A Systematic Review on the Therapeutic Relevance of Hydroxychloroquine/Chloroquine in the Management of COVID-19

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Abstract

Background: The coronavirus disease-2019 (COVID-19) pandemic is coming to the fore and has surfaced as a public health emergency of international concern. The lack of vaccines or an effective treatment has led to the global hunt for potential pharmaceuticals in adequately managing this disease. This systematic review highlights the efficacy of chloroquine and its derivative hydroxychloroquine in the treatment of COVID-19 and also explores the safety profile of these drugs. Methods: EMBASE, COCHRANE, and PubMed databases were searched for studies on the use of hydroxychloroquine or chloroquine in the treatment of COVID-19. Results: Twenty articles were selected including expert opinions, National Guidelines, three small randomized controlled trials, and one prospective study. Both hydroxychloroquine and chloroquine have shown promising results including reduction in hospital length of stay and overall mortality. Moreover, concomitant use with azithromycin seems to reduce viral load to a greater extent. Conclusions: Considering the known safety profile of these drugs in the treatment of other diseases, their availability and affordability, chloroquine and hydroxychloroquine are potential antiviral agents in the treatment of COVID-19. However, reported side effects of these drugs when used in conjunction with azithromycin in patients with comorbidities have raised significant safety concerns. High-quality randomized clinical trials are warranted to provide more comprehensive evidence of the safety of these drugs in patients infected with COVID-19.

Keywords: Chloroquine, coronavirus, coronavirus disease 2019, hydroxychloroquine, pneumonia, severe acute respiratory syndrome-CoV-2

Introduction

In December 2019, the first case of a novel disease was reported in Wuhan, in Hubei province of China. On further investigation, it was discovered that this was a new variant of Severe Acute Respiratory Syndrome (SARS) coronavirus or SARS-CoV. As of August 17, 2020, coronavirus disease 2019 (COVID-19) has spread across 215 countries and territories worldwide, with total cases crossing 21.8 million and a mortality of over 773,000.[1] It was deciphered that its main mode of transmission is from Human-Human via direct contact or droplets.[2,3] However, airborne transmission of SARS-CoV-2 can also occur during medical interventions with aerosol-generating procedures.

Although a vast majority of cases showed mild flu-like symptoms such as fever, malaise, and cough, a significant proportion of these cases progressed to develop acute respiratory distress syndrome, respiratory failure, and multiple organ failure caused by uncontrolled cytokine storms.[1,4] As the pandemic of coronavirus disease (COVID-19) continues to undermine public health in numerous countries, global efforts are being geared toward developing a vaccine against this virus. As of now, there is no known proven specific pharmacological treatment for the disease. Globally, the

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treatment has been focused on symptomatic and respiratory support.\[5\] Moreover, poor prognosis associated with the use of resuscitation fluids (hypotonic crystalloids, starches, or gelatine) and systemic corticosteroids, calls for the cautious use of positive end-expiratory pressure and intravenous fluids. Hence, significantly limiting the therapeutic options for COVID-19 pneumonia.\[6\]

In the hunt for an effective treatment to improve remission from COVID-19 infection and reduce mortality, multiple drugs including a range of antivirals and immunomodulators such as chloroquine and hydroxychloroquine are being validated for their efficacy and safety in numerous clinical trials. In vitro studies and smaller clinical trials held in China and France have suggested that chloroquine and hydroxychloroquine are effective in reducing viral replication and consequently decreasing viral load in numerous infections including those caused by SARS-associated coronavirus (CoV) and MERS-CoV\[7-9\]. Chloroquine has been widely used for over half a century for the treatment of malaria in different regions of the world and figures in the World Health Organization (WHO) list of essential medications. Nonetheless, the efficacy and safety of this drug for treatment of SARS-CoV-2 pneumonia has not been sufficiently studied. Its high availability, low cost, and an established clinical profile makes it a potential candidate for treatment of this public health emergency.\[10\] In this perspective, this systematic review summarizes all the available evidence till date including opinions, guidelines, preliminary, and prospective studies evaluating the use of chloroquine and hydroxychloroquine in patients with COVID-19 and sheds light on the efficacy and safety profile of these drugs in treating this infection.

