Hydroxychloroquine or Chloroquine for treating Coronavirus Disease 2019 (COVID-19) – a PROTOCOL for a systematic review of Individual Participant Data

Authors

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BACKGROUND

In the face of the pandemic of SARS CoV2, urgent research is needed to test potential therapeutic agents against the disease. Reliable research shall inform clinical decision makers. Currently, there are several studies testing the efficacy and safety profiles of different pharmacological interventions. Among these drugs, we can cite antimalarial, antivirals, biological drugs, interferon, etc. As of 6 April 2020 there are three published reports and 100 ongoing trials testing hydroxychloroquine/chloroquine alone or in association with other drugs for COVID-19.

This prospective systematic review with Individual Participant data aims to assess the rigour of the best-available evidence for hydroxychloroquine or chloroquine as treatment for COVID-19 infection. The PICO framework is:

P: adults with COVID-19 infection

I: chloroquine or hydroxychloroquine (alone or in association)

C: placebo, other active treatments, usual standard care without antimalarials

O: efficacy and safety outcomes

OBJECTIVES

To assess the effects (benefits and harms) of chloroquine or hydroxychloroquine for the treatment of COVID-19 infection.

METHODS

This protocol is registered in PROSPERO under the code CRD42020178667 (https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=178667)

Criteria for considering studies for this review

Types of studies

We shall include randomized controlled trials (RCTs) with a parallel design. We intend to include even small trials (<50 participants), facing the urgent need for evidence to respond to the current pandemic.

Quasi-randomized, non-randomized, or observational studies will be excluded due to a higher risk of confounding and selection bias (1).

Types of participants

Adults (≥16 years) with a diagnosis of COVID-19 infection, confirmed by a valid laboratory test. We shall not pose restrictions related to clinical presentation or setting (ambulatory, regular wards, or intensive care units).

Types of interventions

- Intervention – chloroquine or hydroxychloroquine in any dose, frequency or route of administration, and duration of treatment. We will include chloroquine/hydroxychloroquine isolated or in association with other interventions, provided we can assess the effects of antimalarials alone.
- Comparators (control group)-
    1. Placebo
    2. Usual standard care

3. Antivirals
4. Other antimalarials (including, but not limited to primaquine, artemether, atovaquone/proguanil, mefloquine, doxycycline, pyrimethamine-sulfadoxine)
5. Biologics

Types of outcome measures

Primary outcomes

- Mortality related to COVID-19 infection - defined by the proportion of deaths related to the disease in the comparison groups.
- Pneumonia / Acute respiratory distress syndrome (ARDS) - defined by the proportion of participants experiencing progression to pneumonia/ARDS in the comparison groups.

  Pneumonia will be considered irrespective of the causal microorganism, i.e. viral, bacterial or fungal. Pneumonia diagnostic criteria will follow the NICE guidance. (2)

  The criteria for ARDS will follow the BERLIN definition, which proposes three mutually exclusive categories of ARDS, based on the degree of hypoxemia: mild (200 mm Hg < PaO_2/FIO_2 ≤ 300 mm Hg), moderate (100 mm Hg < PaO_2/FIO_2 ≤ 200 mm Hg), and severe (PaO_2/FIO_2 ≤ 100 mm Hg) and four ancillary variables for severe ARDS: radiographic severity, respiratory system compliance (≤40 mL/cm H_2O), positive end-expiratory pressure (≥10 cm H_2O), and corrected expired volume per minute (≥10 L/min). (3)
- Adverse events - defined by the proportion of participants experiencing at least one serious adverse event in the comparison groups. We will follow the World Health Organization's definitions (i.e. results in death, is life-threatening, requires inpatient hospitalization or causes prolongation of existing hospitalization, results in persistent or significant disability/incapacity, may have caused a congenital anomaly/birth defect, or requires intervention to prevent permanent impairment or damage)(4). In case any trial reports adverse events at more than one time, we shall consider all events occurring from

the beginning to the end of the records of the patients, even if the events occur after the end of the treatment.

Secondary outcomes

- All-cause mortality - defined by the proportion of all-cause deaths in the comparison groups.
- Hospitalization - defined by the proportion of participants admitted to the hospital in the comparison groups
- Admission to the intensive care unit (ICU) - defined by the proportion of participants admitted to the ICU in the comparison groups.
- Time to clinical improvement - defined as the number of days to the absence of symptoms.
- Virus clearance by a valid method (PCR, rt-PCR and others)

Timing of outcome assessment

We shall assess all outcomes listed above at any time. However, we shall only pool taken at similar times, as follows: short term (up to 7 days, inclusive) or long term (more than 7 days). When a study reports an outcome more than once in the same period, we shall consider the last measurement.

