

Hydroxychloroquine and chloroquine for survival in COVID-19: an international collaborative meta-analysis of randomized trials

Registered protocol, version 1.0 [June 23, 2020]

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Abstract

Background: COVID-19 is a potentially severe and lethal disease without established treatment. Hydroxychloroquine and chloroquine are investigated in many trials as potential drug treatments for COVID-19.

Objective: To estimate the effect of hydroxychloroquine and chloroquine on the survival of COVID-19 patients.

Design: Collaborative meta-analysis of randomized clinical trials (RCTs).

Data Sources: Mortality data from published and unpublished RCTs that were systematically identified in trial registries, literature databases and other repositories, including ClinicalTrials.gov, WHO International Clinical Trials Registry Platform, PubMed, and the Cochrane COVID-19 register until June 11, 2020. Mortality data from unpublished trials will be requested from trial investigators.

Eligibility Criteria for Selecting Studies: All ongoing and completed RCTs that recruited at least 1 patient before June 1, 2020 with confirmed or suspected SARS-CoV-2 infection, which evaluate hydroxychloroquine or chloroquine. Trials are eligible regardless of what their primary or secondary outcomes are.

Outcomes and results: A random effects meta-analysis will be used to combine the all-cause mortality effects from all eligible trials, assessed separately for hydroxychloroquine and chloroquine. Between-trial heterogeneity will be described and treatment effect estimates will be reported as odds ratio with 95% confidence intervals.

Conclusions: Our interpretation will be based on the summary estimate for mortality to determine whether there are benefits or harms for treating patients with hydroxychloroquine or chloroquine.

Registration: This protocol is registered at the Open Science Framework.

Keywords: Meta-analysis, SARS-CoV-2, COVID-19, Hydroxychloroquine, Chloroquine

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What is already known on this topic: COVID-19 is a potentially severe and lethal disease. Hydroxychloroquine and chloroquine are investigated in many trials as possible drug treatments for COVID-19. One large trial (RECOVERY) stopped the hydroxychloroquine arm because of no benefit and trend of harm, but many other trials have collected data on these drugs.

What this study adds: This study will estimate the effects of hydroxychloroquine and chloroquine on survival across all trials with available data.

Introduction

In December 2019, the detection of a new coronavirus, later named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was reported. The rapid spread of the virus led to the declaration of a public health emergency in January 2020 and a pandemic on March 11 by the World Health Organization (WHO).¹ Coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2 is characterized by symptoms like fever, cough and fatigue² with the potential of rapid progression of respiratory failure meeting the criteria of acute respiratory distress syndrome.³ More than 450,000 patients have died by June 19⁴ and no standard treatment apart from symptomatic therapy has been established. This global health crisis has caused a hitherto unprecedented search for possible therapies, with almost 700 clinical trials initiated in the first quarter of 2020.⁵ Hydroxychloroquine (HCQ) and chloroquine (CQ) are established in the treatment of malaria and rheumatic disorders, while HCQ is frequently preferred as treatment in rheumatic disorders due its favourable safety profile.⁶ Based on its immunomodulatory capacities,⁶ in-vitro data,^{7,8} and a small study from France,⁹ HCQ and CQ gained remarkable awareness as a potential treatment for COVID-19 and led to an Emergency Use Authorization of HCQ by the US Food and Drug Administration.¹⁰ In our recently established database of COVID-19 trials (COVID-evidence),¹¹ we found that among a variety of possible interventions, one in five trials investigated HCQ or CQ. Moreover, the drugs are in use outside of clinical studies; during March 2020, prescriptions skyrocketed in the US.¹² At the same time there has been conflicting information regarding the potential benefits and harms of HCQ and CQ. While early studies suggested beneficial effects of HCQ⁹ later studies could not confirm this, but instead highlighted potential meaningful adverse events;¹³ this led to a temporary pause from May 23 to June 3 of the HCQ arm within the large, international Solidarity trial.¹⁴ A Lancet publication highlighting possible harms of HCQ in the treatment of COVID-19 was retracted on June 5 due to concerns regarding its veracity.¹⁵ On the same day, the RECOVERY mega-trial stopped enrollment to its HCQ arm since interim analysis results showed no meaningful benefit of the drug regarding mortality

or other outcomes and even a trend for increased deaths with HCQ was noted.¹⁶ After a reassessment of the evolving data the FDA revoked the Emergency Use Authorization for CQ and HCQ on June 15.¹⁷ This uncertainty, as well as parallel use of HCQ and CQ outside the setting of clinical studies, could not only cause unnecessary harm to patients by treating them with a potential ineffective or even harmful drug, but also impair a large part of the worldwide research agenda in relation to COVID-19 and endanger the completion of many studies, which could lead to research waste. At this point, clinicians and clinical trialists remain without robust, conclusive data for the effectiveness and concerns about possible increased side effects of HCQ and CQ. In addition, continued use of HCQ and CQ outside of clinical trials requires rapid evaluation of potential benefits and harms. Given the unfavorable RECOVERY results and the revoked Emergency Use Authorization, continued recruitment into HCQ and CQ trials may be jeopardized and many trials may run the risk of ending in futility. A joint and rapid examination of data on mortality from as many trials as possible may offer the best evidence to guide next steps.

With COVID-evidence, we have a readily available infrastructure to contact all investigators of HCQ/CQ trials in COVID-19. While other efforts are planned to follow-up and perform systematic reviews on the effects of HCQ or CQ in the longer term,^{18,19} there is an immediate need for evidence to inform both the clinical and the research agenda by focusing on the most vital outcome: mortality.

We therefore invite all investigators who are running trials on HCQ or CQ to participate in an international collaborative meta-analysis of the currently available data on mortality with these two drugs in COVID-19 patients and co-author a timely publication describing the meta-analysis.

Methods

The protocol for the COVID-evidence project is registered at the Open Science Framework.²⁰

We aim to identify and combine all RCTs investigating the effects of HCQ or CQ on COVID-19 patients compared to any control arm that is similar to the experimental arm in all aspects except the administration of HCQ or CQ. The focus of the meta-analysis is on all-cause mortality at any time point after randomization. RCTs are eligible regardless of whether they are aiming to evaluate mortality as any outcome (e.g. primary, secondary) or not. We expect that most of these RCTs are still ongoing, and investigators are requested to provide group-level (aggregated) mortality data per arm in their trial.

