials and observational trials are low. Conclusions: Disorderly and intensive clinical trials of COVID-19 using traditional Chinese medicine and Western medicine are ongoing or will be carried out in China. However, based on the poor quality and small sample size and long completion period, we will not be able to obtain reliable, high-quality clinical evidence about COVID-19 treatment for quite a long time in the future. Improving the quality of study design, prioritizing promising drugs, and using different designs and statistical methods are worth advocating and recommending for the clinical trials of COVID-19 in China.
Keywords: COVID-19; 2019-nCoV; new coronavirus pneumonia; registered clinical trial; intervention trial; observational trial; systematic review

As an emerging infectious diseases, coronavirus diseases 2019 (COVID-19) seriously threatens human health. In December 2019, the initial outbreak of COVID-19 in Wuhan city, Hubei province of China, was suspected to be related to the seafood market, while the host of novel coronavirus was suspected to be the chrysanthemum head bat. Patients with COVID-19 will have different respiratory tract infection symptoms, such as fever, cough, pneumonia, and even death. It is estimated that the death rate of the virus disease is about 2% - 4% according to a recent survey. By Feb 30, 2020, more than 80,000 people have been infected around the world, most of them are in China (Figure 1). At present, there are different numbers of infected people in all provinces of China, and Hubei province is the most serious regions (Figure 2), and the signs of infection outbreak are obvious. In addition, more than 40 countries around the world have also seen new cases of COVID-19. As a result, the COVID-19 brings great challenges to public health in the world.

Given the COVID-19 is a new infectious disease, scientists still know little about it. At present, the COVID-19 lacks effective treatment drugs. To date, no clinical intervention trial has been completed and reported. Due to the urgent situation of treatment and prevention and control of the disease, it is necessary to research and develop effective intervention methods of COVID-19 to facilitate disease control. Since the outbreak of the COVID-19, many researchers in China have immediately carried out clinical research scheme, aiming to solve the treatment, prevention and diagnosis of the COVID-19. However, up to now, there is still a lack of systematic review to analyze the characteristics and existing problems of registered clinical trials. Therefore, we conduct the first systematic review of the clinical trials of COVID-19 in order to provide evidence for the control of the COVID-19.

Materials and methods

Inclusion criteria
This review was performed according to the Cochrane Handbook for Systematic Reviews of Interventions and presented based on Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines.

The inclusion criteria of this study are: patients with COVID-19; clinical trial with protocol; involves the diagnosis, prevention and treatment of COVID-19; have clear and specific end-point outcomes; design type can be any type of study design.

**Exclusion criteria**

The exclusion criteria of this study are: animal trials; theoretical research; and unregistered clinical trials.

**Retrieval strategies**

The literature retrieval was independently completed by two researchers. The databases of the Chinese Clinical Trial Registration Center and the ClinicalTrials.gov were included. There was no language limit for the search, and the search deadline was February 9, 2020. The key words were as following: novel coronavirus, COVID-19, 2019-nCoV pneumonia, novel coronavirus pneumonia, 2019-nCoV infection, new coronavirus, etc.

**Data extraction**

The extracted data mainly include registration number, project name, research leader, age, research type, study design, sponsor, implementation unit, start time, completion period, research site, research institute, stage, research object, inclusion standard, exclusion standard, sample size, setting, location, recruitment period, intervention group measures, control group measures, random methods, blind methods, distribution concealment and measurement indicators. All the evaluated literature was independently conducted by two researchers.

**Methodology quality assessment**

The quality evaluation and data extraction of each literature that met the inclusion criteria was conducted independently and cross-check was carried out by two researchers. When the opinions were inconsistent, final decisions were decided by two researchers through discussion. The Intervventional clinical trial was based on Cochrane risk of bias items: randomization sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias [19]. The observational study was based on the quality evaluation by Newcastle-Ottawa scale (NOS) [20].
Summary and synthesis

This review presented a narrative synthesis. This study mainly analyzed and summarized the types of studies, intervention, host organization and address, sample size, research stage, research status, excepted completion time, inclusion and exclusion criteria, outcome measurement and observation time, methodology quality and describes the results with statistics and characteristics respectively. Nonparametric data was represented by median and 95% CI and the statistical analysis used MedCalc statistical software (version 15.2.2, MedCalc Software bvba, Ostend, Belgium; http://www.medcalc.org; 2015). The bias plot was performed by Review Manager (RevMan) [Computer program](version 5.2, Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2012).

Results

Trial search results

Up to February 9, 2020, we retrieved 57 clinical trials of COVID-19 from the Chinese clinical registration center, and 18 clinical trials of COVID-19 from the ClinicalTrials.gov, and a total of 75 clinical trials of COVID-19 were obtained (Table 1 and Table 2). The retrieval process is shown in Figure 3.