**Methods**

A systematic search was carried out using EMBASE, COCHRANE, and PubMed databases from the onset of the COVID-19 epidemic to April 01, 2020 to identify articles discussing the use of hydroxychloroquine or chloroquine in the treatment of COVID-19. Two independent reviewers were involved in the identification and screening and extraction of information from these articles. We used the key words “SARS-CoV-2,” “2019-nCoV,” “COVID-19,” “Coronavirus,” “Wuhan,” and these were searched in conjunction with “Chloroquine,” “Hydroxychloroquine,” “Treatment,” “Therapeutics,” and “Therapy.” We also searched for any published data ranging from expert opinion to meta-analysis. Database searches were devoid of language restrictions considering that majority of the data and publications coming from China and Italy were in their native language. In addition, we used the snowballing method to review the references of the selected articles for further potential papers. We did not include any papers specifically discussing in vitro studies. The search was also expanded to the Chinese Clinical Trial Registry, Clinicaltrial.Gov, and the International Clinical Trials Registry Platform (WHO) to retrieve data on ongoing trials and those planned in the near future. Official National Guidelines were also explored for information regarding drugs used in the management of COVID-19. The review team adhered to the Preferred Reporting Items for Systematic Review and Meta-Analysis guidelines.\[11\] Any discrepancies or doubts regarding the exclusion criteria were resolved by mutual consensus.

**Results**

The initial search identified 958 results through the PubMed, EMBASE, and COCHRANE databases and 47 through other sources [Figure 1]. Following screening by title and text and removal of duplicates, we evaluated twenty articles in full text. These selected articles comprising expert opinions, National Guidelines, three small randomized controlled trials, and one prospective study, discussed the use or potential use of chloroquine or hydroxychloroquine in the treatment of COVID-19. The findings from these articles have been summarized in Table 1a-c. To date, 37 clinical trials have been recorded on the trial registries [Table 2a-d].

**Discussion**

Among the 20 articles analyzed in this systematic review on chloroquine and hydroxychloroquine usage for the treatment of COVID 19, the majority were based on expert opinions and National Guidelines, with only three small randomized control trials and one prospective cohort study. All the National Guidelines recommended the use of these drugs in the treatment regimen of patients testing positive for COVID-19 [Table 1a]. In addition, the ICMR guidelines of India were the first to implement the use of hydroxychloroquine in asymptomatic health-care workers treating suspected or confirmed cases and household contacts of infected patients.\[12\]

The efficacy of chloroquine against other viral infections in in vitro studies was highlighted in an Editorial by French researchers, with the aim of encouraging the inclusion of this drug in clinical trials.\[13\] They further argued that the favorable risk–benefit balance, the high safety, and the relatively lower cost of this drug justifies its relevance in addressing the current COVID-19 pandemic. The expert consensus published by a multicenter collaboration group of Department of Science and Technology of Guangdong Province and Health Commission of Guangdong Province recommended the use of chloroquine phosphate in patients with SARS-CoV-2 pneumonia, classified as mild, moderate, or severe, provided there was no evidence of contraindications to this drug.\[14\]

Based on the apparent efficacy and acceptable safety of chloroquine phosphate in patients with COVID-19 pneumonia in multicenter clinical trials conducted in China, this drug was recommended for treating this infection in a larger population.\[5\] A letter from the Chinese researchers stated that the State Council of People’s Republic of China had included the use of Chloroquine Phosphate in the 6th Edition of the Guidelines for the Prevention, Diagnosis, and Treatment of Pneumonia Caused by COVID-19, for the treatment of novel coronavirus pneumonia.
Using a similar model, chloroquine/hydroxychloroquine was approved for treatment later by the respective control bodies in Italy, India, France, and USA after its trial use lead to patient recovery in multiple centers across these countries.