Eligibility criteria

We include trials that meet the following criteria:

1. Is described as a randomized controlled trial.
2. Includes any persons with SARS-CoV-2 infection/COVID-19 (proven or highly suspected) regardless of healthcare setting (e.g., in-patient, outpatient)
3. Persons in one experimental study group are intended to be treated with HCQ or CQ for any duration in any dose.
4. Persons in one study group are intended to not be treated with HCQ or CQ, but may optionally receive placebo. Beyond HCQ, CQ, or placebo, there are no intended differences in how the comparison groups are treated.
5. Started recruitment before June 1.
6. Data are available for all-cause mortality at any time point.

We will include trials regardless of their progress (i.e., with ongoing recruitment, completed, or terminated). There are no other eligibility criteria; in particular, we include trials regardless of whether mortality is a key outcome in the trial itself or not. We put no restrictions on language, geographical region, or healthcare setting.

Participants

We will include participants of any age with clinically suspected or confirmed (e.g. by reverse transcriptase–polymerase-chain-reaction test from a nasopharyngeal swab) SARS-CoV-2 infection.

Intervention and control

Participants have to be treated with HCQ or CQ in any frequency and dose for COVID-19.

The control must be placebo, no treatment or standard of care.

Information sources and search strategy

We searched for eligible trials registered at ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform [ICTRP] as of June 11, 2020 via the COVID-evidence¹¹ database. We additionally searched PubMed and the Cochrane COVID-19 trial registry (covering preprints, trial registries and literature databases) using terms related to HCQ and CQ combined with terms for COVID-19 and a standard RCT filter.²¹ For a detailed search strategy see Appendix 1.

The design, interventions and outcomes of the trials were extracted independently by two expert reviewers in the COVID-evidence team. For the purposes of the current collaborative meta-analysis, two authors (CA and AMS) evaluated independently the COVID-evidence database of trials regarding the inclusion criteria for the current study (see Figure 1 for a flow chart of the trial identification process).

Data extraction

As we assume that currently almost all eligible RCTs are still ongoing, using an individualized data extraction template, we will reach out to the principal investigators via email (see Appendices 2-3) and ask for each trial arm the number of: (1) randomized patients and (2) patients who died. Investigators who do not answer will receive two email reminders.

From all included RCTs, we will extract the following information, which will be verified by the investigators: current status of trial (ongoing or completed; unpublished or published), study location, number of recruited patients, start date of recruitment, and details on the participants (e.g. severity of disease), treatment(s) and control group(s).

The invitation to contribute data will be repeated de novo on July 31 (with a reminder after 5 days) and September 15 (with a reminder after 5 days) so as to continue capturing data from trials that may wish to contribute to updates of the analysis that could also be published. We anticipate that more trials may be completed or stopped in this time frame.

Outcome

We will analyze all-cause mortality.

Assessment of risk of bias across studies

As we focus only on all-cause mortality, a very objective and well-documented outcome, we expect that detection biases are of minor relevance. Potential impact of being aware of the group allocation may be indicated by the subgroup analysis focusing on placebo controls. Potential impact resulting from missing data may be indicated by the subgroup analysis focusing on missing outcome information.

Statistical analysis and data synthesis

The main analysis will evaluate separately the effect of HCQ versus control and CQ versus control. We will present the results for all-cause mortality with absolute numbers and proportions. The treatment effect estimate will be calculated as an odds ratio (odds of death in the intervention group that receives HCQ or CQ divided by the odds of death in the control group that does not receive HCQ or CQ). For multi-arm studies, we will ask for data on all arms and calculate separate treatment effect estimates for each eligible comparison. We will combine mortality effects from all RCTs based on binary outcome data (2x2 contingency tables) in meta-analyses using random effects models according to the Hartung-Knapp-Sidik-Jonkman approach^{22,23} and describe the statistical heterogeneity using the I^2 -statistic.²⁴ We will report 95% confidence intervals. Cases of zero events will be corrected by adding the reciprocal of the size of the contrasting study arm.^{25,26} The main analysis will be done using R version 3.5.1 and the 'meta' package.²⁷

Analysis of subgroups

For exploratory subgroup analyses we will stratify trials that investigate HCQ and trials that investigate CQ by:

- COVID-19 severity: trials with patients outside hospital, trials with patients in-hospital but not in an intensive care unit (ICU), and trials with ICU patients.
- SARS-CoV-2 status: trials with confirmed SARS-CoV-2 cases versus trials with unconfirmed, suspected cases.
- Type of comparator: trials with placebo control vs other.
- Amount of missing data: trials with more than 10% missing outcome information vs less than 10%. The amount of missing outcome information is expected to be low in the trials, in particular given the short follow-up and the expected high number of studies with hospitalized patients.

Interpretation criteria

The conclusions of this report will be guided by the summary estimates on mortality to determine our assessment of the benefits or harms of treating patients with HCQ or CQ compared to placebo or standard of care. We will deem HCQ or CQ to be beneficial when the upper limit of the 95% CI of the summary treatment effect estimate excludes the 1; we will assume it to be harmful if the lower limit of the 95% CI excludes the 1; and we will define results as inconclusive if the 95% CI includes the 1. Interpretation will be based on the main analysis. In case the main analysis and the sensitivity analyses yield different conclusions, or show the same trend with different certainty, the results will be interpreted with more caution. In this protocol, we outline the results presentation below to be followed as closely as possible in the final publication together with a supplementary table describing any non-trivial changes.

Patient involvement

All-cause mortality is a core outcome in three independent core outcome sets for COVID-19 (<http://www.comet-initiative.org/Studies/Details/1538>). Some being developed with input from patients, these core outcome sets underline the patient-relevance of the research question. Since we prioritize conducting this meta-analysis as rapid as possible, we have not planned to involve patients in the definition of the research question, nor in the interpretation or writing up of results. Data relating to the impact of the intervention on participants' quality of life will not be requested.

Data sharing

All relevant data from the RCTs used for this study will be published in the article and further information on the meta-analysis will be provided on the Open Science Framework.²⁰

Results

We will report the results of the collaborative meta-analysis according to the PRISMA guidelines ²⁸ (Figure 1), including the proportion of trials of which we received data on mortality. For the eligible trials we will report characteristics on the status of the trial, study location, recruited and planned total sample size, and details on the experimental and control arms as well as the included patient population (Table 1).

