South African National Department of Health
Brief Report of Rapid Review
Component: COVID-19

TITLE: CHLOROQUINE AND HYDROXYCHLOROQUINE FOR PREVENTION OF COVID-19: EVIDENCE REVIEW OF CLINICAL BENEFITS AND HARMS

Date: 19 MARCH 2021 *(update of initial review dated 18 June 2020)*

Key findings

- We conducted an updated rapid review of available published clinical evidence regarding use of chloroquine or hydroxychloroquine for prevention of COVID-19.
- We identified one recently published Cochrane Review regarding use of chloroquine (CQ) or hydroxychloroquine (HCQ) for prevention and post-exposure prophylaxis of COVID-19. In this brief report we summarise the findings.
- The review identified two clinical trials comparing HCQ to placebo for post-exposure prophylaxis of COVID-19. The trials took place in North America and Europe, including 1521 participants. One trial was stopped early when no benefit was found. HCQ did not make a differences to the number of new COVID-19 infections (combined laboratory confirmed and clinically diagnosed) (low certainty evidence). There were probably 2-fold greater adverse events (moderate certainty) and no serious adverse events (low certainty evidence).
- In people exposed to COVID-19, we suggest not using HCQ for post-exposure prophylaxis (conditional recommendation).

NEMLC THERAPEUTIC GUIDELINES SUB-COMMITTEE RECOMMENDATION:

Type of recommendation	We recommend against the option and for the alternative **(strong)**	We suggest not to use the option **(conditional)**	We suggest using either the option or the alternative **(conditional)**	We suggest using the option **(conditional)**	We recommend the option **(strong)**
	X				

Recommendation: Based on this evidence review the NEMLC Subcommittee recommends that HCQ/CQ not be used for the prevention of COVID-19, unless there is new evidence of efficacy that shows benefit.

Rationale: Evidence from one trial of HCQ compared to placebo for prevention of COVID-19 found no difference in the incidence of presumed new infections (low certainty evidence) but a 2-fold greater number of participants complaining of adverse events (moderate certainty evidence). The trial was stopped early for futility according to preplanned stopping rules.

Level of Evidence: II to III Low to moderate certainty evidence

(Refer to Appendix 1 for the evidence to decision framework)

Therapeutic Guidelines Sub-Committee for COVID-19: Marc Blockman, Karen Cohen, Renee De Waal, Andy Gray, Tamara Kredo, Gary Maartens, Jeremy Nel, Andy Parrish *(Chair),* Helen Rees, Gary Reubenson *(Vice-chair).*

BACKGROUND

Strategies to minimise the transmission and acquisition of COVID-19 have been instituted in most countries globally, including physical distancing, hand hygiene practices and use of masks by communities. Despite this, COVID-19 cases continue to rise, placing health systems under extreme pressure to provide adequate care for those who become ill and require care in health facilities. Prevention of transmission of COVID-19 is one strategy to reduce case-load, illness and strain on the health system.

In addition to the non-pharmaceutical approaches to prevent transmission, medicines may offer another strategy to prevent infections. Globally, the research community is trying to find effective and safe medicine to use for prophylaxis or use following exposure to a possible case of COVID-19 (post-exposure prophylaxis). To date, there are no globally accepted recommended medicines to prevent transmission, but several are being explored. Chloroquine (CQ) and hydroxychloroquine (HCQ) are amongst the medicines receiving substantial public attention and interest.

CQ and HCQ are 4-aminoquinoline compounds, quinine derivatives, and have been used successfully to prevent and treat malaria for decades until resistance arose. Chloroquine iscurrently used in South Africa to manage rheumatological diseases (SAMF, 13th ed., 2020). Following the COVID-19 outbreak, several in vitro studies have reported that CQ or HCQ inhibit SARS-CoV-2 activity (Wang 2020, Liu 2020), suggesting a potential role of CQ and HCQ for preventing infection.

Both the efficacy and safety of a new medical intervention are important to consider. Medicines for preventing conditions are given to those who do not have the illness and may be otherwise well. Therefore the benefits should clearly outweigh the harms. CQ and HCQ have been in use for decades and have a well-known safety profile outside of use in COVID-19 with several common adverse effects (gastrointestinal effects, skin rash, headache, vertigo, and blurred vision at higher doses) and rare effects (ototoxicity, blood dyscrasias, cardiovascular, such as QT interval prolongation and neuropsychiatric effects) (SAMF, 13th ed., 2020). However, there have been reports from studies in COVID-19 patients that suggest important safety concerns that require consideration, particularly for cardiovascular events due to QT prolongation.

A systematic review of CQ and HCQ for COVID-19 treatment and prophylaxis reported safety outcomes of all its included studies (Hernandez 2020). Although there do not seem to be differences in events for most minor adverse events, there have been several signals about QTc Interval Prolongation or arrhythmias. The review reported that one cohort study evaluating HCQ (Mahe'vas 2020) and another assessing CQ (Borba 2020a, Borba 2020b) versus control found increases in QTc interval prolongation to 500 ms or greater. HCQ increased the QTc interval of more than 60 ms from baseline, whereas CQ increased the number of patients experiencing ventricular tachycardia versus control. Another cohort study assessed the effect of HCQ with and without azithromycin on the QTc interval in 90 patients (mean age, 60 years; 51% male) (Mercuro 2020). Slightly more patients receiving HCQ plus azithromycin had a QTc interval of 500 ms or greater (11 of 53 [20.8%] vs. 7 of 37 [18.9%]; mean difference, 1.8% [95% CI, –14.9% to 18.5%]). More patients had a QTc interval increase of 60 ms or more from baseline (7 of 53 [13.2 %] vs. 3 of 37 [8.1%]; mean difference, 5.1% (CI, –7.6% to 17.8%]) versus hydroxytoluene alone. One patient receiving HCQ and azithromycin had a QTc interval of 499 ms and developed torsade de pointes' (Hernandez 2020). Although the evidence from controlled studies remains underpowered, it is important that safety and drug interactions of CQ and HCQ use is closely monitored in COVID-19 studies. Particularly because of the higher doses and co-medications, some with known drug interactions used in these studies compared to typical use for rheumatological or malaria indications.

This summary of a recent Cochrane Review (Singh 2021) aims to summarise the available research evidence for the efficacy and safety of CQ and HCQ for prophylaxis and post-exposure prophylaxis of COVID-19 infections.

RESEARCH QUESTION: Should chloroquine or hydroxychloroquine be used for prevention or post-exposure prophylaxis for COVID-19 compared to no intervention or an alternative intervention?

METHODS

The recent Cochrane Review (Singh 2021) conducted a comprehensive search of Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, Embase, Current Controlled Trials (www.controlled-trials.com), the World Health Organizations International Clinical Trials Registry Platform (www.who.int/clinical-trials-registry-platform) and the COVID-19-specific resources: www.covid-nma.com and www.covid-19.cochrane.org for studies of any publication status or language, up to 15 September 2020. In addition, researchers were contacted to identify any unpublished or

ongoing studies to include in the review. This review's search strategy can be accessed on Pages 89 – 91 of the review (Singh 2021).

In the Cochrane Review, two reviewers independently conducted each step of the study selection and data extraction, as outlined below. Reviewers resolved disagreements through discussion. Two reviewers independently screened the search results using Covidence and retrieved full-text articles for all potentially relevant trials. Each trial was examined to ensure that multiple publications from the same trial were only included once. Data were extracted from included studies using a piloted data extraction form (Table 1), then the methodological quality of studies were assessed using Cochrane's Risk of Bias tool by two reviewers. In addition, two reviewers used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system for grading evidence.

For the rapid review, reviewers extracted evidence from the Cochrane review and reported it here.

Eligibility criteria for review

Population: People at risk of SARS-CoV-2 exposure or have had a possible exposure, as defined by study authors. No restriction on age or occupational setting.

Intervention: Chloroquine (CQ) or hydroxychloroquine (HCQ) given by any route of administration, any dose, used alone or in combination with other pharmacological agents, for prophylaxis or post-exposure prophylaxis of COVID-19 infection. No restriction on the timing of dosing to time of potential exposure/s to SARS-CoV-2.

Comparators: no comparator or an active comparator.

Outcomes:

Efficacy outcomes:

- Development of laboratory confirmed COVID-19
- Disease severity of participants who develop COVID-19, as defined by study investigators

Safety outcomes

- Adverse reactions
- Serious adverse events

Study designs: Systematic review of randomised controlled trials (RCTs).

RESULTS

We included a recent Cochrane review for the rapid review. We used the AMSTAR 2 tool (Appendix 1) to assess the methodological quality of this Cochrane Review. It was rated as 'moderate' for overall confidence in the results. The evidence to decision framework is reported in a table in appendix 2 and the planned/ ongoing trials tables is reported in a table in appendix 3.

The Cochrane review included 12 RCTs (8 569 participants in total) that compared chloroquine or hydroxychloroquine to placebo or standard of care (10 RCTs) or lopinavir/ritonavir (1 RCT), or febuxostat (1 RCT), see figure 1. Of these, two trials examined the prevention of COVID-19 in asymptomatic people with a history of exposure to people with laboratory confirmed SARS-CoV-2. However, no eligible RCT were identified for the prevention of COVID-19 in people at risk of SARS-CoV-2.

Results of the two relevant included trials (Boulware 2020; Mitja 2020b) on the outcomes of interest are summarised in the Summary of Findings Table 2 and are presented below. These trials were conducted in the U.S.A and Canada (Boulware 2020) as well as Spain (Mitja 2020b), 1521 participants without COVD-19 who were exposed to someone with COVID-19 were randomised to either HCQ or placebo (folate tablets). The North American trials Data Safety Monitoring Board decided to terminate the trial early for futility, before reaching the planned sample size, according to planned stopping rules (Boulware 2020).

The results suggest that the effect of HCQ on the prevention of COVID-19 is susceptible to differences in administration to an individual, versus a cluster of individuals all in contact with one index person. The results were therefore not pooled from the individually-randomised RCT (Boulware 2020) with those from the cluster-RCT (Mitjà 2020b).