Nonetheless, recommendations from researchers in China advocate the use of hydroxychloroquine over chloroquine, considering the relatively severe side effects of the latter. They also emphasized that hydroxychloroquine has a similar antiviral activity to chloroquine, while having a safer clinical profile, being more cost effective, and readily available than chloroquine. In addition, a randomized controlled trial conducted in China reported a significant reduction in time taken for clinical recovery and resolution of pneumonia in patients receiving hydroxychloroquine. The expert opinions also suggested that hydroxychloroquine treatment can potentially improve outcomes in terms of decrease in length of stay in hospitals and decline in overall mortality.

An open-label nonrandomized clinical trial documented a remarkable reduction in viral load of SARS-CoV-2, when hydroxychloroquine was concurrently administered with azithromycin. However, one randomized controlled trial in China and a prospective cohort study in France refuted these claims and reported no additional of using hydroxychloroquine over conventional treatment and no evidence of a strong antiviral activity from the combined therapy of hydroxychloroquine and azithromycin, respectively. Amidst the reports with promising results from the use of chloroquine and hydroxychloroquine in treatment of COVID-19, many researchers and clinicians have also expressed concern over the safety profile of these drugs, especially when used in conjunction with azithromycin and have cited the possibility of QTc prolongation, particularly in patients with underlying cardiovascular conditions.

The National Guidelines from Italy are contradictory in this aspect and suggest the use of chloroquine or hydroxychloroquine in a wide range of patients, ranging from those with mild respiratory symptoms and comorbidities to patients with severe respiratory failure. Some reports also recommend practitioners to exercise caution when prescribing chloroquine/hydroxychloroquine for COVID-19 patients. For instance, a public document released by the Dutch Center of Disease control laid emphasis on the need to discontinue...
Table 1a: National guidelines assessing the use of chloroquine and hydroxychloroquine in effectively managing patients with Coronavirus disease 2019 infection