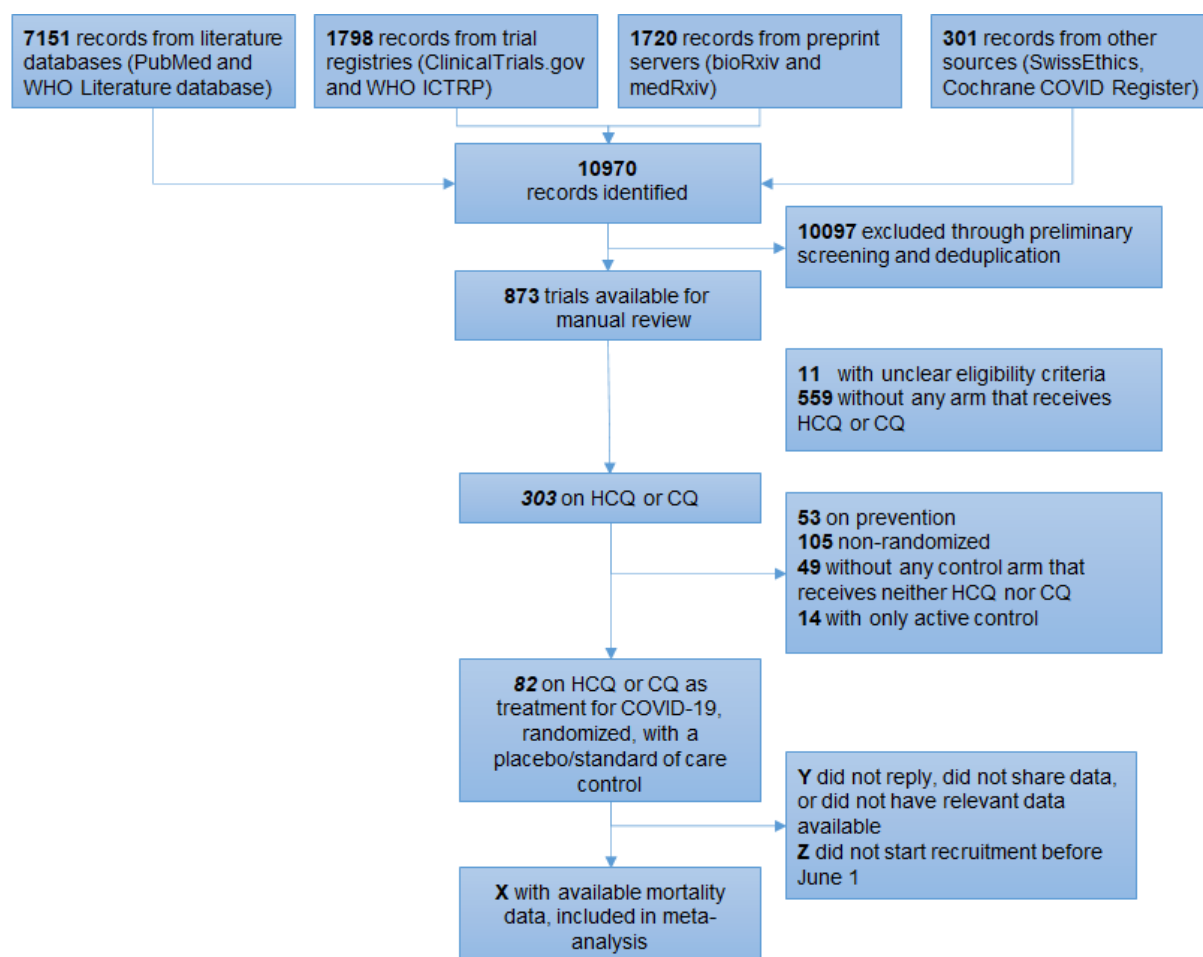


Figure 1 [in the planned publication]. Flowchart of included randomized clinical trials.

Sources searched up to June 11 (PubMed, ClinicalTrials.gov, WHO ICTRP, Cochrane COVID Register) or April 9 (WHO Literature database, bioRxiv, medRxiv, SwissEthics). Abbreviations: chloroquine (CQ), COVID-evidence (COVe), hydroxychloroquine (HCQ), World Health Organization International Clinical Trials Registry Platform (WHO ICTRP).

Table 1 [in the planned publication]. Group-level characteristics of randomized clinical trials evaluating hydroxychloroquine or chloroquine as treatment for COVID-19.

	All RCTs	RCTs assessing HCQ	RCTs assessing CQ	Eligible RCTs that did not share data
Date of recruitment start (mdn, IQR)				
Not started recruitment, n(%)		0	0	
Continent				
Africa, n(%)				
Asia, n(%)				
Australia/Oceania, n(%)				
Europe, n(%)				
North America, n(%)				
South America, n(%)				
Recruited sample size (mdn, IQR)				NA
Planned sample size (mdn, IQR)				
Placebo control, n(%)				
Number of arms				
Two arms, n(%)				
More than two arms, n(%)				
Severity				
Patients outside hospital, n(%)				
In-hospital patients but not ICU, n(%)				
ICU patients, n(%)				
Blinding				
No blinding, n(%)				
Double-blinded, n(%)				

For the eligible RCTs that do not share data, all information will be extracted from registrations or publications.

Supplementary Table 1 [in the planned publication; column names shown here]. Characteristics of randomized clinical trials evaluating hydroxychloroquine or chloroquine as treatment for COVID-19

Principal investigator last name (unpublished trial); First author name (published trial)

Trial status (unpublished or published)

Total number of randomized patients per arm (June 20, 2020)

Start date of recruitment

Patient recruitment site (outside hospital, in hospital, in ICU)

SARS-CoV-2 status (confirmed or non-confirmed)

Intervention(s) and control (each arm separately)

Blinding (none, caregiver, patient, outcome assessment)

URL to registration or publication

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Appendix 1. Search strategy

The COVID-evidence database includes trials registered on ClinicalTrials.gov or the WHO International Clinical Trials Registry Platform up to June 11, 2020, as well as trials published on the following sources up to April 9, 2020: PubMed, medRxiv, bioRxiv, the WHO COVID-19 literature database, and a listing of all trials with ethical approval in Switzerland (for details please see the COVID-evidence study protocol on the Open Science Framework:

<http://dx.doi.org/10.17605/OSF.IO/GEHFX>).

This Appendix describes the search strategy used to complement the COVID-evidence database with trials registered or published after April 9, 2020.