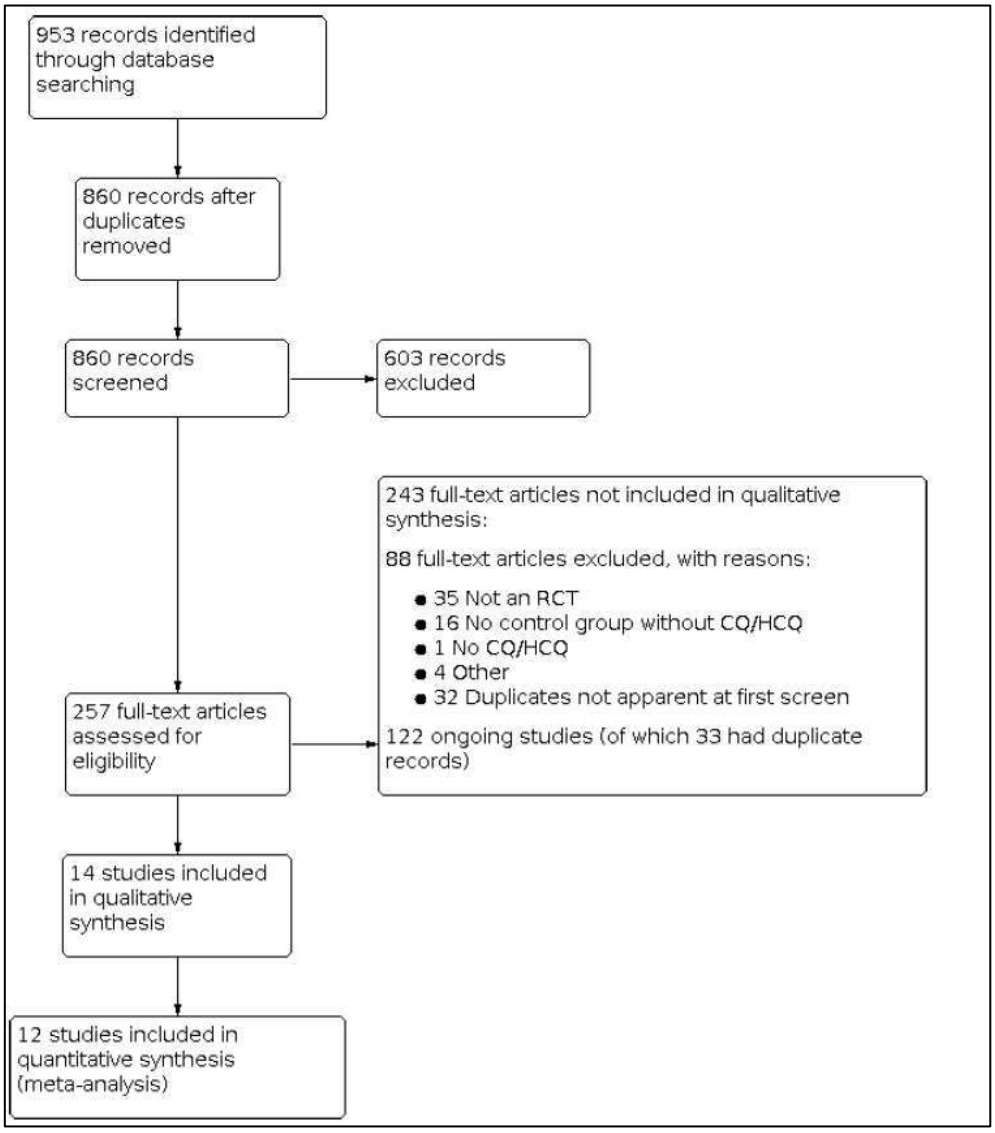

Figure 1. PRISMA flowchart of study selection process (Singh 2021) – 2 of 12 studies were relevant for COVID-19 prophylaxis

HCQ versus placebo by individual randomisation

One trial (821 participants) reported this comparison (Boulware 2020). See Summary of Findings table 2.

- Development of laboratory confirmed COVID-19: There was no difference between the two arms: relative risk (RR) 1.20 (95% confidence interval (CI) 0.50 to 2.87), based on one RCT, n = 821, very low certainty evidence.
- Disease seveity was not reported, we report hospitalization from the review: There is low certainty evidence regarding the effect of HCQ on hospitalization, RR 0.98 (95% CI 0.06 to 15.66), n = 821, 1 RCT, low certainty evidence.
- Adverse effects: Participants receiving at least one dose of HCQ had an increased risk of adverse events compared to those not receiving HCQ: RR 2.39 (95% CI 1.83 to 3.11), based on one RCT, n = 700, moderate certainty evidence.
- Serious adverse events: there were none reported in either arm. QTinterval prolongation on ECG was not reported, but the follow-up was performed remotely using an online survey, so ECG was not performed as part of the trial (Boulware 2020).

HCQ versus standard care by cluster randomisation

One trial (2525 participants) reported this comparison (Mitjà 2020b). Due to the cluster-RCT design and the trial authors' analysis, adjusted risk ratios have been reported.

- Development of laboratory confirmed COVID-19: This did not differ between participants randomised to HCQ (64/1116; 5.7%) and those allocated to standard care (74/1198; 6.2%): the adjusted RR 0.89 (95% CI 0.54 to 1.46), based on one RCT, n=2314 (Mitjà 2020b).

Five participants in the HCQ clusters (with a denominator of 1197, which is unexplained in its deviation from the randomised total of 1225) and 8/1300 in the standard care clusters died (Mitjà 2020b). Causes of death were not reported.

- Adverse events: Reported in 671/1197 (56%) participants in the HCQ clusters versus 77/1300 (6%) participants in the clusters not receiving HCQ; a relative effect estimate was not reported (Mitjà 2020b).
- Serious adverse events: These were reported, but it was not clear whether they were reported as number of events or number of participants, and did not match the intensity grading reported by the pharmacovigilance consultants employed by the trial (Mitjà 2020b). QT-interval prolongation was not measured in this trial.

CONCLUSION

The use of HCQ for people exposed to a patient infected with COVID-19 probably does not reduce the incidence of new COVID-19 infections. Reviewers found that adverse events are tripled compared to placebo while there were very few recorded serious adverse events. These results make it less likely that the drug effectively protects people from infection.

Reviewers: Eugene Davids, Ameer Hohfeld, Marc Blockman, Tamare Kredo.

Declaration of interests: None to declare in respect of this topic. TK, ED, AH (Cochrane South Africa, South African Medical Research Council, SA GRADE Network), MB (Division of Clinical Pharmacology, Department of Medicine, Groote Schuur Hospital, University of Cape Town).

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Table 1. Characteristics of included comparative studies

Study ID	Methods	Participants	Interventions	Outcomes	Risk of Bias
Boulware 2020	Double-blind RCT comparing outcomes in people receiving HCQ as post-exposure prophylaxis vs those receiving placebo. Follow-up involved sending participants surveys by email – completed online on REDCap: at days 1, 5, 10, and 14; then at 4 to 6 weeks. "Participants who did not respond to follow-up surveys received text messages, e-mails, telephone calls, or a combination of these to ascertain their outcomes. When these methods were unsuccessful, the emergency contact provided by the enrollee was contacted to determine the participant's illness and vital status. When all communication methods were exhausted, Internet searches for obituaries were performed to ascertain vital status."	Setting: community; recruitment via social media. Number of participants: 821 total: 414 allocated to HCQ; 407 allocated to placebo. Inclusion criteria: "known exposure (by participant report) to a person with laboratory-confirmed COVID-19, whether as a household contact, a health care worker, or a person with other occupational exposures". Recruited < 3 days after presumptive-case exposure (17 March); then updated to < 4 days after confirmed-case exposure (23 March). Exposure was defined as < 6-feet distance, for > 10 minutes, without full personal protection. This was subdivided into high risk (no mask and no eye protection) and moderate risk (wearing a mask but no eye protection). Exclusion criteria: < 18 years old; hospitalised; symptoms of COVID-19; PCR positive for SARS-CoV-2; others listed in appendix, such as certain medical conditions and co-medications. Age: HCQ arm: median 41 years (interquartile range: 33 to 51); placebo arm: median 40 years (interquartile range: 32 to 50). Sex: HCQ arm female:male 218:196; placebo arm female:male 206:201. Types of participant: HCQ arm: 275 healthcare workers, 125 household contacts, 14 exposure not reported; placebo arm: 270 healthcare workers, 120 household contacts, 17 exposure not reported. Definition of development of COVID-19: confirmed: by PCR; probable: "presence of cough, shortness of breath, or difficulty breathing, or the presence of two or more symptoms of fever, chills, rigors, myalgia, headache, sore	HCQ "800 mg (4 tablets) once, then 600 mg (3 tablets) 6 to 8 hours later, then 600 mg (3 tablets) daily for 4 more days for a total course of 5 days (19 tablets total)." Oral; could split doses if developed gastrointestinal upset . Placebo = folate tablets (? Whether they look similar is not clear); taken as per the HCQ schedule.	Primary – at day 14 from enrolment: development of confirmed or probable COVID-19 (see Participants for definitions). Secondary: hospitalisation for COVID-19 or death; PCR-confirmed SARS-CoV-2 infection; COVID-19 symptoms; discontinuation of the trial intervention - from any cause; "severity of symptoms (if any) at days 5 and 14 according to a visual analogue scale (scores ranged from 0 [no symptoms] to 10 [severe symptoms])." Adverse events: directed questioning for common side effects along with open-ended free text. The authors stated regarding losses to follow-up: Of the 821 participants who underwent randomisation, 96 did not complete the day 14 follow-up survey, of whom 8 formally withdrew from the trial (4 in each group). Investigators confirmed the vital status and lack of infection in 19 participants (10 in the hydroxychloroquine group and 9 in the control group); 17 completed some follow-up surveys without symptoms before being lost to follow-up (13 in the hydroxychloroquine group and 4 in the control group). A total of 52 participants never completed any surveys after enrolment and did not respond to investigators e-mails, text messages, or telephone calls (23 in the hydroxychloroquine group and 29 in the control group).	Random sequence generation (selection bias) = low risk Allocation concealment (selection bias) = low risk Blinding of participants and personnel (performance bias) = low risk Blinding of outcome assessment (detection bias) = low risk Incomplete outcome data (attrition bias) = low risk Selective reporting (reporting bias) = unclear risk

Study ID	Methods	Participants	Interventions	Outcomes	Risk of Bias
		throat, and new olfactory and taste disorders"; possible: "presence of one or more compatible symptoms, which could include diarrhoea". Probable and possible were defined by 4 blinded physicians. Comorbidities: HCQ arm (total 414) vs placebo arm (total 407): 4 vs 2 cardiac disease; 51 vs 48 hypertension; 12 vs 16 diabetes mellitus; 1 vs 0 HIV; 2 vs 2 other immunosuppression; 31 vs 31 asthma; 3 vs 0 other chronic lung disease; 1 vs 2 cancer/malignancy; 0 vs 3 chronic kidney disease.			