| Title                                                                 | Published Date | Article type       | Country | Trial summary                                                                                                                                                                                                 |
|----------------------------------------------------------------------|----------------|--------------------|---------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| ICMR National COVID-19 task force[12]                                | March 17, 2020 | National guideline | India   | Hydroxychloroquine for prophylaxis of SARS-CoV-2 infection is recommended for:                                                                                                                                   |
|                                                                      |                |                    |         | Asymptomatic healthcare workers involved in the care of suspected or confirmed cases: 400 mg twice a day on day 1, followed by 400 mg once weekly for next 7 weeks; to be taken with meals                                    |
|                                                                      |                |                    |         | Asymptomatic household contacts of laboratory confirmed cases: 400 mg twice a day on day 1, followed by 400 mg once weekly for next 3 weeks; to be taken with meals                                                   |
| Expert consensus on Chloroquine phosphate for the Treatment of novel coronavirus pneumonia (Original Article in Chinese)[11] | March 12, 2020 | National guideline | China   | Chloroquine phosphate tablet, 500 mg twice/day for 10 days for patients diagnosed as mild, moderate and severe cases of COVID-19 pneumonia without contraindications to chloroquine                                |
| Italian Society of Infectious and Tropical disease (Lombardy section) (Original Article in Italian)[14] |                | National guideline | Italy   | Use of chloroquine 500 mg x 2/day or hydroxychloroquine 200 mg/day for 10 days, the treatment duration may vary from 5 to 20 days according to clinical severity                                                             |
|                                                                      |                |                    |         | The suggested target population ranges from patients with mild respiratory symptoms and comorbidities to patients with severe respiratory failure                                                              |
| FDA grants emergency authorisation to Chloroquine for COVID-19[19]    | March 31, 2020 | National guideline | USA     | The chloroquine phosphate may only be used to treat adult and adolescent patients who weigh 50 kg or more and are hospitalized with COVID-19, for whom a clinical trial is not available, or participation is not feasible |
|                                                                      |                |                    |         | The hydroxychloroquine sulphate may only be used to treat adult and adolescent patients who weigh 50 kg or more hospitalized with COVID-19 for whom a clinical trial is not available, or participation is not feasible |
| Discovering drugs to treat COVID-19[16]                               | February 29, 2020 | Communication     | China   | Latest version of the guidelines for the prevention, diagnosis, and treatment of novel coronavirus-induced pneumonia issued by the NHC of the People’s Republic of China for tentative treatment of COVID-19 |
|                                                                      |                |                    |         | Fifth edition of the guidelines recommends antivirals including IFN-α, lopinavir/ritonavir, and ribavirin for treatment of COVID-19. Chloroquine phosphate and arbidol are included in the sixth edition of the guidelines based on the preliminary outcomes of clinical studies |
| Dutch Centre for disease control[13]                                 |                | Public document    | Netherlands | The suggested regimen in adults requiring admission to hospital needing oxygen therapy/ICU admission consists of: 600 mg of chloroquine base followed by 300 mg after 12 h on day 1, then 300 mg x 2/day/ os on days 2-5 days |
|                                                                      |                |                    |         | This document also underlined:                                                                                                                          |
|                                                                      |                |                    |         | The need for stopping the treatment at day 5 to reduce the risk of side effects, considering the long half-life of the drug (30 h)                                                                           |
|                                                                      |                |                    |         | The need to differentiate between regimens based on chloroquine phosphate and chloroquine base since 500 mg of the first correspond to 300 mg of the second                                                        |
| Chloroquine phosphate has shown apparent efficacy in treatment of COVID-19 associated pneumonia in clinical studies[13] | February 19, 2020 | Recommendation   | China   | Chloroquine phosphate has been recommended for inclusion in the next version of the guidelines for the prevention, diagnosis, and treatment of pneumonia caused by COVID-19 issued by the NHC of the People’s Republic of China for treatment of COVID-19 infection in larger populations in the future |
| COVID-19 adult treatment algorithm[11]                               | April 01, 2020 | Hospital guideline | USA     | Use of hydroxychloroquine for 5 days as 1st line regimen in confirmed nonsevere COVID-19 patients with comorbidities                                                                                         |

ICMR: Indian Council For Medical Research, FDA: Food and Drug Administration, COVID-19: Coronavirus disease 2019, NHC: National Health Commission, IFN-α: Interferon alfa, ICU: Intensive care unit, SARS-CoV-2: Severe acute respiratory syndrome associated coronavirus 2

chloroquine after 5 days of treatment since the drug has a long half-life (30 h) and to minimize the risk of side effects.[17] This document also stated that it is crucial to differentiate between regimens based on chloroquine phosphate and chloroquine base due to the difference in composition of the active compound [Table 1a].

The clinical trials identified from the trial registries comprise numerous randomized controlled trials with larger patient...
coauthors. The outcomes primarily assessed are mortality, viral load, and time to recovery [Table 2a-d]. Data from these trials are much awaited to provide greater insight into the effectiveness of chloroquine/hydroxychloroquine for treatment of COVID-19. Following completion of the randomized controlled trials underway, an updated systematic review or meta-analysis will enable a more accurate assessment of the risk–benefit balance of administering these drugs in COVID-19 patients. Although other drugs, in particular Remdesivir, Lopinavir-ritonavir have been identified as possible therapeutic options, the widespread availability and affordability of chloroquine/hydroxychloroquine makes them a more desirable candidate for treatment of this global pandemic, subject to proven efficacy and safety in clinical trials. Countries like India already have a high manufacturing capacity and considerable supplies of this widely proclaimed “game-changer” drug. This manufacturing capacity will be of immense aid if and when the off label use of chloroquine might lead to major drug shortage in the fight against Malaria.