General characteristics of the clinical trials

In addition to the two observational trials from France (NCT04262921, NCT04259892), the others were sponsored by Chinese organizations. These organizations are responsible for three or more: the First Affiliated Hospital of Zhejiang University, Xinhua Hospital of Hubei University of Traditional Chinese medicine, Hubei Integrated Hospital of Traditional Chinese and Western Medicine, Chengdu University of Traditional Chinese Medicine Affiliated Hospital, Beijing Hospital of Traditional Chinese medicine, Zhejiang University of Traditional Chinese Medicine, and Tongji Hospital, etc., among which the most undertakers were the First Affiliated Hospital of Zhejiang University, 7 items in total. The addresses of the organizers are Hubei, Beijing, Zhejiang, Guangdong, Sichuan, Shanghai, etc., with the largest number of Hubei Province, totalling 25 (Figure 4). From the perspective of research types, most of them are intervention control studies (63) aiming at drug therapy, followed by observation studies totalling 12 (6 studies on the efficacy
of traditional Chinese medicine, 2 preventive studies, 4 studies on prognosis, rehabilitation and devices).

Most of the trials have passed the ethical review, most of the studies are still in the preparation stage, only 11 trials have started to recruit patients, and all the registered clinical trials have not been completed. The first to register was on January 3, 2020 was a randomized controlled trial of "Chinese medicine for severe pneumonia with severe coronavirus pneumonia" on January 3, 2020, which is sponsored by Dongzhimen Hospital of Beijing University of Traditional Chinese Medicine.

In terms of trial stages, 20 trials are exploratory studies or in the preliminary experiment stage, 9 items in the extended validation of drugs on the market, only 2 trials in stage (NCT04252664, "Mild/Moderate 2019-nCoV Remdesivir RCT" and NCT04257656, "Severe 2019-nCoV Remdesivir RCT" by Cao et al), and other unspecified items. In terms of sample size, the median sample size of the intervention study group (cases) was 60 (95% CI: 50 – 80), and the median sample size of the control group (cases) was 50 (95% CI: 30 – 60). The median (days) of intervention study was 180 (95% CI: 146.3 – 328.9) and the median (days) of the observation period was 334 (95% CI: 166.6 – 363.4).

**Characteristics of inclusion criteria**

The common characteristics of inclusion criteria included: signing informed consent; age over 18 years; laboratory test (RT-PCR) confirmed infection of COVID-19 (diagnostic criteria for pneumonia diagnosis in line with “Protocol of Prevention and Control of Novel Coronavirus Pneumonia”); chest imaging confirmed lung involvement; participants were willing to be assigned to any designated treatment group randomly; agree not to participate in another study of the investigator until the study was completed. Most of the subjects were limited to light (ordinary subjects), and few of the studies included severe patients.

**Characteristics of exclusion criteria**

The common characteristics of the exclusion criteria are: severe and critical patients with COVID-19; pregnant and lactating women; allergic patients; patients with serious heart, brain, kidney, tumor, hemoglobin disease and other diseases; patients with mental disorders, drug abuse or dependence history; those who do not get informed consent; the researchers think the subject is not suitable.
**Intervention and comparison**

The main intervention methods of registered clinical trials include traditional Chinese medicine treatment, western medicine treatment and integrated traditional and Western medicine treatment, etc.; the outcome of treatment observation mainly includes clinical rehabilitation time, the incidence of using mechanical ventilation, the incidence in ICU, mortality, all kinds of complications and virological detection indicators, etc.; the medication methods mainly include oral, injection, atomization inhalation, etc.; the majority of medication time is more than one week. The time limit of outcome observation was more than 2-4 weeks. The controls were mainly treated with placebo or routine treatment.

In the registered clinical trials, there are 32 western medicine treatments, and the intervention methods mainly include: i) antiviral drugs, such as: rhteicvir, abidol, fabiravir, chloroquine phosphate, asc09/ritonavir compound tablets, lopinavir/ritonavir (Coriolus), hydroxychloroquine, chloroquine, baloxavir, darunavir/Corbis, etutabine/propofol tenofovir, etc.; ii) antiviral drug combination biological agents, for example: lucotinib combined with mesenchymal stem cell therapy, recombinant cytokine-gene derived protein injection combined with abidol or lopinavir/ritonavir, recombinant virus macrophage inflammatory protein for aerosol inhalation injection or lopinavir/ritonavir tablets combined with thymosin A1, lopinavir/ritonavir and interferon-\(\alpha\)2b; iii) biological agents (products), for example: uterine blood stem cells, interferon, cord blood mononuclear cells, cord mesenchymal stem cell-conditioned medium, recombinant cytokine gene-derived protein, immunoglobulin, etc.; and iv) steroid therapy, for example, glucocorticoid (intervention in critical patients).