Search methods for identification of studies

Electronic searches

We shall conduct a literature search to identify all published and unpublished RCTs, with no limits on the year of publication, status (abstract, full paper, etc.), or language. The non-English language papers will be translated and fully assessed for potential inclusion in the review as necessary. The period between the date of the last search and the completion of the review will be no more than 6 months.

The following electronic databases will be searched:

- Cochrane Central Register of Controlled Trials (CENTRAL); 2018, Issue 4)
- MEDLINE (from 1966 to date)
- Embase (from 1988 to date)

The keywords and search strategy are described in Appendix 1.

Searching other resources

We intend to check reference lists/bibliographies of all primary studies and review articles for additional trials. We shall contact the authors of identified studies, manufacturers, and experts in the field to ask them to help identify other published and unpublished studies.

We shall search for errata or retractions from eligible studies on Pubmed and report the date on which that is done. Additionally, we shall access the following grey literature databases and clinical trials registers:

Grey literature databases

- Health Management Information Consortium (HMIC) database
- National Technical Information Service (NTIS) database
- OpenGrey

Clinical trials registers

- ClinicalTrials.gov
- EU Clinical Trials Register
- International Clinical Trials Registry Platform Search Portal
- International Federation of Pharmaceutical Manufacturers and Associations (IFPMA) Clinical Trials Portal

Data collection and analysis

Selection of studies

Two review authors will independently screen titles and abstracts of all the publications retrieved and decide whether to include them for full-text assessment. We shall retrieve the full texts of the included studies, and two review authors will independently screen them for final inclusion/exclusion. We shall identify and record the reasons for exclusion of ineligible studies. Disagreement will be resolved through discussion or, if required, consultation with a third review author. We shall list the numbers of studies and participants for which IPD were sought and for which IPD were obtained. For studies whose IPD were not available, we shall provide the numbers of studies and participants for which aggregate data were available. Furthermore, we shall report reasons for non-availability of IPD. We shall record the selection process in sufficient detail to complete a PRISMA flow diagram (5), and a 'Characteristics of excluded studies' table.

Data extraction and management

We shall contact the study investigators by e-mail and perform a comprehensive search in data-sharing repositories or platforms (such as Yale Open Data, Clinical Study Data Request, DataSphere, or Vivli) to try to obtain the following individual participant data (IPD) from all trials that meet our inclusion criteria:

Trial methods

- method of generation of the random sequence
- method of allocation concealment
- stratification factors or minimization procedures
- blinding methods (patients, personnel, outcome assessors)

Participant covariates

- sex
- age
- clinical presentation at the time of enrollment
- the time between diagnosis of COVID-19 and randomization
- setting (outpatients, inpatients, etc.) before randomization, with dates.
- the presence of ARDS

- laboratory results
- computerized tomography/magnetic resonance imaging (CT/MRI) results

Follow-up data

- treatment allocation
- date of randomization
- dates of follow-up
- dates of each outcome after randomization or outcome frequency data between follow-up visits
- types and doses of antimalarials
- dates of dose changes

We intend to obtain the largest proportion of eligible trials and participants possible, aiming for more than 90% of IPD (6). If we cannot achieve this threshold, we shall obtain the maximum available IPD and perform power calculations to detect the prespecified outcomes reliably (7).

Data security and confidentiality will be preserved through a data sharing and use agreement between the original investigators and the IPD review team. This agreement will cover details of how data will be held securely, accessed only by authorized members of the project team, and will not be copied or distributed elsewhere. We shall also ask that individual participants be adequately de-identified in the supplied data, by removing or recoding identifiers (8).

Ethics approval will not be pursued, on the premise that we shall address the same research question as to the original studies for which participants have already given their informed consent (8).

We shall give investigators clear instructions on which data we need and the preferred data format and coding for each variable (6). If study investigators are unwilling or unable to prepare data according to this pre-specified format, we shall accept data in whatever format is most

convenient, and recode them as necessary. A copy of the data, as supplied, will be archived before carrying out conversions or modifications, and any alterations will be properly logged.

We shall check the integrity and completeness of incoming data against any relevant study publications or results repositories to ensure that the included data are consistent (8).