**Conclusions**

As the number of COVID-19 cases continue to increase exponentially in multiple regions of the world, it is imperative to develop an effective approach to stem this tide. The known clinical profile of chloroquine from its long-standing use, its low cost, and widespread availability has led to extensive research on its potential application in the management of COVID-19. In the light of preliminary data from recent randomized controlled trials suggesting potential improvement in clinical outcomes, both chloroquine and hydroxychloroquine are promising antiviral agents in the treatment of COVID-19 pneumonia. However, the reported side effects of these drugs when used in conjunction with azithromycin in patients with comorbidities have raised significant safety concerns and led to a need for further high-quality randomized clinical trials. Adequately coordinated clinical studies such as pan-continental multicentre trials, which include a larger cohort of patients, would not only provide more comprehensive evidence of the

**Table 1b: Editorial, commentary, and opinion pieces assessing the use of chloroquine and hydroxychloroquine in effectively managing patients with coronavirus disease 2019 infection**

| Title                                                                 | Published date  | Article type | Country | Trial summary                                                                                                                                 |
|----------------------------------------------------------------------|-----------------|--------------|---------|-----------------------------------------------------------------------------------------------------------------------------------------------|
| Chloroquine for the 2019 novel coronavirus SARS-CoV-2[19]             | February 15, 2020 | Editorial    | France | The authors underlined the *in vitro* efficacy of chloroquine in other viral infections, especially SARS, to advocate their use in clinical trials. They also discussed the potentially favourable risk-benefit balance, the high safety, and the low expenditure of this drug. Consequently, they suggested its use to fight against the current COVID-19 outbreak. |
| Of Chloroquine and COVID-19[20]                                      | March 05, 2020   | Commentary   | France | The use of chloroquine in the treatment of SARS-CoV-2 should be examined, while taking into account the potential detrimental effect of the drug observed in previous attempts to treat acute viral diseases. |
| New insights on the antiviral effects of Chloroquine against coronavirus: What to expect for COVID-19[9][10] | March 11, 2020   | Opinion piece | France | Similar to the emphasis already made in 2007 in the same journal, the possibility of using chloroquine to fight orphan viral infections was advocated. |
| Could Chloroquine/ hydroxychloroquine be harmful in COVID-19 treatment? [21] | March 03, 2020   | Opinion piece | Italy  | Despite the *in vivo* antiviral activity, no acute virus infection has been successfully treated by chloroquine/hydroxychloroquine in human. Chloroquine/hydroxychloroquine did not show any anti SARS-CoV effect on *in vivo* model. |
| COVID-19: A recommendation to examine the effect of Hydroxychloroquine in preventing infection and progression[22] | March 20, 2020   | Opinion piece | China  | It was proposed that hydroxychloroquine, which exhibits an antiviral effect highly similar to that of chloroquine, could serve as a better therapeutic approach. It has a safer clinical profile and is suitable for those who are pregnant. It is cheaper and more readily available in China. |
| Aminoquinolines against COVID-19: Chloroquine or hydroxychloroquine [23] | March 16, 2020   | Opinion piece | Iran   | Although there are more clinical data on the anti-coronaviral activity of chloroquine than that of hydroxychloroquine, both of these agents are theoretically similar in their antiviral activity. Moreover, chloroquine is not as widely available as hydroxychloroquine in some countries. In addition, chloroquine is associated with greater adverse effects than hydroxychloroquine. For example, in patients with COVID-19, prolongation of QTc interval can result from the interaction of chloroquine and lopinavir/ritonavir. Hence, it is important to administer hydroxychloroquine instead of chloroquine. |
**Table 1c: Clinical trials and review articles assessing the use of chloroquine and hydroxychloroquine in effectively managing patients with coronavirus disease 2019 infection**