There are 22 clinical registration trials treated with traditional Chinese medicine. Traditional Chinese medicine treatment drugs are mainly various kinds of compound Chinese herbal medicines (decoction, capsule, granule, etc.), including Feiyanyihao, Qingfeijiedutang, Xinguanyihao, Lianhuaqingwen capsule, etc. The main ingredients are antiviral and immunomodulatory Chinese herbal formulas. In addition, traditional Chinese medicine treatment also involves some injections from herbal extract, such as Shuanghuanglian Injection, Xue-Bi-Jing Injection and Tanreqing Injection.
There are 6 clinical registration trials of the combination of Chinese medicine and Western medicine, and the intervention means is to use the combination of the above Chinese herbs and Western medicine antiviral drugs.

**Observation outcomes and measure timing**

The observation outcomes included: cure rate, cure time, incidence of adverse outcomes, clinical improvement time, ratio of normal progression to severe disease, time to heavy progression, death, virus nucleic acid copies, coronavirus nucleic acid conversion time, pneumonia severity index, Murray lung injury score, chest CT, the survival rate and mortality of patients.

Additionally, some laboratory tests novel coronavirus were also selected, including routine blood test, urine routine test, C-reactive protein, procalcitonin, erythrocyte sedimentation rate, muscle enzyme, troponin, myoglobin, D dimer, blood gas analysis, coagulation routine, new coronavirus nucleic acid examination, and T cell subgroup analysis, hospital length etc.

The follow-up timing of the outcome measure is mostly 2-4 weeks, but some studies do not set forth a plan.

**Methodology quality**

According to the Cochrane bias risk assessment results (Figure 5), the quality assessment of the interventional study methodology is generally low. Most trials reported randomization, while the other trials had high risk of biases in randomization (17 trials did not mention randomization and 6 trials were judged as non-randomized trials); few trials conducted distribution concealment; only nine trials implemented blinding of participants, personnel and outcome assessment; None of the 63 trials clarified drop-out and follow-up bias. However, other bias risks, such as the risk of conflict of interest among drug manufacturers, are unclear.

The NOS scores of the observational trials are from 4 to 6 (Table 3). Most of the observational trials have high risk of biases in assessment outcome, follow-up of outcome and adequacy of follow up of cohorts (Figure 6). Therefore, the overall quality of registered observational trials is low.

**Discussion**
COVID-19 is a new infectious disease, which is still poorly understood, so there is no recognized effective treatment. This sudden health incident has caused great harm to China and seriously threatened people’s health\textsuperscript{21-23}. In order to deal with the disease, researchers have carried out many clinical studies intensively. According to the search results, the current studies are concentrated in China, mainly involving the treatment and intervention of traditional Chinese medicine, Western medicine and the combination of traditional Chinese and Western medicine. Clinical research institutes are mainly hospitals of China. As far as the stage was concerned, most of the studies are still the exploratory research or in pre-experiment stage, and there are nine extended validation studies of the indications of drugs on the market (chloroquine phosphate, abidol, fabiravir, asc09/ritonavir compound tablets, lopinavir/ritonavir, hydroxychloroquine, chloroquine), etc., while only two of the three-phase clinical trials. From the perspective of sample size, the intervention trials are small sample studies, hence, the evidence level is low and the clinical significance will be limited.

At present, the treatment of this disease is mainly antiviral, improving patients’ immunity, intervening in autoimmune damage (against immune storm caused by cytokines) and symptomatic treatment. According to the in vitro cell test, the antiviral effect of Western drugs is obviously superior to that of traditional Chinese medicine (the concentration value of the inhibitory effect is low). But considering that Chinese herbs have both antiviral and immunomodulatory effects, it has a certain application prospect in disease prevention and treatment; at present, the combination of Chinese and Western Medicine (Qingfeipaidutang and chloroquine phosphate, abidol, lopinavir/Rito) is considered as a better treatment method by experts, and has been listed in “Protocol of Prevention and Control of Novel Coronavirus Pneumonia”, but there is still a lack of high-quality evidence, which needs clinical verification.

According to the existing preliminary evidence, the antiviral drug Remdesivir (two three-phase clinical trials for light, moderate and heavy patients respectively, expected to end on April 27, 2020) has a promising application prospect. The reasons are as follows: i) cell test results both in vitro and in vivo showed that very low concentration can play an antiviral role\textsuperscript{24-25}; ii) animal test is safe \textsuperscript{26}; and iii) clinical test is anti-Ebola (the same as new coronavirus) RNA virus is effective \textsuperscript{27-28}; and iv) clinical case report is effective \textsuperscript{29}. In addition, some of the validation drugs, such as Chloroquine Phosphate, Abidol, Darunavir, and Lopinavir/Ritonavir (Coriolus Versicolor),
have been proved to be safe and have strong antiviral potential in vitro. Therefore, these Western antiviral drugs have an application potential and need to be verified in clinical practice.

In this review, we found that many trials used biological products for immunotherapy of the disease. In light of the experience and lessons of severe acute respiratory syndrome (SARS), steroid therapy has been used cautiously in the treatment of the disease, so there are few trials based on the retrieval results.