PubMed and the Cochrane COVID-19 trial registry were searched from inception to June 11, 2020. Search terms included extensive controlled vocabulary and Medical Subject Headings (MeSH). Search terms were the following:

corona[ti] OR covid*[ti] OR sars[ti] OR severe acute respiratory syndrome[ti] OR ncov*[ti] OR "severe acute respiratory syndrome coronavirus 2" [Supplementary Concept] OR "COVID-19" [Supplementary Concept] OR (wuhan[tiab] AND coronavirus[tiab]) OR (wuhan[tiab] AND pneumonia virus[tiab]) OR COVID19[tiab] OR COVID-19[tiab] OR coronavirus 2019[tiab] OR SARS-CoV-2[tiab] OR SARS2[tiab] OR SARS-2[tiab] OR "severe acute respiratory syndrome 2"[tiab] OR 2019-nCoV[tiab] OR (novel coronavirus[tiab] AND 2019[tiab]) NOT (animals[mesh] NOT humans[mesh]) AND ("2019/12/01"[EDAT] : "3000/12/31"[EDAT]) AND

((hydroxychloroquine[MeSH Terms]) OR (chloroquine[MeSH Terms])) OR (hydroxychloroquine[Title/Abstract]) OR (chloroquine[Title/Abstract])

AND

(randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR placebo[tiab] OR clinical trials as topic[mesh:noexp] OR randomly[tiab] OR trial[ti] NOT (animals[mh] NOT humans [mh]))

Appendix 2. Invitation email

Subject: Invitation to co-author a large-scale international collaborative meta-analysis on mortality in COVID-19 trials

Dear Dr. <last name>,

We are currently conducting a large-scale international collaborative meta-analysis on mortality in all ongoing or completed randomized clinical trials evaluating hydroxychloroquine or chloroquine for COVID-19. We are inviting all research groups worldwide testing these drugs to provide urgently needed evidence. We have no commercial interest with this work and aim to rapidly publish the results in a peer-reviewed journal. **Your core team is invited to co-author the publication.**

We use our COVID-evidence database (www.covid-evidence.org) for this work. COVID-evidence is supported by the Swiss National Science Foundation (Project ID 196190) and a large collaboration of researchers from Switzerland, the US, China, Canada, UK, France, Germany, Austria, Sweden, Netherlands, and other countries.

Our registered protocol can be found **attached** as well as registered on the Open Science Framework: **[link]**. Trials that are eligible for this project can be found at the end of the protocol.

Your study <url> is of high importance for this project. We would like to ask you how many patients died in your trial (see short questions below). We will use standard methods of meta-analysis and focus only on group-level (aggregated) mortality (no individual patient data needed). We will not do an in-depth review of the included trials as we aim to rapidly provide results, ideally from all trials worldwide. We describe the details of the study in the attached protocol.

HCQ and CQ for survival in COVID-19: an international collaborative meta-analysis of randomized trials. Email: caxfors@stanford.edu. COVID-evidence | www.covid-evidence.org

For the meta-analysis, we kindly ask you to answer the following questions before July 7. If you are interested in collaborating, please let us know of your interest as soon as possible.

Question 1: Could you please confirm that these criteria apply to your trial?

- a) The trial is randomized and started enrollment before June 1, 2020
- b) The trial has at least one group of patients who receive hydroxychloroquine or chloroquine
- c) The trial has at least one control group that does not receive hydroxychloroquine or chloroquine

Question 2: For each of your study arms,

- a) What intervention did this group receive?
- b) How many patients were randomized to this group?
- c) Of these patients, how many have died?
- d) Of these patients, for how many it is unknown if they are dead or alive?

Please note that we are interested in these raw numbers regardless of the results of any statistical test. The numbers will be used to finalize the manuscript described in our registered protocol (attached).

We strive for a rapidly available, maximally informative publication with full transparency on methods. **With this publication we aim to make sure that all clinical trial data hitherto**

collected (unpublished or published) will be of use, regardless of whether the target sample size of each trial was reached or not. We invite your core investigator team as co-authors. The manuscript will be shared with all co-authors for comments and the finalized manuscript will be uploaded as a preprint at medRxiv in parallel with submission to a peer-reviewed medical journal such as JAMA or the BMJ.

Thank you for considering our request! We kindly ask for your answer **before July 7**. If you are interested in collaborating, but are uncertain whether the data may be shared before July 7, please respond as soon as possible.

Should you have any questions or comments, please let us know.

Best regards,

Cathrine Axfors, Andreas Schmitt, David Moher, Steve Goodman, John Ioannidis and Lars Hemkens for the COVID-evidence team

www.covid-evidence.org

Appendix 3. Eligible randomized trials (n=82) investigating hydroxychloroquine or chloroquine in COVID-19.