Study ID	Methods	Participants	Interventions	Outcomes	Risk of Bias
Mitjà 2020b	Open-label cluster-randomised trial comparing HCQ with standard care when given to individuals with a history of exposure to SARS-CoV-2, for prevention of COVID-19. Follow-up was up to day 28, using in-person visits to the participant's home on days 1 and 14, and telephone interviews on days 3, 7, and 28.	Setting: community; "screened using the electronic registry of the Epidemiological Surveillance Emergency Service of Catalonia (SUVEC) of the Department of Health. During the COVID-19 outbreak in Catalonia, a public health ordinance required all patients who tested positive for COVID-19 in any of the designated diagnostic laboratories to be notified to the SUVEC." Number of participants: 2525 total: 1225 allocated to HCQ; 1300 allocated to standard care. (Note that baseline characteristics and efficacy outcomes use a modified ITT population as their denominator: 1116 HCQ; 1198 standard care. Adverse events are reported for all randomised participants: 1225 HCQ; 1300 standard care.) Inclusion criteria: "adult individuals ≥ 18 years of age with a recent history of close contact exposure to a PCR confirmed COVID-19 case (i.e., > 15 minutes within two meters, up to seven days before enrolment) and absence of COVID-19-like symptoms on the two weeks preceding enrolment, as either a healthcare worker, a household contact, a nursing home worker or a nursing home resident." Exclusion criteria: symptoms or signs of COVID-19 at baseline assessment; "all eligibility criteria are listed in the Supplementary Appendix." (No appendix was available with the preprint publication.) Age: HCQ arm: mean 48.6 (SD 18.7) years; standard care arm: mean 48.7 (SD 19.3) years. Gender: HCQ arm F:M 813:303; standard care arm F:M 875:323. Types of participant: HCQ arm: 131 (12%) healthcare workers; 302 (27%) household contacts; 550 (49%) nursing home workers; 133 (12%) nursing home residents. Standard care arm: 130 (11%) healthcare	HCQ: 800 mg orally on day 1, followed by 400 mg once daily for 6 days. Total 7 days. Standard care: no treatment. Co-interventions not reported.	Primary outcome: "confirmed COVID-19 episode, defined as symptomatic illness (at least one of the following symptoms: fever, cough, difficulty breathing, myalgia, headache, sore throat, new olfactory and taste disorder(s), or diarrhoea) and a positive SARS-CoV-2 RT-PCR test. The primary outcome was assessed in all asymptomatic individuals, irrespective of the PCR result; in a post hoc analysis, we explored the outcome in individuals with positive and negative PCR separately. Time-to-event was defined as the number of days from the date of randomisation/exposure to the confirmed date of the onset of symptomatic illness." Secondary efficacy outcomes: • "incidence of SARS-CoV-2 infection, defined as either the RT-PCR detection of SARS-CoV-2 in a nasopharyngeal specimen or the presence of any of the aforementioned symptoms compatible with COVID-19" • "serological positivity (IgM/IgG) of contacts at day 14" Safety outcomes: "frequency and severity of adverse events (AE), serious AE (SAE), and AE of special interest (e.g., cardiac) up to 28 days from treatment start. Causality was assessed by an external panel of pharmacovigilance consultants." (Note that this included death and hospitalisation.)	Random sequence generation (selection bias) = unclear risk Allocation concealment (selection bias) = unclear risk Blinding of participants and personnel (performance bias) = high risk Blinding of outcome assessment (detection bias) = high risk Incomplete outcome data (attrition bias) = low risk Selective reporting (reporting bias) = high risk Other bias = high risk

Study ID	Methods	Participants	Interventions	Outcomes	Risk of Bias
		workers; 338 (28%) household contacts; 584 (49%) nursing home workers; 160 (13%) nursing home residents. (Note that the denominator for the standard care arm is 1212 rather than 1198.) Definition of development of COVID-19: "confirmed COVID-19 episode, defined as symptomatic illness (at least one of the following symptoms: fever, cough, difficulty breathing, myalgia, headache, sore throat, new olfactory and taste disorder(s), or diarrhoea) and a positive SARS-CoV-2 RT-PCR test"; “SARS-CoV-2 infection, defined as either the RT-PCR detection of SARS-CoV-2 in a nasopharyngeal specimen or the presence of any of the aforementioned symptoms compatible with COVID-19”. Comorbidities: 1. cardiovascular disease: HCQ: 130 (11.6%) and standard care: 178 (14.9%); 2. respiratory disease: HCQ: 64 (5.7%) and standard care: 47 (3.9%); 3. metabolic disease: HCQ: 99 (8.9%) and standard care: 94 (7.8%); 4. nervous system disease: HCQ: 170 (15.2%) and standard care: 170 (14.2%).			

Table 2. Summary of Findings table

Hydroxychloroquine (HCQ) compared to placebo for the prevention of COVID-19 in people who have been exposed to SARS-CoV-2					
Patient or population: Individuals exposed to SARS-CoV-2 **Setting**: Communities **Intervention**: Hydroxychloroquine (HCQ) **Comparison**: Placebo					
Outcomes	**Anticipated absolute effects* (95% CI)**		**Relative effect (95% CI)**	**№ of participants (studies)**	**Certainty of the evidence (GRADE)**
	Risk with placebo	**Risk with Hydroxychloroquine (HCQ)**			
Development of COVID-19 at 14 days from enrolment	2 per 100	**2 per 100** (1 to 6)	**RR 1.20** (0.50 to 2.87)	821 (1 RCT)	⊕◯◯◯ LOW [a,b]
Hospitalised due to COVID-19[c]	2 per 1000	**2 per 1000** (0 to 31)	**RR 0.98** (0.06 to 15.66)	821 (1 RCT)	⊕◯◯◯ LOW [a,b]
Participants with any adverse events	17 per 100	**41 per 100** (31 to 53)	**RR 2.39** (1.83 to 3.11)	700 (1 RCT)	⊕⊕⊕◯ MODERATE [a]
Participants with serious adverse events	0 per 1000	**0 per 1000** (0 to 0)	Not estimated	700 (1 RCT)	⊕⊕◯◯ LOW [a,d]

Explanations

A Downgraded by one level for serious indirectness: one trial, limited to North America; few older and comorbid participants, possibly due to social media-based recruitment and internet-based data collection (Boulware 2020).

B Downgraded by two levels for very serious imprecision: confidence interval around effect estimate includes appreciable benefit and appreciable harm.

C This outcome, as reported by Boulware 2020, was closest to our predefined outcome of 'disease severity of participants who develop COVID-19, as defined by study authors'.

D Downgraded by one level for imprecision: no events in either group, therefore risk ratio is not estimable. The optimal information size to be confident that this is a true reflection of risk of serious adverse events would be larger than the total number of participants in this trial. Risk difference = 0% (95% CI −1% to 1%).

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low certainty: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Appendix 1: Evaluating the methodological quality of the Singh et al (2021) systematic review and meta-analysis – AMSTAR 2 tool (Shea 2017[1])

Date: 18 February 2021
Assessors: Trudy Leong, Milli Reddy

No.	Criteria	Yes/ Partial Yes/ No
1	Research questions and inclusion criteria for the review included the components of PICO	Yes
2*	Report of the review contained an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol	Yes
3	Review authors explained selection of the study designs for inclusion in the review	Yes
4*	Review authors used a comprehensive literature search strategy	Partial yes
5	Review authors perform study selection and data extraction in duplicate	Yes
6	Review authors provided a list of excluded studies and justify the exclusions	Yes
7*	Review authors described the included studies in adequate detail	Yes
8	Review authors used a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review	Yes
9*	Review authors reported on the sources of funding for the studies included in the review?	Yes
10	For meta-analyses, review authors used appropriate methods for statistical combination of results	Yes
11*	For meta-analyses, review authors assessed the potential impact of RoB in individual RCTs on the results of the meta-analysis or other evidence synthesis	Yes
12	Review authors accounted for RoB in individual RCTs when interpreting/ discussing the results of the review	Yes
13*	Review authors provided a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review	Yes
14	For quantitative synthesis, review authors carried out an adequate investigation of publication bias (small study bias) and discussed its likely impact on the results of the review	No
15*	Review authors reported any potential sources of conflict of interest, including any funding they received for conducting the review	Yes

** Critical domains*

Rating overall confidence in the results of the review

• *High:* No or one non-critical weakness: the systematic review provides an accurate and comprehensive summary of the results of the available studies that address the question of interest

• *Moderate:* More than one non-critical weakness**: the systematic review has more than one weakness but no critical flaws. It may provide an accurate summary of the results of the available studies that were included in the review

• *Low:* One critical flaw with or without non-critical weaknesses: the review has a critical flaw and may not provide an accurate and comprehensive summary of the available studies that address the question of interest

• *Critically low*: More than one critical flaw with or without non-critical weaknesses: the review has more than one critical flaw and should not be relied on to provide an accurate and comprehensive summary of the available studies

(**Multiple non-critical weaknesses may diminish confidence in the review and it may be appropriate to move the overall appraisal down from moderate to low confidence).