From the perspective of inclusion and exclusion criteria, some people were excluded, such as children and adolescents, pregnant women, patients with serious liver and kidney damage. Therefore, this will lead to the lack of clinical evidence in this part of the population.

The outcomes of clinical trial observation includes clinical observation outcomes, physical examination and laboratory test results, but some outcomes are subjective, which may cause measurement bias.

Based on Cochrane risk of bias items and NOS, we evaluated the quality of intervention trials and observational trials, respectively. The evaluation results showed that the overall quality of registered clinical research was low. Therefore, it indicates that most of the registered clinical studies have a greater risk of bias, and the level of evidence is relatively low in the future, which belittles the practice significance of the research. We believed that the main reasons for the low quality of the registered clinical trial protocols are: i) the researchers' clinical research ability is not enough, and ii) the researchers lack experience in dealing with sudden health events.

We believed that it is necessary to improve the quality of research and to the registered clinical research programmes in strict accordance with the guidelines for clinical trials. In addition, current clinical trials by different hospitals conducted spontaneously are not effectively organized and coordinated, so more scattered and disorderly. Some drugs that have not been tested in vitro or whose safety is of great concern are also being tested in clinical trials, which not only increase the risk of clinical trials, but also waste research resources. Hence, the National Administration of scientific research should strengthen their management and coordination and a small number of promising drugs, such as Remdesivir, should be prioritized for clinical trials and allowed to run smoothly.

From these registered clinical studies, we found a serious limitation: most of the registered clinical research did not consider the "timeliness", and still followed the conservative traditional
study design paradigm. The research duration was more than 5 months, and the median (days) of the intervention research was 180 (95% CI: 146.3 – 328.9), which is very unfavorable for the current urgent situation. We believed that, in the current situation, we should pay more attention to "timeliness" in the design of clinical trials (otherwise, the epidemic situation may have ended after drug approval; the research also lost its social significance). Therefore, in response to this emerging public health event, we can refer to the "sequential design" for clinical trials; "sequential design" not only saves the sample size, but also significantly shortens the research period, so it is very conducive to the screening and discovery of some drugs with significant efficacy 36-37. In addition, a very difficult problem is the treatment of severe and critical patients with COVID-19. For these patients, we suggested that: based on the "compassionate use drug" principle, with safe and obvious antiviral potential drugs, to conduct a staged small batch and single-arm clinical trials is feasible. We believed that "compassionate use drug" can not only meet the special needs of patients but also carry out clinical effectiveness observation, research and analysis, so as to improve the research efficiency and benefit patients 38-42. Also, given a large number of clinical cases have accumulated information, and using available existing data for statistics and analysis with the help of new statistical methods such as clinical data-mining 43-45 and real-world study 46-48, etc., can also quickly obtain some very valuable information and save research time.

In brief, under the condition that there are a large number of cases to be selected at present, it is of great value for the treatment and prevention of COVID-19 to try to complete various clinical trial designs and data analysis scientifically and efficiently with a variety of clinical research designs and statistical analysis methods, and researchers should try in future.

**Conclusions**

Disorderly and intensive clinical trials of COVID-19 using traditional Chinese medicine and Western medicine are ongoing or will be carried out in China. However, based on the poor quality and small sample size and long completion period, we will not be able to obtain reliable, high-quality clinical evidence about COVID-19 treatment for quite a long time in the future. In order to effectively deal with the current sudden health emergencies, the National Administration of scientific research should strengthen their management and coordination to improve the study quality based on the guidelines for clinical trials. Also, it is important to ensure that some
promising projects are prioritized. In addition, we suggest that using a variety of study designs and statistical methods to scientifically and efficiently conduct the clinical trials, which has an extremely important value for the control of COVID-19.

**Declaration of interests**

The authors declare that there is no conflict of interest.