Trial Nr	Contact name	Title	Arms (n)	Relevant comparisons		Other groups (not relevant)	Target sample (n)	Location	Setting	URL
				Experimental group (HCQ or CQ)	Control group					
1	Abayomi	Lagos COVID-19 Chloroquine Treatment Trial (LACCTT)	3	HCQ CQ	Placebo Placebo		600	Nigeria	Inpatient	https://pactr.samrc.ac.za/TrialDisplay.aspx?TrialID=10928
2	Abd-El salam	Efficacy of Chloroquine in COVID-19 Treatment	2	CQ	SoC		40	Egypt	Unclear	https://clinicaltrials.gov/show/NCT04353336
3	Abenhaim	Effect of Hydroxychloroquine in COVID-19 Positive Pregnant Women	2	HCQ	Placebo		600	Canada	Outpatient	https://clinicaltrials.gov/show/NCT04354441
4	Ader	Multi-centre, Adaptive, Randomized Trial of the Safety and Efficacy of Treatments of COVID-19 in Hospitalized Adults	4	HCQ	SoC	Remdesivir; Lopinavir - ritonavir; Lopinavir - ritonavir + Interferon beta;	3100	International	Inpatient	https://clinicaltrials.gov/ct2/show/record/NCT04315948
5	Albritton	Hydroxychloroquine in SARS-CoV-2 (COVID-19) Pneumonia Trial	2	HCQ	Soc		120	United States	Inpatient	https://clinicaltrials.gov/show/NCT04382625
6	Amaravadi	The PATCH Trial (Prevention And Treatment of COVID-19 With Hydroxychloroquine)	6	HCQ (3 arms with 3 different doses)	Placebo	2 Prevention Arms	400	United States	Inpatient	https://clinicaltrials.gov/ct2/show/record/NCT04329923
7	Arreola Guerra	Hydroxychloroquine and Ivermectin for the Treatment of COVID-19 Infection	5	HCQ	Placebo	Ivermectin (2 Arms), Placebo	200	Mexico	Inpatient	https://clinicaltrials.gov/show/NCT04391127
8	Aukrust	The Efficacy of Different Anti-viral Drugs in COVID 19 Infected Patients	3	HCQ + Remdesivir	Remdesivir	HCQ	700	Europe	Inpatient	https://clinicaltrials.gov/ct2/show/NCT04321616?term=NCT04321616&draw=2&rank=1
9	Azhar	Pakistan Randomized and Observational Trial to Evaluate Coronavirus Treatment	8	HCQ + Oseltamivir HCQ + Azithromycin HCQ + Azithromycin + Oseltamivir	Oseltamivir Azithromycin Azithromycin + Oseltamivir	HCQ	500	Asia	Inpatient	https://clinicaltrials.gov/ct2/show/record/NCT04338698
10	Benfield	Efficacy and Safety of Novel Treatment Options for Adults With COVID-19 Pneumonia	5	HCQ	Placebo	Convalescent anti-SARS-CoV-2 plasma; Sarilumab; Baricitinib;	1500	Denmark	Inpatient	https://clinicaltrials.gov/show/NCT04345289
11	Berdal	NORWEGIAN CORONAVIRUS DISEASE 2019 (NO COVID-19) STUDY: AN OPEN LABELED RANDOMIZED CONTROLLED	2	HCQ	Placebo		200	Europe	Inpatient	https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2020-001010-38

Trial Nr	Contact name	Title	Arms (n)	Relevant comparisons		Other groups (not relevant)	Target sample (n)	Location	Setting	URL
				Experimental group (HCQ or CQ)	Control group					
		PRAGMATIC TRIAL TO EVALUATE THE ANTIVIRAL EFFECT OF CHLOROQUINE IN ADULT PATIENTS WITH SARS-COV-2 INFECTION								
12	Bitzer	Test and Treat COVID 65plus+	2	HCQ	Placebo		350	Germany	Outpatient	https://clinicaltrials.gov/show/NCT04351516
13	Blanc	Efficacy of Hydroxychloroquine, Telmisartan and Azithromycin on the Survival of Hospitalized Elderly Patients With COVID-19	4	HCQ	Soc	Azithromycin, Telmisartan	1600	France	Inpatient	https://clinicaltrials.gov/show/NCT04359953
14	Boulware	Post-exposure Prophylaxis or Preemptive Therapy for SARS-Coronavirus-2: A Pragmatic Randomized Clinical Trial	2	HCQ	Placebo		3000	International	Outpatient	https://clinicaltrials.gov/ct2/show/record/NCT04308668
15	Butler	Platform Randomised trial of Interventions against COVID-19 in older people (PRINCIPLE) A trial evaluating treatments for suspected coronavirus infection in people aged 50 years and above with pre-existing conditions and those aged 65 years and above	2	HCQ	SoC		3000	Europe	Inpatient	http://isrctn.com/ISRCTN86534580
16	Centre Hospitalier Universitaire de Bordeaux	Home treatment of elderly patients with symptomatic SARS-CoV-2 infection (COVID-19): a multiarm, multi-stage (MAMS) randomized trial to assess the efficacy and safety of several experimental treatments to reduce the risk of hospitalization or death (COVERAGE trial) - COVERAGE	5	HCQ	Placebo	Imatinib; Favipiravir; Telmisartan	1057	France	Outpatient	https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2020-001435-27
17	Cheng	Efficacy and Tolerability of Hydroxychloroquine in Adult Patients With COVID-19	2	HCQ	SoC		45	Taiwan	Unclear	https://clinicaltrials.gov/show/NCT04384380
18	CHU Angers	HYCOVID - Hydroxychloroquine versus placebo chez les patients ayant une infection COVID-19 risque d'aggravation secondaire : Etude prospective multicentrique randomisee en double aveugle	2	HCQ	Placebo		1300	France	Inpatient	https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2020-001271-33
19	Dalgard	Norwegian Coronavirus Disease 2019 Study: An Open Labelled Randomized Controlled Pragmatic Trial to Evaluate	2	HCQ	SoC		202	Norway	Inpatient	https://clinicaltrials.gov/ct2/show/record/NCT04316377

Trial Nr	Contact name	Title	Arms (n)	Relevant comparisons		Other groups (not relevant)	Target sample (n)	Location	Setting	URL
				Experimental group (HCQ or CQ)	Control group					
20	Day	the Antiviral Effect of Chloroquine in Adult Patients With SARS-CoV-2 Infection A Multi Center Randomized Open Label Trial on the Safety and Efficacy of Chloroquine for the Treatment of Hospitalized Adults With Laboratory Confirmed SARS-CoV-2 Infection in Vietnam	2	CQ	SoC		250	Asia	Inpatient	https://clinicaltrials.gov/ct2/show/record/NCT04328493
21	Deng	A randomized, double-blind, parallel, controlled trial for comparison of phosphoric chloroquine combined with standard therapy and standard therapy in mild/common patients with novel coronavirus pneumonia (COVID-19)	2	CQ	Placebo		120	China	Inpatient	http://www.chictr.org.cn/showproj.aspx?proj=49806
22	Dubee	Hydroxychloroquine Versus Placebo in Patients Presenting COVID-19 Infection and at Risk of Secondary Complication: a Prospective, Multicentre, Randomised, Double-blind Study	2	HCQ	Placebo		1300	France	Inpatient	https://clinicaltrials.gov/ct2/show/NCT04325893?term=NCT04325893&draw=2&rank=1
23	Duda-Sikula	Multicenter, Randomized, Open-label, Non-commercial, Investigator-initiated Study to Evaluate the Effectiveness and Safety of Chloroquine Phosphate in Combination With Telemedicine in the Reduction of Risk of Disease-related Hospitalization or Death, in Ambulatory Patients With COVID-19 at Particular Risk of Serious Complications	2	CQ	SoC		400	Poland	Inpatient	https://clinicaltrials.gov/ct2/show/NCT04331600
24	Egger-Adam	Hydroxychloroquine for the Treatment of Mild COVID-19 Disease (COMIHY)	2	HCQ	Placebo		2700	Europe	Outpatient	https://clinicaltrials.gov/ct2/show/record/NCT04340544
25	Egger-Adam	Hydroxychloroquine for COVID-19 (COV-HCQ)	2	HCQ	Placebo		220	Europe	Inpatient	https://clinicaltrials.gov/ct2/show/record/NCT04342221
26	Farooq	Effectiveness of Hydroxychloroquine in Covid-19 Patients: A Single Centred Single-blind RCT Study	3	HCQ	Placebo	Azithromycin	75	Asia	Unclear	https://clinicaltrials.gov/ct2/show/NCT04328272
27	Frantisek	Azithromycin Added to Hydrochloroquine in Patients Admitted to Intensive Care With COVID-19: Randomised Controlled Trial (AZIQUINE-ICU)	3	HCQ	Placebo	HCQ + Azithromycin	240	Europe	Inpatient	https://clinicaltrials.gov/ct2/show/record/NCT04339816