OVERALL ASSESMENT: Moderate

Rationale: Two non-critical flaws (#4:partial yes; and #14)

Conclusion: The AMSTAR assessment shows that the review has more than one non-critical weakness, but no critical flaws, and may provide an accurate summary of the results of the available studies that were in

[1] Shea BJ, Reeves BC, Wells G, Thuku M, Hamel C, Moran J, Moher D, Tugwell P, Welch V, Kristjansson E, Henry DA. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ. 2017 Sep 21;358:j4008.

Appendix 2: Evidence to decision framework

	JUDGEMENT	EVIDENCE & ADDITIONAL CONSIDERATIONS
EVIDENCE OF BENEFIT	**What is the size of the effect for beneficial outcomes?** Large [ ] Moderate [ ] Small [ ] None [X] Uncertain [ ]	1 trial, 821 participants. New COVID-19 infections (lab and clinically confirmed): RR 0.83 (95% CI 0.58 to 1.18). There would be 118 per 1,000 cases in the HCQ group compared to 143 per 1,000 (95% CI 83 to 168), that is 25 more cases per 1000 people exposed to COVID-19.
EVIDENCE OF HARMS	**What is the size of the effect for harmful outcomes?** Large [ ] Moderate [X] Small [ ] None [ ] Uncertain [ ]	No serious adverse events. 2-fold greater number of participants in the HCQ group reported adverse events.
BENEFITS & HARMS	**Do the desirable effects outweigh the undesirable harms?** Favours intervention [ ] Favours control [X] Intervention = Control *or* Uncertain [ ]	
QUALITY OF EVIDENCE	**What is the certainty/quality of evidence?** High [ ] Moderate [ ] Low [X] Very low [ ] *High quality:* confident in the evidence *Moderate quality:* mostly confident, but further research may change the effect *Low quality:* some confidence, further research likely to change the effect *Very low quality:* findings indicate uncertain effect	Low certainty for development of COVID-19 and moderate certainty for adverse effects.
FEASABILITY	**Is implementation of this recommendation feasible?** Yes [x] No [ ] Uncertain [ ] **Note:** As there was no evidence of benefit, the Committee did not adjudicate on feasibility.	Chloroquine is available as SAHPRA registered Nivaquine® and Plasmoquine®, but there have been historic supply challenges. Hydroxychloroquine(unavailable) 200 mg is equivalent to 155 mg chloroquine base; and 200 mg chloroquine sulfate is equivalent to 150 mg chloroquine base (British National Formulary, 2019 edition). **Note:** MHRA has stopped all prevention and treatment studies in the UK; and SAHPRA has suspended the prevention study in South Africa.
RESOURCE USE	**How large are the resource requirements?** More intensive [ ] Less intensive [ ] Uncertain [ ] **Note:** As there was no evidence of benefit, the Subcommittee did not adjudicate on resource use.	**Price of medicine/ treatment course:** Hydroxychloroquine 800mg immediately, 600mg 6-8 hours later, then 600mg daily for 4 days. - comparable estimated doses: HCQ 200 mg = chloroquine sulfate 200mg **Medicine** *(see note below)* / **Tender price*** / **SEP*** Chloroquine 200 mg x 19 tablets / n/a / R52.82 to R92.72 *Chloroquine is not currently on public sector contract. SEP price ranges from R2.78 to R4.88 per capsule/tablet, containing 200 mg chloroquine sulfate (Plasmoquine® and Nivaquine®, respectively). SEP database, 28 December 2020 **Additional resources:** Safety monitoring and management of adverse drug reactions.
VALUES, PREFERENCES, ACCEPTABILITY	**Is there important uncertainty or variability about how much people value the options?** Minor [ ] Major [ ] Uncertain [ ] **Is the option acceptable to key stakeholders?** Yes [ ] No [ ] Uncertain [ ]	People without COVID-19 would likely value additional methods to prevent transmission and prevention of illness and hospitalisation with low safety concerns. No data about acceptability, but this medicine may be acceptable to stakeholders if use was supported by evidence that the benefit outweighed the harm. **Note:** As there was no evidence of benefit, the Committee did not adjudicate on values, preferences and acceptability
EQUITY	**Would there be an impact on health inequity?** Yes [x] No [ ] Uncertain [ ] **Note:** As there was no evidence of benefit, the Committee did not adjudicate on equity.	This would depend on access and capacity to deliver the intervention to all who need it. We have not data on this. If this option is used and is not effective, this would detract from medications that may work and deviate resources away from appropriate healthcare spend.

Appendix 3. Planned and ongoing studies (source: www.covid-nma.com 15 March 2020)

Treatment (per arm)		n	Severity at enrollment	Sponsor/Funder	Reg. number
1	(1) Hydroxychloroquine vs (2) Standard of care	78	Mild/moderate	The First Hospital of Peking University	ChiCTR2000029740
2	(1) Chloroquine vs (2) Hydroxychloroquine vs (3) Remdesivir vs (4) Lopinavir + ritonavir + interferon beta1 vs (5) Standard of care	1000	Moderate/severe/critical	Vilnius University Hospital Santaros Klinikos	EUCTR2020-001366-11-LT
3	(1) Hydroxychloroquine + lopinavir + ritonavir vs (2) Hydroxychloroquine + azithromycin	108	Moderate	Basque Health Service	EUCTR2020-001605-23-ES
4	(1) Hydroxychloroquine vs (2) Placebo	714	Mild	Barcelona Institute for Global Health	NCT04410562
5	(1) Hydroxychloroquine vs (2) Hydroxychloroquine + favipiravir vs (3) Hydroxychloroquine + azithromycin vs (4) Favipiravir vs (5) Favipiravir vs (6) Favipiravir + azithromycin	1000	Mild/moderate	Ministry of Health, Turkey	NCT04411433
6	(1) Hydroxychloroquine vs (2) Placebo	1500	No restriction on type of patients	McGill University Health Centre/Research Institute of the McGill University Health Centre	NCT04421664
7	(1) Hydroxychloroquine vs (2) Standard of care	320	Health workers	Universidad Peruana Cayetano Heredia	NCT04414241
8	(1) Hydroxychloroquine vs (2) Hydroxychloroquine + azithromycin	40	Moderate/severe	Quality Improvement of Intensive Care Research Center-Shahid Beheshti University	IRCT20200428047228N2
9	(1) Hydroxychloroquine vs (2) Hydroxychloroquine + raltegravir vs (3) Hydroxychloroquine + interferon beta + raltegravir	60	Severe	Jahrom University of Medical Sciences	IRCT20200412047042N1
10	(1) Hydroxychloroquine + azithromycin vs (2) Hydroxychloroquine + azithromycin vs (3) Zinc	384	Mild/moderate	Faculty of Medicine University Cheikh Anta Diop of Dakar Senegal.	PACTR202005622389003
11	(1) Hydroxychloroquine vs (2) Placebo	700	Mild/moderate	WellStar Health System	NCT04429867
12	(1) Hydroxychloroquine + ivermectin vs (2) Ivermectin vs (3) Standard of care	100	Mild/moderate	Ministry of Health and Population, Egypt	NCT04425707
13	(1) Hydroxychloroquine vs (2) Standard of care	582	Close contacts to covid patients	Rambam Health Care Campus	NCT04438837
14	(1) Darunavir + ritonavir + hydroxychloroquine vs (2) Ivermectin	80	Mild	Mahidol University	NCT04435587
15	(1) Hydroxychloroquine vs (2) Placebo	500	Health workers	Hamad Medical Corporation	NCT04437693
16	(1) Hydroxychloroquine vs (2) Povidone-Iodine vs (3) Zinc + vitamin C vs (4) Vitamin C vs (5) Ivermectin	5000	Healthy volunteers	National University Hospital, Singapore	NCT04446104
17	(1) Hydroxychloroquine vs (2) Lopinavir + ritonavir vs (3) Darunavir + (cobicistat vs (4) Favipiravir vs (5) Standard of care	435	Mild	ISTITUTO NAZIONALE PER LE MALATTIE INFETTIVE "LAZZARO SPALLANZANI"	EUCTR2020-001528-32-IT
18	(1) Hydroxychloroquine vs (2) Standard of care	1000	Health workers	OSPEDALE SAN RAFFAELE	EUCTR2020-001987-28-IT
19	(1) Hydroxychloroquine vs (2) Lopinavir + ritonavir vs (3) Interferon beta 1a vs (4) Dexamethasone vs (5) Placebo	2500	Moderate/severe/critical	University of Oxford	EUCTR-2020-001113-21-GB
20	(1) Hydroxychloroquine vs (2) Hydroxychloroquine + baricitinib vs (3) Hydroxychloroquine + Tocilizumab vs (4) Hydroxychloroquine + sarilumab vs (5) Hydroxychloroquine + siltuximab vs (6) Hydroxychloroquine + canakinumab vs (7) Hydroxychloroquine + methylprednisolone	1400	Moderate/severe	SOCIETA' ITALIANA MALATTIE INFETTIVE E TROPICALI	EUCTR2020-001854-23-IT
21	(1) Hydroxychloroquine vs (2) Standard of care	216	Mild	ASUR (Azienda Sanitaria Unica Regionale) Marche	EUCTR2020-001558-23-IT
22	(1) Hydroxychloroquine + ribavirin vs (2) Ribavirin + lopinavir + ritonavir vs (3) SOC	175	No restriction on type of patients	AIIMS Rishikesh	CTRI/2020/06/025575
23	(1) Hydroxychloroquine vs (2) Standard of care	202	Severe	University Hospital, Akershus	NCT04316377
24	(1) Hydroxychloroquine vs (2) Hydroxychloroquine + nitazoxanide	158	Moderate	Dr Reddys Laboratories Limited	CTRI/2020/06/025849
25	(1) Hydroxychloroquine vs (2) Remdesivir vs (3) Lopinavir + ritonavir vs (4) Lopinavir + ritonavir + interferon beta1 vs (5) Standard of care	3100	Moderate/severe/critical	Institut National de la Sant© Et de la Recherche M©dicale, France	NCT04315948
26	(1) Hydroxychloroquine vs (2) Placebo	500	Severe	National Institute of Respiratory Diseases, Mexico	NCT04315896
27	(1) Hydroxychloroquine vs (2) Sofosbuvir + daclatasvir vs (3) Standard of care	90	No restriction on type of patients	PHARCO CORPORATE	DRKS00022203
28	(1) Hydroxychloroquine vs (2) Lopinavir + ritonavir vs (3) Lopinavir + ritonavir + interferon beta1 vs (4) Remdesivir vs (5) Standard of care	800	Severe	Gesundheit Nord gGmbH	EUCTR2020-001549-38-DE
29	(1) Hydroxychloroquine vs (2) Placebo	500	Close contacts to covid patients	Boushehr University of Medical Sciences	IRCT20200513047426N1
30	(1) Hydroxychloroquine vs (2) Paracetamol vs (3) Lopinavir + ritonavir vs (4) Standard of care	3000	Mild/moderate	Drug for Neglected Diseases initiative	PACTR202006537901307
31	(1) Hydroxychloroquine vs (2) Hydroxychloroquine + lopinavir + ritonavir vs (3) Lopinavir + ritonavir vs (4) Standard of care	6400	High risk patients	University Of Birmingham	CTRI/2020/06/026196
32	(1) Hydroxychloroquine + azithromycin vs (2) Hydroxychloroquine + azithromycin + lopinavir + ritonavir	200	Mild	ProgenaBiome	NCT04459702
33	(1) Hydroxychloroquine vs (2) Mucodentol vs (3) Standard of care	180	Health workers	Baqiyatallah Medical Sciences University	NCT04466280
34	(1) Hydroxychloroquine vs (2) Placebo	1300	Mild	Hospital Alem©o Oswaldo Cruz	NCT04466540
35	(1) Hydroxychloroquine + azithromycin vs (2) Isoprinosine + levamisole	60	Mild	Cairo University	NCT04383717
36	(1) Hydroxychloroquine vs (2) Hydroxychloroquine vs (3) Placebo vs (4) Placebo	1930	High risk patients	University of Malaga	NCT04400019