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| No | Register number | Project leader | Project name |
|----|-----------------|---------------|-------------|
| 1  | ChiCTR2000029638| Liu L 2020    | Multicenter randomized controlled trial for novel recombinant high-efficiency compound interferon in the |
| Study ID       | Authors     | Title                                                                 | Details                                                                                                                                 |
|---------------|-------------|----------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------|
| ChiCTR2000029387 | Chen Y 2020a | Comparison of efficacy and safety of three antiviral regimens in patients with mild to moderate novel coronavirus pneumonia (COVID-19): a randomized controlled trial |                                                                                                                                          |
| ChiCTR2000029386 | Chen Y 2020b | Adjunctive Corticosteroid Therapy for Patients with Severe Novel Coronavirus Pneumonia (COVID-19): a Randomized Controlled Trial |                                                                                                                                          |
| ChiCTR2000029435 | Wei L 2020  | Randomized controlled trial for traditional Chinese medicine in the prevention of novel coronavirus pneumonia (COVID-19) in high risk population |                                                                                                                                    |
| ChiCTR2000029430 | Huang C 2020 | A randomized, open-label, blank-controlled trial for the efficacy and safety of lopinavir-ritonavir and interferon-alpha 2b in hospitalization patients with novel coronavirus pneumonia (COVID-19) |                                                                                                                                    |
| ChiCTR2000029400 | Hung L 2020 | Clinical Controlled Trial for Traditional Chinese Medicine in the treatment of Novel Coronavirus Pneumonia (COVID-19) |                                                                                                                                    |
| ChiCTR2000029418 | Liang T 2020 | Chinese Herbal medicine for Severe novel coronavirus pneumonia (COVID-19): a Randomized Controlled Trial |                                                                                                                                    |
| ChiCTR2000029436 | Li J 2020   | A single arm study for evaluation of integrated traditional Chinese and western medicine in the treatment of novel coronavirus pneumonia (COVID-19) |                                                                                                                                    |
| ChiCTR2000029432 | Yang Z 2020 | A Real World Study for the Efficacy and Safety of Large Dose Tanreqing Injection in the Treatment of Patients with Novel Coronavirus Pneumonia (COVID-19) |                                                                                                                                    |
| ChiCTR2000029431 | Zhao D 2020 | Clinical study for the remedy of M1 macrophages target in the treatment of novel coronavirus pneumonia (COVID-19) |                                                                                                                                    |
| ChiCTR2000029381 | Zhong N 2020 | A prospective comparative study for Xue-Bi-Jing injection in the treatment of novel coronavirus pneumonia (COVID-19) |                                                                                                                                    |
| ChiCTR2000029487 | Su W 2020   | Clinical Study for Gu-Biao Jie-Du-Ling in Preventing of 2019-nCoV Pneumonia (Novel Coronavirus Pneumonia, NCP) in Children |                                                                                                                                    |
| ChiCTR2000029479 | Tang J 2020 | Research for Traditional Chinese Medicine Technology Prevention and Control of 2019-nCoV Pneumonia (Novel Coronavirus Pneumonia, NCP) in the Community Population |                                                                                                                                    |
| ChiCTR2000029468 | Jiang H 2020 | A real-world study for lopinavir/ritonavir (LPV/r) and emtritabine (FTC) / Tenofovir alafenamide Fumarate tablets (TAF) regimen in the treatment of 2019-nCoV pneumonia (novel coronavirus pneumonia, NCP) |                                                                                                                                    |
| Study ID          | Author(s)  | Year | Title                                                                 |
|-------------------|------------|------|-----------------------------------------------------------------------|
| ChiCTR2000029461  | Xia W      | 2020 | A Randomized Controlled Trial for Integrated Traditional Chinese Medicine and Western Medicine in the Treatment of Common Type 2019-nCoV Pneumonia (Novel Coronavirus Pneumonia, NCP) |
| ChiCTR2000029460  | Zheng C    | 2020 | The effect of shadowboxing for pulmonary function and quality of life in patients with 2019-nCoV pneumonia (novel coronavirus pneumonia, NCP) in rehabilitation period |
| ChiCTR2000029459  | Xia W      | 2020 | The effect of pulmonary rehabilitation for pulmonary function and quality of life in patients with 2019-nCoV pneumonia (novel coronavirus pneumonia, NCP) in rehabilitation period |
| ChiCTR2000029439  | Wang Y     | 2020 | Combination of traditional chinesemedicine and western medicine in the treatment of common type 2019-nCoV pneumonia (novel coronavirus pneumonia, NCP) |
| ChiCTR2000029438  | Liu Q      | 2020 | A randomized controlled trial of integrated TCM and Western Medicine in the treatment of severe 2019-nCoV pneumonia (novel coronavirus pneumonia, NCP) |
| ChiCTR2000029544  | Qiu Y      | 2020a| A randomized controlled trial for the efficacy and safety of BaloxavirMarboxil, Favipiravir tablets in 2019-nCoV pneumonia (novel coronavirus pneumonia, NCP) patients who are still positive on virus detection under the current antiviral therapy |
| ChiCTR2000029542  | Jiang S    | 2020 | Study for the efficacy of chloroquine in patients with 2019-nCoV pneumonia (novel coronavirus pneumonia, NCP) |
| ChiCTR2000029541  | Wang H     | 2020 | A randomised, open, controlled trial for darunavir/cobicistat or Lopinavir/ritonavir combined with thymosin a1 in the treatment of 2019-nCoV pneumonia (novel coronavirus pneumonia, NCP) |
| ChiCTR2000029539  | Zhao J     | 2020 | A randomized, open-label study to evaluate the efficacy and safety of Lopinavir-Ritonavir in patients with mild 2019-nCoV pneumonia (novel coronavirus pneumonia, NCP) |
| ChiCTR2000029518  | Wen C      | 2020a| Chinese medicine prevention and treatment program for 2019-nCoV pneumonia (novel coronavirus pneumonia, NCP): a perspective, double-blind, placebo, randomised controlled trial |
| ChiCTR2000029517  | Wen C      | 2020b| Chinese medicine prevention and treatment program for suspected 2019-nCoV pneumonia (novel coronavirus pneumonia, NCP): a perspective, double-blind, placebo, randomised controlled trial |
| ChiCTR2000029496  | Gong G     | 2020 | A randomized, open label, parallel controlled trial for evaluating the efficacy of recombinant cytokine |
| Study ID          | First Name | Last Name | Year | Title                                                                 |