Trial Nr	Contact name	Title	Arms (n)	Relevant comparisons		Other groups (not relevant)	Target sample (n)	Location	Setting	URL
				Experimental group (HCQ or CQ)	Control group					
28	Gaitán-Duarte	Effectiveness and Safety of Medical Treatment for SARS-CoV-2 (COVID-19) in Colombia	4	HCQ	SoC	Lopinavir - Ritonavir + HCQ; HCQ + Azithromycin	1600	Colombia	Inpatient	https://clinicaltrials.gov/show/NCT04359095
29	Goldstein	Chloroquine for Mild Symptomatic and Asymptomatic COVID-19 in A Two Staged, Multicenter, Open Label and Randomized Trial	3	CQ (2 arms with different doses)	SoC		210	Asia	Inpatient	https://clinicaltrials.gov/ct2/show/NCT04333628
30	Green	Randomized, Embedded, Multifactorial Adaptive Platform Trial for Community-Acquired Pneumonia	23	HCQ + Lopinavir - Ritonavir	Lopinavir - Ritonavir	21 further arms	7100	Oceania	ICU	https://clinicaltrials.gov/show/NCT02735707
31	Griffin	PATCH 2&3: Prevention & Treatment of COVID-19 (Severe Acute Respiratory Syndrome Coronavirus 2) With Hydroxychloroquine	4	HCQ	Placebo	2 Prevention arms	850	United States	Outpatient	https://clinicaltrials.gov/show/NCT04353037
32	Guochao Shi	Hydroxychloroquine treating novel coronavirus pneumonia (COVID-19): a randomized controlled, open label, multicenter trial	2	HCQ	SoC		360	China	Inpatient	http://www.chictr.org.cn/showproj.aspx?proj=49524
33	Harris	Qatar Prospective RCT Of Therapy Eliminating Covid Transmission	3	HCQ + Placebo	Placebo	HCQ + Azithromycin	456	Qatar	Inpatient	https://clinicaltrials.gov/show/NCT04349592
34	Hays	Trial of Early Therapies During Non-hospitalized Outpatient Window for COVID-19	3	HCQ	Placebo	Lopinavir - Ritonavir	900	United States	Inpatient	https://clinicaltrials.gov/show/NCT04372628
35	Hoepelman	Chloroquine, Hydroxychloroquine or Only Supportive Care in Patients Admitted With Moderate to Severe COVID-19	3	CQ HCQ	Soc Soc	HCQ CQ	950	Netherlands	Inpatient	https://clinicaltrials.gov/show/NCT04362332
36	Horby	Randomized evaluation of COVID-19 therapy	5	HCQ	SoC	Lopinavir-Ritonavir; Azithromycin; Convalescent plasma; Tocilizumab	12000	Europe	Inpatient	https://clinicaltrials.gov/ct2/show/NCT04381936
37	Huang	Clinical study on the safety and effectiveness of Hydroxychloroquine Sulfate tablets in the treatment of patients with novel coronavirus pneumonia (COVID-19)	4	HCQ (3 arms with 3 different doses)	SoC		240	China	Inpatient	http://www.chictr.org.cn/showproj.aspx?proj=49400
38	Huang	A randomized, open-label, controlled trial for the efficacy and safety of hydroxychloroquine sulfate tablets in the	2	HCQ	SoC		60	China	Inpatient	http://www.chictr.org.cn/showproj.aspx?proj=49404

Trial Nr	Contact name	Title	Arms (n)	Relevant comparisons		Other groups (not relevant)	Target sample (n)	Location	Setting	URL
				Experimental group (HCQ or CQ)	Control group					
39	Hussain	treatment of patients with severe novel coronavirus pneumonia (COVID-19) Randomized Comparison of Combination Azithromycin and Hydroxychloroquine vs. Hydroxychloroquine Alone for the Treatment of Confirmed COVID-19	3	HCQ	Placebo	HCQ + Azithromycin	160	United States	Inpatient	https://clinicaltrials.gov/ct2/show/record/NCT04336332
40	Jankowska	A multicenter, open, randomized, non-commercial study to evaluate the efficacy and safety of chloroquine phosphate in the Outpatient treatment of COVID-19 in combination with telemedicine care for patients with SARS-CoV-2 infection with the risk of developing complications to reduce the risk of COVID-19-related hospitalization and death	2	CQ + telemedicine	telemedicine		400	Poland	Outpatient	https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2020-001469-35
41	Jing Xu	Efficacy and safety of chloroquine phosphate inhalation combined with standard therapy in the treatment of novel coronavirus pneumonia (COVID-19)	2	CQ	Placebo		30	China	Inpatient	http://www.chictr.org.cn/showproj.aspx?proj=50279
42	Johnston	Treatment for SARS-CoV-2 in High-Risk Adult Outpatients	3	HCQ + Placebo	Placebo	HCQ + Azithromycin	630	United States	Outpatient	https://clinicaltrials.gov/show/NCT04354428
43	Gautier	A Prospective, Controlled, Randomized, Multicenter Study to Compare the Efficacy of a Chloroquine Analog (GNS561), an Anti PD-1 (Nivolumab) and an Anti-interleukine-6 Receptor (Tocilizumab) Versus Standard of Care in Patients With Advanced or Metastatic Cancer and SARS-CoV-2 (COVID-19) Infection	6	CQ	SoC	Nivolumab; Tocilizumab; Monalizumab; Avdoralimab	384	France	Inpatient	https://clinicaltrials.gov/ct2/show/record/NCT04333914
44	Kim	Randomized Controlled Clinical Trials of Lopinavir/Ritonavir or Hydroxychloroquine in Patients With Mild Coronavirus Disease (COVID-19)	3	HCQ	SoC	Lopinavir - ritonavir	150	Asia	Inpatient	https://clinicaltrials.gov/ct2/show/record/NCT04307693
45	Lacerda	Phase IIb Study to Evaluate the Efficacy and Safety of Chloroquine Diphosphate in the Treatment of Patients With Comorbidities, Without Severe Acute Respiratory Syndrome, Under the New	2	CQ	Placebo		210	Americas	Inpatient	https://clinicaltrials.gov/ct2/show/record/NCT04342650