37	(1) Hydroxychloroquine vs (2) Standard of care	40	Moderate	Mansoura University	NCT04477083
38	(1) Hydroxychloroquine vs (2) Placebo	40	Healthy volunteers	CHDR	NL8726
39	(1) Hydroxychloroquine vs (2) Ivermectin vs (3) Placebo	45	Moderate	Carmen Hidalgo	EUCTR2020-001971-33-ES
40	(1) Hydroxychloroquine vs (2) Placebo	340	Mild	ANTONIO ANTELA LOPEZ	EUCTR2020-002449-41-ES
41	(1) Chloroquine vs (2) Placebo	40000	Health workers	University of Oxford	ISRCTN10207947
42	(1) Hydroxychloroquine vs (2) Clarithromycin vs (3) Standard of care	45	Patients recovered from covid	Iran University of Medical Sciences	IRCT20200718048129N1
43	(1) Hydroxychloroquine vs (2) Standard of care	3000	Mild	Department of Health	EUCTR-2020-001209-22-GB
44	(1) Hydroxychloroquine vs (2) Placebo	600	Mild/moderate	Porin kaupunki	EUCTR2020-002038-33-FI
45	(1) Hydroxychloroquine vs (2) Lopinavir + ritonavir vs (3) Placebo vs (4) Placebo	1200	Health workers	Centre Hospitalier Universitaire de Saint Etienne	NCT04328285
46	(1) Hydroxychloroquine vs (2) Standard of care	1116	Mild/moderate	Rambam Health Care Campus	NCT04323631
47	(1) Hydroxychloroquine vs (2) Placebo	1600	Close contacts to covid patients	Columbia University	NCT04318444
48	(1) Hydroxychloroquine vs (2) Placebo	400	Health workers	National Institute of Respiratory Diseases, Mexico	NCT04318015
49	(1) Unfractioned heparin OR Low molecular weight heparin (LMWH) vs (2) Hydroxychloroquine vs (3) Hydroxychloroquine + lopinavir + ritonavir vs (4) Oseltamivir vs (5) Lopinavir + ritonavir vs (6) Interferon beta-1a vs (7) Convalescent plasma treatment vs (8) Simvastatin vs (9) Anakinra vs (10) Tocilizumab vs (11) Sarilumab vs (12) Hydrocortisone vs (13) Vitamin C vs (14) Ceftriaxone + macrolide vs (15) Levofloxacin OR Moxifloxacin vs (16) Piperacillin-tazobactam + macrolide vs (17) Ceftaroline + macrolide vs (18) Amoxicillin-clavulanate + macrolide vs (19) Standard of care	1000	No restriction on type of patients	University Medical Center Utrecht	NCT02735707
50	(1) Hydroxychloroquine vs (2) Hydroxychloroquine + azithromycin vs (3) Placebo	75	No restriction on type of patients	Ayub Medical College, Abbottabad	NCT04328272
51	(1) Losartan vs (2) Hydroxychloroquine vs (3) Lopinavir + ritonavir vs (4) Placebo	4000	Moderate/severe/critical	Bassett Healthcare	NCT04328012
52	(1) Hydroxychloroquine + oseltamivir vs (2) Hydroxychloroquine + darunavir + ritonavir + oseltamivir vs (3) Hydroxychloroquine + darunavir + ritonavir + oseltamivir vs (4) Hydroxychloroquine + darunavir + ritonavir + favipiravir vs (5) Lopinavir + ritonavir + oseltamivir vs (6) Lopinavir + ritonavir + oseltamivir vs (7) Lopinavir + ritonavir + favipiravir vs (8) Standard of care	80	Mild	Rajavithi Hospital	NCT04303299
53	(1) N-acetylcysteine + serine + L-carnitine tartrate + nicotinamide riboside vs (2) SOC	400	Mild/moderate	ScandiBio Therapeutics AB	NCT04573153
54	(1) Hydroxychloroquine vs (2) Remdesivir vs (3) Standard of care	700	Severe/critical	Oslo University Hospital	NCT04321616
55	(1) Hydroxychloroquine vs (2) Placebo	1600	Healthy volunteers	Dr. William Schilling	PACTR202009786901147
56	(1) Chloroquine vs (2) Hydroxychloroquine vs (3) Ivermectin	167	Severe	Universidade Federal de Roraima - Boa Vista; RR; Brazil	RBR-8h7q82
57	(1) Hydroxychloroquine vs (2) Placebo	1300	Moderate	University Hospital, Angers	NCT04325893
58	(1) Hydroxychloroquine vs (2) Hydroxychloroquine + azithromycin	440	Moderate/severe	Hospital Israelita Albert Einstein EMS Hospital do Coracao Hospital Sirio-Libanes Brazilian Research In Intensive Care Network Crist©lia Produtos Qu©micos Farmac©uticos Ltda.	NCT04321278
59	(1) Hydroxychloroquine vs (2) Hydroxychloroquine vs (3) Standard of care	93	Close contacts to covid patients	Regional Center for Disease Control and Prevention, Jordan	NCT04597775
60	(1) Hydroxychloroquine vs (2) Hydroxychloroquine + azithromycin vs (3) Standard of care	630	Moderate/severe	Hospital do Coracao Hospital Israelita Albert Einstein Hospital Sirio-Libanes Brazilian Research In Intensive Care Network EMS	NCT04322123
61	(1) Hydroxychloroquine + nitazoxanide + ribavirin vs (2) Placebo	70	Mild/moderate	Rutgers, The State University of New Jersey	NCT04605588
62	(1) Hydroxychloroquine vs (2) Hydroxychloroquine vs (3) Placebo	3500	Health workers	University of Minnesota	NCT04328467
63	(1) Hydroxychloroquine vs (2) Doxycycline© vs (3) Standard of care©	45	Moderate/severe	Dept of Pediatrics Medical College Kolkata	CTRI/2020/10/028234
64	(1) Hydroxychloroquine vs (2) Placebo	3000	Close contacts to covid patients	University of Minnesota	NCT04308668
65	(1) Hydroxychloroquine + azithromycin + zinc vs (2) Lopinavir + ritonavir + azithromycin + zinc vs (3) Standard of care	210	Mild	National Institute for Pharmaceutical Research and Development NIPRD	PACTR202010519682638
66	(1) Hydroxychloroquine vs (2) Paracetamol vs (3) Lopinavir + ritonavir	1000	Mild/moderate	DNDi	PACTR202010781639956
67	(1) Hydroxychloroquine vs (2) Paracetamol vs (3) Lopinavir + ritonavir	2800	Mild/moderate	DNDi	PACTR202010718451278
68	(1) Hydroxychloroquine + lopinavir + ritonavir vs (2) Hydroxychloroquine + atazanavir + ritonavir	120	Moderate/severe	Mazandaran University of Medical Sciences	IRCT20200328046886N2
69	(1) Hydroxychloroquine vs (2) Placebo	2000	Close contacts to covid patients	University of Washington	NCT04328961
70	(1) Hydroxychloroquine vs (2) Azithromycin	300	Mild/moderate	Intermountain Health Care, Inc.	NCT04329832
71	(1) Hydroxychloroquine vs (2) Standard of care	2486	Close contacts to covid patients	Gangnam Severance Hospital	NCT04330144
72	(1) Hydroxychloroquine vs (2) Placebo	800	High risk patients	Instituto de Investigaci©n Marqu©s de Valdecilla	NCT04330495
73	(1) Hydroxychloroquine + ciclesonide vs (2) Ciclesonide vs (3) Standard of care	141	Mild	Korea University Guro Hospital	NCT04330586
74	(1) Hydroxychloroquine vs (2) Remdesivir vs (3) Standard of care	443	Moderate/severe/critical	Oslo University Hospital	EUCTR2020-000982-18-NO
75	(1) Hydroxychloroquine + lopinavir + ritonavir vs (2) Budesonide + formoterol + levamisole	30	Mild/moderate	Fasa University of Medical Sciences	NCT04331470
76	(1) Hydroxychloroquine + azithromycin vs (2) Hydroxychloroquine + azithromycin + tocilizumab	276	Mild	Fundaci© Institut de Recerca de l'Hospital de la Santa Creu i Sant Pau	NCT04332094