| Title | Published date | Article type | Country | Trial summary |
|-------|----------------|--------------|---------|---------------|
| Hydroxychloroquine and azithromycin as a treatment of COVID-19: Results of an open-label nonrandomized clinical trial | March 20, 2020 | Open labelled non randomised RCT | France | Despite its small sample size, the survey shows that hydroxychloroquine treatment is associated with a significant viral load reduction/disappearance in COVID-19 patients and its effect is reinforced by azithromycin. Twenty cases were treated in this study and showed a significant reduction of the viral carriage at day 6 compared to controls, and much lower average disease duration than reported for untreated patients. Combination treatment with azithromycin and hydroxychloroquine proved to be more efficient for virus elimination. |
| A pilot study of hydroxychloroquine in the treatment of patients with COVID-19 | February 29, 2020 | RCT | China | Use of hydroxychloroquine has no benefit over standard treatment in terms of negative viral RNA test and radiological progression. |
| Efficacy of Hydroxychloroquine in patients with COVID-19: Results of a RCT | April 01, 2020 | RCT | China | Use of hydroxychloroquine could significantly shorten TTCR and promote absorption of pneumonia. |
| No Evidence of Rapid Antiviral Clearance or Clinical Benefit with the Combination of Hydroxychloroquine and Azithromycin in Patients with Severe COVID-19 Infection | March 28, 2020 | Prospective cohort study | France | No evidence of a strong antiviral activity or clinical benefit of the combination of hydroxychloroquine and azithromycin for the treatment hospitalized patients with severe COVID-19, was observed. |
| A systematic review on the efficacy and safety of chloroquine for the treatment of COVID-19 | March 10, 2020 | Systematic analysis | Italy | Chloroquine is widely used, safe, cheap, and shown to be effective in viral infections in preclinical studies. Specific preclinical evidence and expert opinions suggest potential use against SARS-CoV-2. A search in trial registries shows that 23 clinical trials are on-going in China. There is an urgent need of high-quality clinical data from different geographic areas. |
| Chloroquine and Hydroxychloroquine as available weapons to fight COVID-19 | March 14, 2020 | A review of evidence from *in vitro* studies systematic review and recommendations | France | The antiviral activity of hydroxychloroquine is probably the same as that of chloroquine, due to their similar mechanism of actions. Hydroxychloroquine, can considered as a safer therapeutic option for the treatment of SARS-CoV-2, since it will be prescribed over a longer period of time. For optimal treatment, it may be necessary to administer a loading dose followed by a maintenance dose. |

RCT: Randomized controlled trial, COVID-19: Coronavirus disease 2019, TTCR: Time to clinical recovery, SARS-CoV-2: Severe acute respiratory syndrome associated coronavirus 2

**Table 2a: Characteristics of clinical trials evaluating the efficacy and safety of chloroquine in patients infected with coronavirus disease 2019**

| ID | Current recruiting status | Study design | Country | Population (with COVID-19 pneumonia) | Intervention group | Comparison group | Primary outcomes |
|----|---------------------------|--------------|---------|-------------------------------------|-------------------|-----------------|------------------|
| ChiCTR2000029939 | Yes | Single blind RCT | China | 50 | Chloroquine phosphate | According to the guidance of the “Diagnosis and Treatment Scheme of COVID-19” published by the NHC | Length of hospital stay |
| ChiCTR2000029837 | No | Double blind RCT | China | 120 | Chloroquine | Placebo | NAAT |
| ChiCTR2000029826 | No | Double blind RCT | China | 45 | Chloroquine | Placebo | Mortality rate |
| ChiCTR2000031204 | No | Multicentre single blind RCT | China | 300 | Oral chloroquine phosphate | Placebo | Clearance time of viral RNA |
| ChiCTR2000030718 | Yes | RCT | China | 80 | Chloroquine phosphate | None | TTCR |