|------------------|------------|-----------|------|----------------------------------------------------------------------|
| ChiCTR2000029495 | Huang M    | 2020     |      | Traditional Chinese Medicine, Psychological Intervention and Investigation of Mental Health for Patients With 2019-nCoV Pneumonia (Novel Coronavirus Pneumonia, NCP) in Convalescent Period |
| ChiCTR2000029493 | Zhang J    | 2020     |      | Traditional Chinese Medicine for Pulmonary Fibrosis, Pulmonary Function and Quality of Life in Patients With 2019-nCoV Pneumonia (Novel Coronavirus Pneumonia, NCP) in Convalescent Period: a Randomized Controlled Trial |
| ChiCTR2000029580 | Zhou J     | 2020     |      | A prospective, single-blind, randomized controlled trial for Ruxolitinib combined with mesenchymal stem cell infusion in the treatment of patients with severe 2019-nCoV pneumonia (novel coronavirus pneumonia, NCP) |
| ChiCTR2000029589 | Liu Q     | 2020b    |      | An open, prospective, multicenter clinical study for the efficacy and safety of Reduning injection in the treatment of 2019-nCoV pneumonia (novel coronavirus pneumonia, NCP) |
| ChiCTR2000029600 | Liu Y     | 2020     |      | Clinical study for safety and efficacy of Favipiravir in the treatment of 2019-nCoV pneumonia (novel coronavirus pneumonia, NCP) |
| ChiCTR2000029601 | Tong X    | 2020a    |      | Community based prevention and control for Chinese medicine in the treatment of 2019-nCoV pneumonia (novel coronavirus pneumonia, NCP) in the isolate suspected and confirmed population |
| ChiCTR2000029602 | Tong X    | 2020b    |      | Clinical study for community based prevention and control strategy of novel coronavirus pneumonia (COVID-19) in the isolate suspected and confirmed population |
| ChiCTR2000029603 | Qiu Y     | 2020a    |      | A Randomized, Open-Label, Multi-Centre Clinical Trial Evaluating and Comparing the Safety and Efficiency of ASC09/Ritonavir and Lopinavir/Ritonavir for Confirmed Cases of 2019-nCoV Pneumonia (Novel Coronavirus Pneumonia, NCP) |
| ChiCTR2000029605 | Liu C     | 2020     |      | A randomized, open-label, blank-controlled, multicenter trial for Shuang-Huang-Lian oral solution in the treatment of 2019-nCoV pneumonia (novel coronavirus pneumonia, NCP) |
| ChiCTR2000029578 | Wen C     | 2020     |      | Chinese medicine prevention and treatment program for 2019-nCoV pneumonia (novel coronavirus pneumonia, NCP): a perspective, sing-arm trial |
| No. | CT Number       | Author | Year | Title                                                                 |
|-----|-----------------|--------|------|----------------------------------------------------------------------|
| 37  | ChiCTR2000029573 | Li L   | 2020 | A multicenter, randomized, open-label, positive-controlled trial for the efficacy and safety of recombinant cytokine gene-derived protein injection combined with abidole, lopinavir/ritonavir in the treatment of 2019-nCoV pneumonia (novel coronavirus pneumonia, NCP) patients |
| 38  | ChiCTR2000029572 | Pei B  | 2020a| Safety and efficacy of umbilical cord blood mononuclear cells in the treatment of severe and critically 2019-nCoV pneumonia (novel coronavirus pneumonia, NCP): a randomized controlled clinical trial |
| 39  | ChiCTR2000029569 | Pei B  | 2020b| Safety and efficacy of umbilical cord blood mononuclear cells conditioned medium in the treatment of severe and critically 2019-nCoV pneumonia (novel coronavirus pneumonia, NCP): a randomized controlled clinical trial |
| 40  | ChiCTR2000029559 | Zhang Z| 2020 | Therapeutic effect of hydroxychloroquine on 2019-nCoV pneumonia (novel coronavirus pneumonia, NCP) |
| 41  | ChiCTR2000029558 | Xie C  | 2020a| Recommendations of Integrated Traditional Chinese and Western Medicine for Diagnosis and Treatment of 2019-nCoV Pneumonia (Novel Coronavirus Pneumonia, NCP) in Sichuan Province |
| 42  | ChiCTR2000029550 | Xie C  | 2020b| Recommendations for Diagnosis and Treatment of Influenza Patients in the Hospital of Chengdu University of Traditional Chinese Medicine Under the Raging of 2019-nCoV Pneumonia (Novel Coronavirus Pneumonia, NCP) |
| 43  | ChiCTR2000029549 | Xie C  | 2020c| Recommendations of Integrated Traditional Chinese and Western Medicine for 2019-nCoV Pneumonia (Novel Coronavirus Pneumonia, NCP) |
| 44  | ChiCTR2000029548 | Qiu Y  | 2020b| Randomized, open-label, controlled trial for evaluating of the efficacy and safety of BaloxavirMarboxil, Favipiravir, and Lopinavir-Ritonavir in the treatment of 2019-nCoV pneumonia (novel coronavirus pneumonia, NCP) patients |
| 45  | ChiCTR2000029636 | Hu B   | 2020 | Efficacy and safety of aerosol inhalation of vMIP in the treatment of 2019-nCoV pneumonia (novel coronavirus pneumonia, NCP): a single arm clinical trial |
| 46  | ChiCTR2000029626 | Fang X | 2020 | Immune Repertoire (TCR & BCR) Evaluation and Immunotherapy Research in Peripheral Blood of 2019-nCoV Pneumonia (Novel Coronavirus Pneumonia, NCP) Patients |
| 47  | ChiCTR2000029621 | Qu J   | 2020 | Clinical study of arbidol hydrochloride tablets in the treatment of 2019-nCoV pneumonia (novel coronavirus pneumonia, NCP) |
| 48  | ChiCTR2000029609 | Shan H | 2020 | A prospective, open-label, multiple-center study for the efficacy of chloroquine phosphate in patients with 2019-nCoV pneumonia (novel coronavirus pneumonia, NCP) |
| Study ID   | Author(s)   | Title                                                                 |
|-----------|-------------|----------------------------------------------------------------------|
| ChiCTR2000029606 | Li L 2020b | Clinical Study for Human Menstrual Blood-Derived Stem Cells in the Treatment of Acute Novel Coronavirus Pneumonia (NCP) |
| ChiCTR2000029625 | Cai H 2020 | Construction of Early Warning and Prediction System for Patients with Severe / Critical 2019-nCoV Pneumonia (Novel Coronavirus Pneumonia, NCP) |
| NCT04252274 | Lu 2020b    | Efficacy and Safety of Darunavir and Cobicistat for Treatment of Pneumonia Caused by 2019-nCoV |
| NCT04261517 | Lu 2020b    | Efficacy and Safety of Hydroxychloroquine for Treatment of Pneumonia Caused by 2019-nCoV (HC-nCoV) |
| NCT04260594 | QU 2020     | Clinical Study of Arbidol Hydrochloride Tablets in the Treatment of Pneumonia Caused by Novel Coronavirus |
| NCT04261907 | QIU 2020    | Evaluating and Comparing the Safety and Efficiency of ASC09/Ritonavir and Lopinavir/Ritonavir for Novel Coronavirus pneumonia |
| NCT04257656 | Cao B 2020a | Severe 2019-nCoV Remdesivir RCT |
| NCT04244591 | Du B 2020   | Glucocorticoid Therapy for Novel Coronavirus Critically Ill Patients With Severe Acute Respiratory Failure |
| NCT04251871 | Wang R 2020 | Treatment and Prevention of Traditional Chinese Medicines (TCMs) on 2019-nCoV Infection |
| NCT04263402 | HanM 2020a  | The Efficacy of Different Hormone Doses in 2019-nCoV Severe Pneumonia |
| NCT04254874 | HanM 2020 b | A Prospective, Randomized Controlled Clinical Study of Interferon Atomization in the 2019-nCoV Pneumonia |
| NCT04261270 | HanM 2020 c | A Randomized, Open, Controlled Clinical Study to Evaluate the Efficacy of ASC09F and Ritonavir for 2019-nCoV Pneumonia |
| NCT04252664 | Cao B 2020b | Mild/Moderate 2019-nCoV Remdesivir RCT |
| NCT04261426 | Li 2020     | The Efficacy of Intravenous Immunoglobulin Therapy for Severe 2019-nCoV Infected Pneumonia |
| NCT04255017 | HanM 2020 d | A Prospective, Randomized Controlled Clinical Study of Antiviral Therapy in the 2019-nCoV Pneumonia |
Table 2: Summary of observational registered clinical trials.