77	(1) Hydroxychloroquine vs (2) Placebo	510	Moderate/severe	Massachusetts General Hospital	NCT04332991
78	(1) Hydroxychloroquine vs (2) Standard of care	28	Moderate/severe	King Hussein Cancer Center	NCT04731051
79	(1) Hydroxychloroquine vs (2) Placebo	220	Moderate/severe/critical	University Hospital Tuebingen	NCT04342221
80	(1) Hydroxychloroquine vs (2) Standard of care	3000	Close contacts to covid patients	Tan Tock Seng Hospital	NCT04342156
81	(1) Hydroxychloroquine vs (2) Placebo	400	Mild	University of Utah	NCT04342169
82	(1) Hydroxychloroquine vs (2) Hydroxychloroquine vs (3) Hydroxychloroquine vs (4) Placebo	1450	Healthy volunteers	United States Department of Defense	NCT04343677
83	(1) Telmisartan vs (2) Hydroxychloroquine vs (3) Favipiravir vs (4) Imatinib vs (5) Placebo	1057	Mild	CENTRE HOSPITALIER UNIVERSITAIRE DE BORDEAUX, ETABLISSEMENT PUBLIC	EUCTR2020-001435-27-FR
84	(1) Hydroxychloroquine vs (2) Hydroxychloroquine + dexamethasone	122	Severe	Groupe Hospitalier Paris Saint-Joseph	EUCTR2020-001333-13-FR
85	(1) Hydroxychloroquine vs (2) Hydroxychloroquine + dexamethasone	122	Severe	Groupe Hospitalier Paris Saint-Joseph	EUCTR2020-001421-31-ES
86	(1) Hydroxychloroquine vs (2) Hydroxychloroquine vs (3) Standard of care	1530	Health workers	Sociedad Espa©ola de Farmacia Hospitalaria	EUCTR2020-001606-33-ES
87	(1) Hydroxychloroquine vs (2) Hydroxychloroquine + azithromycin vs (3) Ibuprofen	132	Mild/moderate	Instituto Investigaci©n Sanitario Biocruces Bizkaia	NCT04779047
88	(1) Remdesivir + tocilizumab vs (2) Hydroxychloroquine + tocilizumab	150	Moderate/severe	October 6 University	NCT04338698
89	(1) Hydroxychloroquine vs (2) Hydroxychloroquine + oseltamivir vs (3) Hydroxychloroquine + azithromycin vs (4) Hydroxychloroquine + azithromycin + oseltamivir vs (5) Oseltamivir vs (6) Oseltamivir + azithromycin vs (7) Azithromycin	500	No restriction on type of patients	Shehnoor Azhar	NCT04343768
90	(1) Hydroxychloroquine + lopinavir + ritonavir vs (2) Hydroxychloroquine + lopinavir + ritonavir + interferon beta1b vs (3) Hydroxychloroquine + lopinavir + ritonavir + interferon beta1b	60	Moderate/severe	Shahid Beheshti University of Medical Sciences	EUCTR2020-001565-37-ES
91	(1) Hydroxychloroquine vs (2) Placebo	440	Health workers	ISGlobal	EUCTR2020-001188-96-FR
92	(1) Hydroxychloroquine vs (2) Lopinavir + ritonavir vs (3) Placebo vs (4) Placebo	1200	Health workers	CHU de Saint Etienne	NCT04335552
93	(1) Hydroxychloroquine vs (2) Hydroxychloroquine + azithromycin vs (3) Azithromycin vs (4) SOC	500	Moderate/severe	Duke University	NCT04336748
94	(1) Hydroxychloroquine vs (2) Placebo	440	Health workers	Medical University of Vienna	NCT04334382
95	(1) Hydroxychloroquine vs (2) Azithromycin	1550	No restriction on type of patients	Intermountain Health Care, Inc.	NCT04334967
96	(1) Hydroxychloroquine vs (2) Vitamin C	1250	Mild	Providence Health & Services	NCT04340349
97	(1) Hydroxychloroquine + bromhexine vs (2) Bromhexine	100	Health workers	Instituto Nacional de Rehabilitacion	NCT04340544
98	(1) Hydroxychloroquine vs (2) Placebo	2700	Mild	University Hospital Tuebingen	NCT04336332
99	(1) Hydroxychloroquine vs (2) Hydroxychloroquine + azithromycin vs (3) Standard of care	160	No restriction on type of patients	Rutgers, The State University of New Jersey	NCT04341870
100	(1) Hydroxychloroquine + azithromycin + sarilumab vs (2) Sarilumab	60	Moderate/severe	Assistance Publique - H©pitaux de Paris	NCT04341493
101	(1) Hydroxychloroquine vs (2) Hydroxychloroquine + nitazoxanide	86	No restriction on type of patients	Hugo Mendieta Zeron	NCT04334928
102	(1) Hydroxychloroquine vs (2) Hydroxychloroquine + emtricitabine vs (3) Emtricitabine vs (4) Placebo	4000	Health workers	Plan Nacional sobre el Sida (PNS)	IRCT20130306012728N8
103	(1) Hydroxychloroquine vs (2) Placebo	500	Close contacts to covid patients	Tabriz University of Medical Sciences	IRCT20200318046812N2
104	(1) Hydroxychloroquine + lopinavir + ritonavir vs (2) Hydroxychloroquine + azithromycin + prednisolone + naproxen vs (3) Hydroxychloroquine + azithromycin + naproxen	906	Moderate/severe	Bagheiat-allah University of Medical Sciences	IRCT20150808023559N20
105	(1) Hydroxychloroquine + favipiravir vs (2) Hydroxychloroquine + lopinavir + ritonavir	100	Moderate/severe	Ardabil University of Medical Sciences	IRCT20200405046953N1
106	(1) Hydroxychloroquine vs (2) Remdesivir vs (3) Lopinavir + ritonavir vs (4) Lopinavir + ritonavir + interferon vs (5) Standard of care	3000	Moderate/severe	Iranian Ministry of Health and Medical Education, Deputy of Research and Technology	IRCT20200405046958N1
107	(1) Hydroxychloroquine vs (2) Placebo	60	High risk patients	Mashhad University of Medical Sciences	IRCT20180725040596N2
108	(1) Hydroxychloroquine + lopinavir + ritonavir vs (2) Hydroxychloroquine + umifenovir	100	No restriction on type of patients	Iran University of Medical Sciences	IRCT20200403046926N1
109	(1) Hydroxychloroquine vs (2) Hydroxychloroquine + sofosbuvir + daclatasvir	60	No restriction on type of patients	Mazandaran University of Medical Sciences	IRCT20190122042450N4
110	(1) Hydroxychloroquine vs (2) Standard of care	1000	Close contacts to covid patients	Iran University of Medical Sciences	NCT04349241
111	(1) Hydroxychloroquine + oseltamivir vs (2) Favipiravir	100	Mild/moderate	Ain Shams University	NCT04350281
112	(1) Hydroxychloroquine vs (2) Hydroxychloroquine + interferon beta 1b	80	Moderate/severe/critical	The University of Hong Kong	NCT04350671
113	(1) Hydroxychloroquine + lopinavir + ritonavir + interferon beta 1a vs (2) Hydroxychloroquine + lopinavir + ritonavir	40	Moderate/severe	Shahid Beheshti University of Medical Sciences	NCT04350684
114	(1) Hydroxychloroquine + lopinavir + ritonavir + interferon beta 1a + umifenovir vs (2) Hydroxychloroquine + lopinavir + ritonavir + interferon beta 1a	40	Moderate/severe	Shahid Beheshti University of Medical Sciences	NCT04351724
115	(1) Renin-Angiotensin-System-Blockade vs (2) Non-RAS blocking antihypertensive agent vs (3) Rivaroxaban vs (4) Hydroxychloroquine vs (5) Lopinavir + ritonavir vs (6) Clazakizumab vs (7) Placebo vs (8) Standard of care vs (9) Standard of care	500	High risk patients	Medical University of Vienna	EUCTR2020-001156-18-ES
116	(1) Hydroxychloroquine vs (2) Lopinavir + ritonavir vs (3) Azithromycin	1000	Severe	Fundaci©n para la investigaci©n Biomedica Hospital Universitario La Paz	EUCTR2020-001303-16-FR
117	(1) Telmisartan vs (2) Hydroxychloroquine vs (3) Curcumin C3 vs (4) Azithromycin	1600	No restriction on type of patients	H©pitaux Universitaires de Strasbourg	EUCTR2020-001587-29-ES
118	(1) Hydroxychloroquine vs (2) Hydroxychloroquine vs (3) Placebo vs (4) Placebo	714	Mild	Barcelona Institute for Global Health (ISGlobal)	IRCT20200318046812N1
119	(1) Hydroxychloroquine + favipiravir vs (2) Hydroxychloroquine + lopinavir + ritonavir	324	Severe/critical	Bagheiat-allah University of Medical Sciences	IRCT20130917014693N10
120	(1) Hydroxychloroquine vs (2) Standard of care	100	Close contacts to covid patients	Shahid Beheshti University of Medical Sciences	NCT04344444