Contd...
Table 2a: Characteristics of clinical trials evaluating the efficacy and safety of chloroquine and hydroxychloroquine in patients infected with coronavirus disease 2019

| ID               | Current recruiting status | Study design          | Country         | Population (with COVID‑19 pneumonia) | Intervention group               | Comparison group                 | Primary outcomes                                           |
|------------------|---------------------------|-----------------------|-----------------|--------------------------------------|----------------------------------|----------------------------------|------------------------------------------------------------|
| ChiCTR2000029898 | No                        | RCT                   | China           | 360                                  | Hydroxychloroquine               | Conventional                     | NAAT                                                       |
| ChiCTR2000029899 | No                        | RCT                   | China           | 320                                  | Hydroxychloroquine               | Conventional                     | NAAT                                                       |
| ChiCTR2000031174 | No                        | Preventive RCT        | China           | 100                                  | Hydroxychloroquine               | Standard                         | NAAT                                                       |
| NCT04325488      | No                        | Parallel RCT          | China           | 300                                  | Hydroxychloroquine               | Standard                         | NAAT                                                       |
| NCT04318444      | No                        | To study PEP          | USA             | 1600                                 | Hydroxychloroquine               | Placebo                          | Hospital mortality                                         |
| NCT04316377      | No                        | RCT                   | Norway          | 203                                  | Hydroxychloroquine sulphate      | Placebo                          | Death (within 14 days)                                     |

RCT: Randomised controlled trial, COVID‑19: Coronavirus disease 2019, NAAT: Nucleic‑acid amplification test, TTCR: Time to clinical recovery

Table 2b: Characteristics of clinical trials evaluating the efficacy and safety of hydroxychloroquine in patients infected with coronavirus disease 2019

| ID               | Current recruiting status | Study design          | Country         | Population (with COVID‑19 pneumonia) | Intervention group               | Comparison group                 | Primary outcomes                                           |
|------------------|---------------------------|-----------------------|-----------------|--------------------------------------|----------------------------------|----------------------------------|------------------------------------------------------------|
| ChiCTR2000029868 | No                        | Multicentre RCT       | China           | 30                                   | Chloroquine phosphate aerosol    | Water for injection treatment    | Temperature returns to normal for >3 days                  |
| ChiCTR2000029542 | Yes                       | Prospective cohort    | China           | 20                                   | Chloroquine                      | Standard                         | NAAT negative time                                         |
| ChiCTR2000029988 | Yes                       | RCT                   | China           | 80                                   | Chloroquine phosphate            | None                             | TTCR                                                       |
| ChiCTR2000029575 | No                        | Single arm RCT        | China           | 10                                   | Chloroquine phosphate            | None                             | TTCR                                                       |
| NCT04325488      | No                        | Parallel RCT          | China           | 112                                  | Chloroquine                      | Lopinavir/ritonavir              | Length of stay                                             |
| NCT04325893      | No                        | RCT                   | Brazil          | 440                                  | Chloroquine diphosphate          | Starch pill                      | Mortality                                                  |

RCT: Randomised controlled trial, COVID‑19: Coronavirus disease 2019, NHC: National Health Commission, NAAT: Nucleic‑acid amplification test, TTCR: Time to clinical recovery

Table 2c: Characteristics of clinical trials evaluating the efficacy and safety of both chloroquine and hydroxychloroquine in patients infected with coronavirus disease 2019

| ID               | Current recruiting status | Study design          | Country         | Population (with COVID‑19 pneumonia) | Intervention group               | Comparison group                 | Primary outcomes                                           |
|------------------|---------------------------|-----------------------|-----------------|--------------------------------------|----------------------------------|----------------------------------|------------------------------------------------------------|
| ChiCTR2000029899 | Yes                       | RCT parallel          | China           | 100                                  | Hydroxychloroquine               | Hydroxychloroquine               | Time to clinical improvement                              |
| ChiCTR2000029898 | Yes                       | RCT parallel          | China           | 100                                  | Hydroxychloroquine               | Hydroxychloroquine               | Clinical recovery time                                     |
| NCT04325488      | No                        | RCT                   | China           | 120                                  | Hydroxychloroquine sulphate 0.2 g| Standard therapy                | Recommended clinical plan for coronavirus pneumonia         |
| NCT04318444      | No                        | To study PEP          | USA             | 1600                                 | Hydroxychloroquine               | Placebo                          | Hospital mortality                                         |
| NCT04316377      | No                        | RCT                   | Norway          | 203                                  | Hydroxychloroquine sulphate      | Placebo                          | Death (within 14 days)                                     |