Trial Nr	Contact name	Title	Arms (n)	Relevant comparisons		Other groups (not relevant)	Target sample (n)	Location	Setting	URL
				Experimental group (HCQ or CQ)	Control group					
		Coronavirus (SARS-CoV2): a Double-blind, Randomized, Placebo-controlled Clinical Trial								
46	Lagos	An Inter-national randomised trial of additional treatments for COVID-19 in hospitalised patients who are all receiving the local standard of care	5	HCQ	SoC	Remdesivir; Lopinavir - ritonavir; Interferon beta-1a	10000	Inter-national	Inpatient	https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2020-001366-11
47	Levin	Efficacy and safety of novel treatment options for adults with COVID-19 pneumonia	5	HCQ	Placebo	BARICITINIB (2 Dosis), SARILUMAB	1500	Denmark	Inpatient	https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2020-001367-88
48	Lu	Efficacy and Safety of Hydroxychloroquine for Treatment of Pneumonia Caused by 2019-nCoV (HC-nCoV)	2	HCQ	SoC		30	China	Inpatient	https://clinicaltrials.gov/ct2/show/record/NCT04261517
49	Lutfy	Hydroxychloroquine in COVID-19 Patients	2	HCQ	SoC		200	Saudi Arabia	unclear	https://clinicaltrials.gov/show/NCT04394442
50	Mao	A randomized, double-blind, parallel, controlled trial for comparison of phosphoric chloroquine combined with standard therapy and standard therapy in mild/common patients with novel coronavirus pneumonia (COVID-19)	2	CQ	Placebo		120	China	Inpatient	http://www.chictr.org.cn/showprojen.aspx?proj=49495
51	Mao	A randomized, double-blind, parallel, controlled trial for comparison of phosphoric chloroquine combined with standard therapy and standard therapy in serious/critically ill patients with novel coronavirus pneumonia (COVID-19)	2	CQ	Placebo		45	China	Inpatient	http://www.chictr.org.cn/showprojen.aspx?proj=49481
52	Maxebengula	Chloroquine Outpatient Treatment Evaluation for HIV-Covid-19	2	HCQ or CQ	SoC		560	South Africa	Outpatient	https://clinicaltrials.gov/show/NCT04360759
53	Metz	A Randomized, Double-blind, Placebo-controlled Trial to Assess the Efficacy and Safety of Oral Hydroxychloroquine for the Treatment of SARS-CoV-2 Positive Patients for the Prevention of Severe COVID-19 Disease	2	HCQ	Placebo		1660	Canada	Inpatient	https://clinicaltrials.gov/ct2/show/record/NCT04329611?term=NCT04329611&draw=2&rank=1
54	Mulligan	Treating COVID-19 With Hydroxychloroquine (TEACH)	2	HCQ	Placebo		626	United States	Inpatient	https://clinicaltrials.gov/show/NCT04369742
55	National Institute of	Hydroxychloroquine Treatment for Severe COVID-19 Respiratory Disease: Randomised Clinical Trial (HYDRA Trial)	2	HCQ	Placebo		500	Mexico	Inpatient	https://clinicaltrials.gov/ct2/show/record/NCT04315896

Trial Nr	Contact name	Title	Arms (n)	Relevant comparisons		Other groups (not relevant)	Target sample (n)	Location	Setting	URL
				Experimental group (HCQ or CQ)	Control group					
	Respiratory Diseases, Mexico									
56	Oldmixon	Outcomes Related to COVID-19 Treated With Hydroxychloroquine Among In-patients With Symptomatic Disease	2	HCQ	Placebo		510	United States	Inpatient	https://clinicaltrials.gov/ct2/show/record/NCT04332991
57	Pacchia	Hydroxychloroquine for Outpatients With Confirmed COVID-19	2	HCQ	Placebo		400	United States	Outpatient	https://clinicaltrials.gov/ct2/show/record/NCT04342169
58	Papanicolaou	A Study of Hydroxychloroquine Compared to Placebo as Treatment for People With COVID-19	2	HCQ	Placebo		120	United States	Inpatient	https://clinicaltrials.gov/show/NCT04379492
59	Paul	Hydroxychloroquine for the Treatment of Patients With Mild to Moderate COVID-19 to Prevent Progression to Severe Infection or Death	2	HCQ	SoC		1116	Israel	Inpatient	https://clinicaltrials.gov/ct2/show/record/NCT04323631
60	Richards	Trial of Hydroxychloroquine In Covid-19 Kinetics	2	HCQ	Placebo		58	United States	Outpatient	https://clinicaltrials.gov/show/NCT04353271
61	Ronghua	A multicenter, single-blind, randomized controlled clinical trial for chloroquine phosphate in the treatment of 2019 novel coronavirus-infected pneumonia	2	CQ	Placebo		300	China	Inpatient	http://www.chictr.org.cn/showproj.aspx?proj=49420
62	Sanofi	A Phase 1b, Randomized, Double-blinded, Placebo-controlled Study of Hydroxychloroquine in Outpatient Adults With COVID-19	2	HCQ	Placebo		210	International	Outpatient	https://clinicaltrials.gov/ct2/show/NCT0433654
63	Sanofi-Aventis	An adaptive Phase 2/3, randomized, open-label study assessing efficacy and safety of hydroxychloroquine for hospitalized patients with moderate to severe COVID-19	2	HCQ	SoC		350	International	Inpatient	https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2020-001270-29
64	Sarwar	Prophylaxis of Exposed COVID-19 Individuals With Mild Symptoms Using chloroquine Compounds	4	CQ HCQ (2 arms with different doses)	Placebo Placebo		400	Pakistan	unclear	https://clinicaltrials.gov/show/NCT04351191
65	Sarwar	Post-Exposure Prophylaxis for Asymptomatic SARS-CoV-2 COVID-19 Patients With chloroquine Compounds	4	HCQ (2 arms with different doses) CQ	Placebo Placebo		400	Pakistan	Outpatient	https://clinicaltrials.gov/show/NCT04346667
66	Semprini	A Randomised, Double Blind, Placebo-Controlled Trial of the Efficacy of Hydroxychloroquine for the Community-	2	HCQ	Placebo		70	Oceania	Outpatient	https://anzctr.org.au/ACTRN12620000457943.aspx