121	(1) Hydroxychloroquine vs (2) Hydroxychloroquine + azithromycin vs (3) Standard of care	600	Moderate/severe	LCMC Health	NCT04347980
122	(1) Hydroxychloroquine vs (2) Hydroxychloroquine + dexamethasone	122	Critical	Centre Chirurgical Marie Lannelongue	NCT04345861
123	(1) Hydroxychloroquine vs (2) Hydroxychloroquine + azithromycin	150	Mild	University Hospital, Montpellier	NCT04346147
124	(1) Hydroxychloroquine + lopinavir + ritonavir vs (2) Hydroxychloroquine + baricitinib vs (3) Hydroxychloroquine + imatinib	165	Moderate	Hospital Universitario de Fuenlabrada	NCT04346329
125	(1) Hydroxychloroquine vs (2) Placebo	86	Health workers	Universidad Nacional de Colombia	RBR-3cbs3w
126	(1) Hydroxychloroquine vs (2) Standard of care	1300	Mild	EMS Farmac©utica - Hortol©ndia, SP, Brazil	RBR-9d8z6m
127	(1) Hydroxychloroquine vs (2) Hydroxychloroquine + azithromycin vs (3) Standard of care	630	Moderate/severe	Hospital do Cora©©o - S©o Paulo, SP, Brazil	PACTR202004801273802
128	(1) Hydroxychloroquine vs (2) Chloroquine vs (3) Placebo	600	Moderate/severe/critical	LAGOS STATE GOVERNMENT	PER-010-20
129	(1) Hydroxychloroquine vs (2) Remdesivir vs (3) Lopinavir + ritonavir vs (4) Lopinavir + ritonavir + interferon beta1 vs (5) Standard of care	1000	Moderate/severe/critical	OMS	NCT04344379
130	(1) Hydroxychloroquine vs (2) Azithromycin vs (3) Placebo	900	Health workers	Assistance Publique - H©pitaux de Paris	NCT04347512
131	(1) Hydroxychloroquine vs (2) Hydroxychloroquine + azithromycin vs (3) Standard of care	405	Moderate/severe	University Hospital, Strasbourg, France	NCT04341727
132	(1) Hydroxychloroquine vs (2) Chloroquine vs (3) Hydroxychloroquine + azithromycin vs (4) Chloroquine + azithromycin	500	Moderate/severe	Washington University School of Medicine	EUCTR2020-001448-24-GB
133	(1) Hydroxychloroquine vs (2) Lopinavir vs (3) Ritonavir vs (4) Lopinavir + ritonavir	6400	High risk patients	University of Birmingham	CTRI/2020/03/024402
134	(1) Hydroxychloroquine vs (2) Hydroxychloroquine	500	Health workers	Dr Remesh Bhasi	IRCT20120826010664N6
135	(1) Hydroxychloroquine vs (2) Hope Biosciences Allogeneic Mesenchymal Stem Cell Therapy (HB-adMSCs)	310	Health workers	Tehran University of Medical Sciences	NCT04347889
136	(1) Hydroxychloroquine vs (2) Vitamin C	1212	Health workers	Stony Brook University	NCT04347915
137	(1) Hydroxychloroquine vs (2) Clevudine	60	Moderate	Bukwang Pharmaceutical	NCT04359095
138	(1) Hydroxychloroquine vs (2) Hydroxychloroquine + lopinavir + ritonavir vs (3) Hydroxychloroquine + azithromycin vs (4) Standard of care	1600	No restriction on type of patients	Universidad Nacional de Colombia	NCT04359316
139	(1) Hydroxychloroquine vs (2) Azithromycin	40	Severe	Shahid Beheshti University of Medical Sciences	NCT04358081
140	(1) Hydroxychloroquine vs (2) Hydroxychloroquine + azithromycin vs (3) Placebo	444	Moderate/severe	Novartis Pharmaceuticals	NCT04359537
141	(1) Hydroxychloroquine vs (2) Hydroxychloroquine vs (3) Hydroxychloroquine vs (4) Placebo	200	Health workers	Shaheed Zulfiqar Ali Bhutto Medical University	NCT04359953
142	(1) Telmisartan vs (2) Hydroxychloroquine vs (3) Azithromycin vs (4) Standard of care	1600	Moderate	University Hospital, Strasbourg, France	NCT04361318
143	(1) Hydroxychloroquine + nitazoxanide vs (2) Standard of care	100	No restriction on type of patients	Tanta University	NCT04361461
144	(1) Hydroxychloroquine vs (2) Hydroxychloroquine + azithromycin	500	Severe	Apsen Farmaceutica S.A.	NCT04354428
145	(1) Hydroxychloroquine vs (2) Hydroxychloroquine + azithromycin vs (3) Placebo	630	No restriction on type of patients	University of Washington	NCT04354441
146	(1) Hydroxychloroquine vs (2) Placebo	600	No restriction on type of patients	Sir Mortimer B. Davis - Jewish General Hospital	NCT04352933
147	(1) Hydroxychloroquine vs (2) Hydroxychloroquine vs (3) Placebo	1000	Health workers	Cambridge University Hospitals NHS Foundation Trust	NCT04355052
148	(1) Hydroxychloroquine+azithromycin vs (2) Hydroxychloroquine+camostat mesilate vs (3)SOC	250	Mild/moderate	Sheba Medical Center	NCT04356495
149	(1) Telmisartan vs (2) Hydroxychloroquine vs (3) Favipiravir vs (4) Imatinib vs (5) Vitamin	1057	Mild	University Hospital, Bordeaux	NCT04355026
150	(1) Hydroxychloroquine vs (2) Hydroxychloroquine + bromhexine	90	Moderate/severe	General and Teaching Hospital Celje	NCT04358068
151	(1) Hydroxychloroquine + azithromycin vs (2) Placebo	1000	No restriction on type of patients	National Institute of Allergy and Infectious Diseases (NIAID)	EUCTR2020-001440-26-ES
152	(1) Hydroxychloroquine vs (2) Placebo	184	Health workers	Fundaci©n P©blica Andaluza para la Gesti©n de la Investigaci©n en Salud de Sevilla (FISEVI)	EUCTR2020-001366-11-IT
153	(1) Hydroxychloroquine vs (2) Remdesivir vs (3) Lopinavir + ritonavir vs (4) Lopinavir+ritonavir + interferon beta1a vs (5) Standard of care	600	No restriction on type of patients	AZIENDA OSPEDALIERA UNIVERSITARIA INTEGRATA VERONA	EUCTR2020-001622-64-ES
154	(1) Hydroxychloroquine + azithromycin vs (2) Hydroxychloroquine + azithromycin + prednisone	200	Moderate	Dra Ana Pueyo Bastida	NCT04349228
155	(1) Hydroxychloroquine vs (2) Placebo	530	Health workers	Abderrahmane Mami Hospital Eshmoun Clinical Research Centre Datametrix	ACTRN12620000501943
156	(1) Hydroxychloroquine vs (2) Placebo	2250	Health workers	Walter and Eliza Hall Institute of Medical Research	NCT04362189
157	(1) Hydroxychloroquine + azithromycin vs (2) Hydroxychloroquine + azithromycin + HB-dMSCs vs (3) HB-adMSCs vs (4) Placebo	110	No restriction on type of patients	Hope Biosciences	NCT04362332
158	(1) Chloroquine vs (2) Hydroxychloroquine vs (3) Standard of care	950	Moderate/severe	UMC Utrecht	NCT04352946
159	(1) Hydroxychloroquine vs (2) Placebo	374	Health workers	GeoSentinel Foundation	NCT04353037
160	(1) Hydroxychloroquine vs (2) Hydroxychloroquine vs (3) Placebo vs (4) Placebo	850	Mild	UnitedHealth Group	NCT04353271
161	(1) Hydroxychloroquine vs (2) Placebo	58	Mild	University of South Alabama	NCT04354597
162	(1) Hydroxychloroquine + azithromycin vs (2) Standard of care	200	Health workers	Iyad Sultan	NCT04369742
163	(1) Hydroxychloroquine vs (2) Placebo	626	No restriction on type of patients	NYU Langone Health	NCT04371406
164	(1) Hydroxychloroquine + azithromycin vs (2) Placebo	2770	No restriction on type of patients	Assistance Publique - H©pitaux de Paris	NCT04364022
165	(1) Hydroxychloroquine vs (2) Lopinavir + ritonavir vs (3) Standard of care	420	Close contacts to covid patients	Calmy Alexandra	NCT04365582
166	(1) Hydroxychloroquine vs (2) Lopinavir + ritonavir vs (3) Azithromycin vs (4) Standard of care	640	Mild	Groupe Hospitalier Paris Saint Joseph	NCT04363203
167	(1) Hydroxychloroquine vs (2) Azithromycin vs (3) Placebo	600	Mild/moderate	Salomeh Keyhani MD	NCT04363450
168	(1) Hydroxychloroquine vs (2) Placebo	1700	Health workers	Louisiana State University Health Sciences Center in New Orleans	NCT04363827