TTCR: Time to clinical recovery, RCT: Randomised controlled trial, COVID‑19: Coronavirus disease 2019
| ID            | Current recruiting status | Study design      | Country   | Population (with COVID-19 pneumonia) | Intervention group                                                                 | Comparison group                  | Primary outcomes                                |
|---------------|---------------------------|-------------------|-----------|--------------------------------------|-----------------------------------------------------------------------------------|-----------------------------------|-------------------------------------------------|
| ChiCTR2000029935 | Yes                       | Single arm clinical trial | China    | 100                                  | Conventional treatment combined with chloroquine                                   | None                              | Length of hospital stay                          |
| ChiCTR2000030987 | Yes                       | RCT                | China    | 150                                  | Faviparvir plus chloroquine phosphate                                              | Faviparvir Placebo                | Improvement or recovery in respiratory symptoms  |
| ChiCTR2000030031 | Cancelled                  |                    | China    | 120                                  | Chloroquine with standard therapy                                                 | Placebo with standard therapy     | Time of conversion of viral NAAT                |
| ChiCTR2000029609 | Yes                       | Multicentre RCT    | China    | 205                                  | Oral chloroquine phosphate (mild-moderate)                                        | Lopinavir/ritonavir               | NAAT                                            |
| NCT04321993    | No                        | Prospective cohort | Canada   | 1000                                 | Lopinavir/ritonavir Hydroxychloroquine sulphate                                    | Standard care                     | Clinical status on day 15                        |
| NCT04307693    | Yes                       | Prospective cohort | South Korea | 150                                  | Lopinavir/ritonavir Hydroxychloroquine sulphate                                    |                                   | Viral load                                      |
| NCT04303507    | No                        | PEP double blind RCT | UK      | 40000                                | Chloroquine Hydroxychloroquine                                                     |                                   | Number of people symptomatic                     |
| NCT04321616    | No                        | Open adaptive RCT  | Sweden   | 700                                  | Hydroxychloroquine Remdesivir                                                     |                                   | Severity of symptoms                             |
| NCT04324463    | No                        |                    | Canada   | 1500                                 | Azithromycin Chloroquine                                                            |                                   | In hospital mortality (3 weeks)                  |
| NCT04321278    | No                        | PEP of hospitalised patients | Brazil | 440                                  | Azithromycin plus hydroxychloroquine                                               | Hydroxychloroquine Placebo        | Clinical status                                 |
| NCT04322396    | No                        | PEP of hospitalised patients | Denmark | 226                                  | Azithromycin plus hydroxychloroquine                                               |                                   | Number of days alive and discharged from hospital within 14 days |
| NCT04322123    | No                        | RCT                | Brazil   | 630                                  | Hydroxychloroquine Hydroxychloroquine plus azithromycin                            |                                   | Clinical status                                 |
| ISRCTN50189673 (recovery trial) | Yes | RCT | UK | Not decided | Lopinavir/Ritonavir Interferon-beta-la Dexamethasone Hydroxychloroquine | No additional treatment | Vital status Hospitalisation Use of ventilation Use of renal dialysis/hemofiltration |

RCT: Randomized controlled trial, PEP: Postexposure prophylaxis, NAAT: Nucleic-acid amplification test, IL-6: Interleukin-6, COVID-19: Coronavirus disease 2019
safety of these drugs in patients infected with COVID-19 but also increase the generalisability of the study.

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Conflicts of interest
There are no conflicts of interest.

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