Trial Nr	Contact name	Title	Arms (n)	Relevant comparisons		Other groups (not relevant)	Target sample (n)	Location	Setting	URL
				Experimental group (HCQ or CQ)	Control group					
		Based Treatment of Adults With Diagnosed COVID-19								
67	Seto	A Randomized, Controlled Clinical Trial: Hydroxychloroquine for the Treatment of COVID-19 in Hospitalized Patients (OAHU-COVID19)	2	HCQ	SoC		350	United States	Inpatient	https://clinicaltrials.gov/ct2/show/record/NCT04345692
68	Song	A Trial of Ciclesonide Alone or in Combination With Hydroxychloroquine for Adults With Mild COVID-19	3	HCQ + Ciclesonide	Ciclesonide	SoC	141	Korea	Inpatient	https://clinicaltrials.gov/ct2/show/record/NCT04330586
69	Stout	Pragmatic Factorial Trial of Hydroxychloroquine, Azithromycin, or Both for Treatment of Severe SARS-CoV-2 Infection	4	HCQ HCQ + Azithromycin	SoC Azithromycin		500	United States	Inpatient	https://clinicaltrials.gov/ct2/show/record/NCT04335552
70	Ting Cai	A Single-blind, Randomized, Controlled Clinical Trial for Chloroquine Phosphate in the treatment of Novel Coronavirus Pneumonia 2019 (COVID-19)	2	CQ	SoC		100	China	Inpatient	http://www.chictr.org.cn/showproj.aspx?proj=49612
71	Tong	Clinical Trial of Favipiravir Tablets Combine With Chloroquine Phosphate in the Treatment of novel coronavirus pneumonia (COVID-19)	3	CQ + Favipiravir	Favipiravir	Placebo	150	China	Inpatient	http://www.chictr.org.cn/showproj.aspx?proj=51329
72	Tong	Australasian COVID-19 Trial (ASCOT). A multi-centre randomised clinical trial to assess clinical, virological and immunological outcomes in patients with SARS-CoV-2 infection (COVID-19) treated with lopinavir/ritonavir and/or hydroxychloroquine compared to standard of care	4	HCQ HCQ + Lopinavir - ritonavir	SoC Lopinavir - ritonavir		2500	International	Inpatient	https://anzctr.org.au/ACTRN12620000445976.aspx
73	UCD	A trial to compare standard of care (SOC) alone with SOC plus hydroxychloroquine or SOC with a combination of hydroxychloroquine and azithromycin in the treatment of coronavirus	3	HCQ	SoC	HCQ + Azithromycin	267	Ireland	unclear	https://www.clinicaltrialsregister.eu/ctr-search/trial/2020-001265-36/IE
74	Van Herreweghe	An open label single center randomized controlled trial to evaluate the effect of hydroxychloroquine on viral shedding in mild COVID-19	2	HCQ	Placebo		206	Belgium	Outpatient	https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2020-001417-21
75	Victory	Comparison Of Therapeutics for Hospitalized Patients Infected With SARS-CoV-2 In a Pragmatic Adaptive	4	HCQ	Placebo	Lopinavir - ritonavir; Losartan	4000	United States	Inpatient	https://clinicaltrials.gov/ct2/show/record/NCT04328012

Trial Nr	Contact name	Title	Arms (n)	Relevant comparisons		Other groups (not relevant)	Target sample (n)	Location	Setting	URL
				Experimental group (HCQ or CQ)	Control group					
		randoMizED Clinical Trial During the COVID-19 Pandemic (COVID MED Trial)								
76	Weehuizen	An open label randomized controlled trial of chloroquine, hydroxychloroquine or only supportive care in patients admitted with moderate to severe COVID-19	3	CQ	SoC		950	Netherlands	Inpatient	https://trialregister.nl/trial/8490
				HCQ	SoC					
77	Yan	Clinical Study of Chloroquine Phosphate in the Treatment of Severe Novel Coronavirus Pneumonia (COVID-19)	2	CQ	SoC		80	China	Inpatient	http://www.chictr.org.cn/showproj.aspx?proj=49218
78	Yan	Clinical Study of Chloroquine Phosphate in the Treatment of 2019-nCoV Infection	2	CQ	SoC		80	China	Inpatient	http://www.chictr.org.cn/showproj.aspx?proj=50843
79	Zampieri	Safety and Efficacy of Hydroxychloroquine Associated With Azithromycin in SARS-Cov-2 Virus (COVID-19) (Coalition-I)	3	HCQ	SoC	HCQ + Azithromycin	630	Brasil	Inpatient	https://clinicaltrials.gov/ct2/show/NCT04322123?term=NCT04322123&draw=2&rank=1
80	Zhenyu	An open randomized controlled trial for Chloroquine phosphate and Hydroxychloroquine sulfate in the treatment of severe novel coronavirus pneumonia (COVID-19)	3	HCQ	SoC	CQ	100	China	Inpatient	http://www.chictr.org.cn/showproj.aspx?proj=49574
				CQ	SoC	HCQ				
81	Zhenyu	An open randomized controlled trial for Chloroquine phosphate and Hydroxychloroquine sulfate in the treatment of mild and common novel coronavirus pneumonia (COVID-19)	3	HCQ	SoC	CQ	100	China	Inpatient	http://www.chictr.org.cn/showproj.aspx?proj=49869
				CQ	SoC	HCQ				
82	Zhang	Efficacy of therapeutic effects of hydroxychloroquine in novel coronavirus pneumonia (COVID-19) patients (randomized open-label control clinical trial)	2	HCQ	SoC		78	China	Inpatient	http://www.chictr.org.cn/showproj.aspx?proj=49317

Abbreviations: Chloroquine (CQ), hydroxychloroquine (HCQ), standard of care (SoC).