| No | Register number | Project leader | Trial name |
|----|-----------------|----------------|------------|
| 1  | ChiCTR2000029637 | Zhang Z 2020a  | An observational study for Xin-Guan-1 formula in the treatment of 2019-nCoV pneumonia (novel coronavirus pneumonia, NCP) |
| 2  | ChiCTR2000029430 | Zhang Z 2020b  | Study for the TCM syndrome characteristics of novel coronavirus pneumonia (COVID-19) |
| 3  | ChiCTR2000029462 | Li J 2020      | Study for clinical characteristics and distribution of TCM syndrome of 2019-nCoV pneumonia (novel coronavirus pneumonia, NCP) |
| 4  | ChiCTR2000029437 | Xia W 2020     | A single arm study for combination of traditional Chinese and Western Medicine in the treatment of novel coronavirus pneumonia (COVID-19) |
| 5  | ChiCTR2000029592 | Zheng X 2020   | Study for Arbidol Hydrochloride in the Prophylaxis of Novel Coronavirus pneumonia in High-risk Population with History of Exposed to 2019-nCoV pneumonia |
| 6  | ChiCTR2000029624 | Lu H 2020      | A real world study for traditional Chinese Medicine in the treatment of 2019-nCoV pneumonia (novel coronavirus pneumonia, NCP) |
| 7  | ChiCTR2000029579 | Zhou J 2020    | Cytokines profiling and their clinical significance analysis of 2019-nCoV pneumonia (novel coronavirus pneumonia, NCP) patients |
| 8  | NCT04262921     | Yazdan 2020    | Clinical Characterization Protocol for Severe Emerging Infections |
| 9  | NCT04256395     | Dong 2020      | Efficacy of a self-test and self-alert mobile applet in detecting susceptible infection of 2019-nCoV |
| 10 | NCT04245631     | Xie 2020       | Development of a simple, fast and portable recombinase aided amplification Assay for 2019-nCoV |
| 11 | NCT04255940     | HAO 2020       | 2019-nCoV outbreak and cardiovascular diseases |
| 12 | NCT04259892     | Duval 2020     | Viral excretion in contact subjects at high/moderate Risk of coronavirus 2019-nCoV infection |
Table 3 The methodology quality of the observational trials using Newcastle-Ottawa scale.