169	(1) Hydroxychloroquine vs (2) Hydroxychloroquine vs (3) Standard of care vs (4) SOC	2300	Close contacts to covid patients	Istituto Scientifico Romagnolo per lo Studio e la cura dei Tumori	NCT04363866
170	(1) Hydroxychloroquine vs (2) Placebo	40	Moderate	Oregon Health and Science University	NCT04370015
171	(1) Hydroxychloroquine vs (2) Placebo	374	Health workers	Services Institute of Medical Sciences, Pakistan	NCT04371523
172	(1) Hydroxychloroquine vs (2) Placebo	1100	Health workers	St. Joseph's Healthcare Hamilton	NCT04372082
173	(1) Hydroxychloroquine vs (2) Diltiazem + niclosamide vs (3) Standard of care	480	Moderate	University Hospital, Lille	NCT04371926
174	(1) Hydroxychloroquine vs (2) Hydroxychloroquine vs (3) Standard of care vs (4) SOC	64	Mild/moderate	Texas Cardiac Arrhythmia Research Foundation	NCT04372017
175	(1) Hydroxychloroquine vs (2) Hydroxychloroquine vs (3) Placebo vs (4) Placebo	1739	Health workers	Sanford Health	ChiCTR2000032487
176	(1) Hydroxychloroquine vs (2) Placebo	2000	Healthy volunteers	Shanghai Public Health Clinical Center	NCT04364815
177	(1) Hydroxychloroquine vs (2) Placebo	960	Close contacts to covid patients	University of the Philippines	NCT04374942
178	(1) Hydroxychloroquine vs (2) Placebo	988	Close contacts to covid patients	Megan Landes	NCT04374903
179	(1) Hydroxychloroquine + sirolimus vs (2) Hydroxychloroquine + azithromycin	58	Severe	King Hussein Cancer Center	NCT04304053
180	(1) Hydroxychloroquine + darunavir + cobicistat vs (2) Standard of care	3040	Mild	Lihir Medical Centre	ACTRN12620000557932
181	(1) Hydroxychloroquine + azithromycin + vitamin D3/B12 + vitamin C + zinc vs (2) Hydroxychloroquine + azithromycin + vitamin D3/B12 + zinc	200	No restriction on type of patients	AProf Dr Karin Ried	ChiCTR2000030054
182	(1) Hydroxychloroquine vs (2) Chloroquine vs (3) Standard of care	100	Mild/moderate	Zhongshan Hospital Affiliated to Xiamen University	NCT04379492
183	(1) Hydroxychloroquine vs (2) Placebo	120	Moderate/severe	Memorial Sloan Kettering Cancer Center	NCT04372628
184	(1) Hydroxychloroquine vs (2) Lopinavir + ritonavir vs (3) Placebo	900	Mild	Vanderbilt University Medical Center	NCT04374019
185	(1) Hydroxychloroquine vs (2) Hydroxychloroquine + azithromycin vs (3) Hydroxychloroquine + ivermectin vs (4) Camostat mesilate	240	Mild/moderate	Susanne Arnold	NCT04374552
186	(1) Hydroxychloroquine + azithromycin vs (2) Placebo	140	Mild	Rutgers, The State University of New Jersey	EUCTR2020-001784-88-FI
187	(1) Hydroxychloroquine vs (2) Remdesivir vs (3) Standard of care	664	Moderate/severe/critical	University of Helsinki / CLUE Working Group	EUCTR2020-002123-11-ES
188	(1) Hydroxychloroquine vs (2) Hydroxychloroquine + ciclosporine	280	Moderate/severe/critical	Tatiana Cobo Ib©©ez	NCT04373733
189	(1) Hydroxychloroquine + azithromycin + zinc vs (2) Favipiravir vs (3) Standard of care	450	Moderate	Chelsea and Westminster NHS Foundation Trust	EUCTR2020-001635-27-FR
190	(1) Hydroxychloroquine vs (2) Masitinib + isoquercetin	200	Moderate/severe	AB Science	EUCTR2020-001265-36-IE
191	(1) Hydroxychloroquine vs (2) Hydroxychloroquine + azithromycin vs (3) Standard of care	267	Moderate/severe	University College Dublin	NCT04377646
192	(1) Hydroxychloroquine vs (2) Hydroxychloroquine + zinc vs (3) Placebo	660	Health workers	Military Hospital of Tunis	EUCTR2020-001449-38-GB
193	(1) Hydroxychloroquine + azithromycin + zinc vs (2) Favipiravir vs (3) Standard of care	450	Moderate/severe	Chelsea and Westminster Hospital NHS Foundation Trust	EUCTR2020-001697-30-ES
194	(1) Hydroxychloroquine vs (2) Standard of care	200	Health workers	NAVARRABIOMED - FUNDACI©N MIGUEL SERVET	NCT04384380
195	(1) Hydroxychloroquine vs (2) Standard of care	45	Mild/moderate	Taoyuan General Hospital	NCT04385264
196	(1) Hydroxychloroquine vs (2) Placebo	800	No restriction on type of patients	Center for Primary Care and Public Health (Unisante), University of Lausanne, Switzerland	NCT04390061
197	(1) Hydroxychloroquine vs (2) Hydroxychloroquine + tofacitinib	116	Moderate	Universit© Politecnica delle Marche	IRCT20200406046963N1
198	(1) Hydroxychloroquine vs (2) Hydroxychloroquine + methylprednisolone	40	Moderate/severe	Artesh University of Medical Sciences	ACTRN12620000566932
199	(1) Hydroxychloroquine vs (2) Placebo	3000	Mild	University of Sydney	IRCT20130812014333N147
200	(1) Hydroxychloroquine vs (2) Hydroxychloroquine + trifluoprazine vs (3) Hydroxychloroquine + sofosbuvir + daclatasvir vs (4) Hydroxychloroquine + lithium	80	Severe	Kermanshah University of Medical Sciences	ChiCTR2000029992
201	(1) Chloroquine vs (2) Hydroxychloroquine vs (3) Standard of care	100	Severe	Zhongshan Hospital Affiliated to Xiamen University	IRCT20180425039414N2
202	(1) Hydroxychloroquine vs (2) Hydroxychloroquine + zinc	80	Severe	Esfahan University of Medical Sciences	PACTR202004893013257
203	(1) Hydroxychloroquine vs (2) Hydroxychloroquine + lopinavir + ritonavir vs (3) Lopinavir + ritonavir vs (4) Standard of care	6400	High risk patients	National Institute of Health Research	NCT04386070
204	(1) Hydroxychloroquine vs (2) Hydroxychloroquine + lopinavir + ritonavir vs (3) Lopinavir + ritonavir vs (4) Standard of care	6400	High risk patients	University of Birmingham	NCT04387760
205	(1) Hydroxychloroquine vs (2) Favipiravir vs (3) Standard of care	150	No restriction on type of patients	Royal College of Surgeons in Ireland - Medical University of Bahrain	IRCT20080901001165N51
206	(1) Hydroxychloroquine vs (2) Standard of care	80	Mild/moderate	Sina Darou Laboratories Company	ChiCTR2000029899
207	(1) Hydroxychloroquine vs (2) Chloroquine	100	Mild/moderate	Peking University Third Hospital	RBR-3k4wxb
208	(1) Hydroxychloroquine + azithromycin vs (2) Hydroxychloroquine + azithromycin vs (3) Standard of care	45	Mild	Hospital Santo Ant©nio - Sinop, MT, Brazil	SLCTR/2020/011
209	(1) Hydroxychloroquine vs (2) Placebo	400	Health workers	Department of Medicine, Faculty of Medicine, University of Kelaniya	CTRI/2020/04/024904
210	(1) Hydroxychloroquine vs (2) Hydroxychloroquine vs (3) Hydroxychloroquine + azithromycin	300	Moderate/severe	Director General Armed Forces Medical Services	ChiCTR2000029898
211	(1) Hydroxychloroquine vs (2) Chloroquine	100	Severe	Peking University Third Hospital	CTRI/2020/05/025067
212	(1) Hydroxychloroquine vs (2) Standard of care	10990	Health workers	George Institute for Global Health India	CTRI/2020/05/025022
213	(1) Hydroxychloroquine vs (2) Standard of care	166	Mild	AIIMS Department of Medicine	NCT04381988
214	(1) Hydroxychloroquine vs (2) Placebo	132	Healthy volunteers	Memorial Sloan Kettering Cancer Center	ChiCTR2000029868
215	(1) Hydroxychloroquine vs (2) Standard of care	200	No restriction on type of patients	Ruijin Hospital, Shanghai Jiaotong University School of Medicine	NCT04382846
216	(1) Hydroxychloroquine + ivermectin vs (2) Nitazoxanide + Azithromycin vs (3) Nitazoxanide + ivermectin vs (4) Nitazoxanide + azithromycin + ivermectin	80	No restriction on type of patients	Tanta University	NCT04390594

217	(1) Hydroxychloroquine vs (2) Hydroxychloroquine + azithromycin	258	No restriction on type of patients	Institut Pasteur de Dakar	CTRI/2020/04/024948
218	(1) Hydroxychloroquine vs (2) Ciclesonide vs (3) Ivermectin vs (4) Standard of care	120	Moderate	Lady Hardinge Medical College	IRCT20151222025660N2
219	(1) Hydroxychloroquine vs (2) Standard of care	140	Health workers	Arak University of Medical Sciences	IRCT20200421047155N1
220	(1) Hydroxychloroquine vs (2) Hydroxychloroquine + tenofovir	86	No restriction on type of patients	Ardabil University of Medical Sciences	NCT04397328
221	(1) Hydroxychloroquine vs (2) Placebo	336	Close contacts to covid patients	Lawson Health Research Institute	NCT04391127
222	(1) Hydroxychloroquine vs (2) Ivermectin vs (3) Placebo	200	Moderate	Centenario Hospital Miguel Hidalgo	NCT04392973
223	(1) Hydroxychloroquine + favipiravir vs (2) Standard of care	520	Moderate/severe	King Abdullah International Medical Research Center	NCT04394442
224	(1) Hydroxychloroquine vs (2) Standard of care	200	No restriction on type of patients	Samah Lutfy	NCT04381936
225	(1) Hydroxychloroquine vs (2) Lopinavir + ritonavir vs (3) Convalescent plasma treatment vs (4) Tocilizumab vs (5) Other corticosteroids vs (6) Azithromycin vs (7) Immunoglobulin vs (8) Standard of care	15000	Moderate/severe/critical	University of Oxford	NCT04392128
226	(1) Hydroxychloroquine + azithromycin vs (2) Placebo	114	Mild	Institut de Cancerologie Strasbourg Europe	ChiCTR2000029803
227	(1) Hydroxychloroquine vs (2) Hydroxychloroquine vs (3) Umifenovir vs (4) Umifenovir	320	Close contacts to covid patients	Renmin Hospital of Wuhan University	EUCTR2020-001704-42-ES
228	(1) Hydroxychloroquine vs (2) Placebo	450	Health workers	IDIVAL Instituto de Investigaci©n Sanitaria Valdecilla	EUCTR2020-001366-11-IE
229	(1) Hydroxychloroquine vs (2) Remdesivir vs (3) Lopinavir + ritonavir vs (4) Lopinavir + ritonavir + interferon beta1 vs (5) Standard of care	1000	No restriction on type of patients	World Health Organisation	NCT04405921
230	(1) Hydroxychloroquine vs (2) Hydroxychloroquine + azithromycin	200	No restriction on type of patients	Centre H©pital Universitaire Farhat Hached	NCT04403100

Appendix 4: Updating of the rapid report

Date	Signal	Rationale
7 December 2020	New efficacy signal	Numerous RCTs published, but Cochrane review in progress

Version	Date	Reviewer(s)	Recommendation and Rationale
First	18 June 2020	TK, SD, MB	Hydroxychloroquine/chloroquine not be used for the prevention of COVID-19, unless there is new evidence of efficacy that shows benefit. One RCT found no difference in the incidence of presumed new infections, but a 2-fold greater number of participants complaining of adverse events, compared to placebo.
Second	19 March 2021	ED, AH, TK and MB	HCQ/CQ not be used for the prevention of COVID-19