| Register number | Representativeness of the exposed cohort | Selectivity of the exposed cohort | Ascertainment of the outcome of exposure | Demonstration that outcome of interest was not present at start of study | Comparability of cohorts on the basis of design or analysis | Assessment of outcome was not measured at baseline | Adequacy of follow-up of cohorts | Was the outcome of interest measured long enough for outcomes to occur | Scores |
|-----------------|----------------------------------------|-----------------------------------|-----------------------------------------|---------------------------------------------------------------|--------------------|----------------------------------------|-----------------------------|----------------------------------------|-------|
| ChiCTR20000029637 | 1                                      | 1                                 | 1                                       | 1                                                            | 0                  | 1                                      | 0                           | 6                                         |       |
| ChiCTR20000029430 | 1                                      | 1                                 | 1                                       | 1                                                            | 1                  | 0                                      | 0                           | 5                                         |       |
| ChiCTR20000029462 | 1                                      | 1                                 | 1                                       | 1                                                            | 0                  | 0                                      | 0                           | 6                                         |       |
| ChiCTR20000029437 | 1                                      | 1                                 | 1                                       | 1                                                            | 1                  | 0                                      | 0                           | 6                                         |       |
| ChiCTR20000029592 | 1                                      | 1                                 | 1                                       | 1                                                            | 1                  | 0                                      | 0                           | 6                                         |       |
| NCT04262921      | 1                                      | 1                                 | 1                                       | 1                                                            | 1                  | 0                                      | 0                           | 6                                         |       |
| NCT04256395      | 1                                      | 1                                 | 1                                       | 1                                                            | 1                  | 0                                      | 0                           | 6                                         |       |
| NCT04245631      | 1                                      | 1                                 | 1                                       | 0                                                            | 0                  | 1                                      | 0                           | 5                                         |       |
| NCT042595940     | 1                                      | 1                                 | 1                                       | 0                                                            | 0                  | 0                                      | 0                           | 4                                         |       |
| NCT04259892      | 1                                      | 1                                 | 1                                       | 1                                                            | 0                  | 1                                      | 0                           | 6                                         |       |
| ChiCTR20000029579 | 1                                      | 1                                 | 1                                       | 1                                                            | 0                  | 0                                      | 0                           | 5                                         |       |

Note: A study can be awarded a maximum of one point for each numbered item within the Selection and Outcome categories. A maximum of two points can be given for Comparability.
Figure 1 Polyline chart of the prevalence trend of COVID-19 in China in 2020.

Note: The data are from the official website of the National Health Commission of the People's Republic of China, http://www.nhc.gov.cn/xcs/xxgzbd/gzbd_index.shtml.

Figure 2 Polyline chart of the prevalence trend of COVID-19 in Hubei province and non-Hubei regions of China.

Note: The data are from the official website of the National Health Commission of the People's Republic of China, http://www.nhc.gov.cn/xcs/xxgzbd/gzbd_index.shtml.
Figure 3 The flowchart of retrieval of the registered clinical trials.

Records identified through ChiCTR searching (n = 78)

Records identified through ClinicalTrials.gov (n = 33)

Records after duplicates removed (n = 111)

Irrelevant records excluded (n = 36)

Clinical trials assessed for eligibility (n = 75)

Figure 4 Addresses of the sponsors of the registered clinical trials by region.
Figure 5 Risk of bias graph across all included interventional clinical trials.

Figure 6 Risk of bias graph across all included observational studies.