Assessment of risks of biases in included studies

Two review authors will independently assess the risk of bias for each study using the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions (8). Any disagreement will be resolved by discussion or by involving a third person. We shall assess the following domains separately for each included trial:

1. Random sequence generation
2. Allocation concealment
3. Blinding of participants and personnel
4. Blinding of outcome assessment
5. Incomplete outcome data
6. Selective outcome reporting
7. Other sources of biases

We shall judge each potential source of bias as high, low, or unclear and provide justifications for judgments given.

We shall ask the authors to provide additional details that have not been reported in the study publication where necessary.

We plan to run sensitivity analyses excluding trials judged to be at a high and unclear risk of bias.

Measures of treatment effect

The estimates of effects for dichotomous outcomes (death, pneumonia, etc.) will be presented as risk ratios. For continuous data, we shall use mean differences or standardized mean differences (SMD). Finally, time-to-event outcomes (time to clinical failure or improvement) will be reported as hazard ratios. All estimates will be presented with 95% confidence intervals. We shall include all randomized participants by intention-to-treat. We will assess the clinical relevance of the observed effect size for each outcome according to *a-priori* determined minimal important differences (MID) (9). A value of 5% relative risk reduction will be set as the MID for mortality and pneumonia/ARDS outcomes.

Where SMD is used as the effect estimate, these will be interpreted as follows: 0.2 SMD – 'small' effect size, 0.5 – 'medium' effect size, 0.8 – 'large' effect size (10). Where possible we will convert SMDs back to their original units to aid clinical interpretation.

We intend to undertake meta-analyses only when the treatments, participants, and the underlying clinical question are similar enough for pooling to make sense. Considering the likelihood of clinical or methodological heterogeneity, we shall use a random-effects model in each meta-analysis, using Review Manager software (REVMAN) version 5. For the analyses that REVMAN is not able to perform, we shall use the STATA package software version 15.1.

We shall use a one-stage approach to analysis, deriving summary estimates from the IPD directly to provide a pooled estimate of effect, allowing for between-study differences (heterogeneity) (8).

Unit of analysis issues

The unit of analysis will be the individual, collecting and analyzing a single measurement of each outcome for each participant.

Dealing with missing data

To avoid data availability bias, we shall seek IPD from published and unpublished studies. Investigators or study sponsors will be contacted to verify key study characteristics and obtain missing outcome data whenever possible (e.g. when a study is identified in abstract only). Data-sharing repositories or platforms will also be checked, as described in the section on data extraction and management.

We shall depict the proportion of trials and participants for which IPD is available and the reasons for the non-availability of data. If substantial amounts of data are missing, data availability bias will be investigated by comparing or combining results based on IPD with those based on aggregate data, to check for coherence and consistency (11). We shall mention this as a potential limitation and how trials without individual participant data might affect the conclusions in the Discussion and Conclusions sections.

Assessment of heterogeneity

We shall assess clinical, methodological, and statistical heterogeneity among the included trials. We shall use the chi² test ($p < 0.10$ indicates significant heterogeneity) to detect and the I^2 statistic to measure statistical heterogeneity among the trials in each meta-analysis. If we identify substantial heterogeneity, we shall explore it by prespecified subgroup analyses. We shall consider an I^2 value greater than 50% as substantial heterogeneity.

Additional analyses

Subgroup analyses

Assessing if effects vary by trial characteristics

We shall perform subgroup and meta-regression analyses for the primary outcomes using the following study variables:

- drug type: chloroquine versus hydroxychloroquine
- different drug doses. If results over a wide enough range of doses in enough individuals are found, we shall explore dose-response relationships.

- duration of the treatment: 5 days versus more than 5 days. All patient records will be analysed in an intention-to-treat principle in the case of patients dropping out or dying before the completion of the allocated regimen.

Assessing if effects vary by participant characteristics

- age (< 60 years old versus > 60 years old)
- sex
- the severity of disease (critically ill versus non-critically ill). Critically ill will be defined by the need of invasive mechanical ventilation, shock, concurrent organ failure caused by COVID-19 or admission to the Intensive Care Unit.

Any interactions between effects and participant characteristics will be explored in two stages. In the first stage, interactions between the variable and the intervention effect at the individual participant level will be estimated in each study. In the second stage (within-study interactions) these interactions will be pooled across studies using standard meta-analysis techniques.

Sensitivity analyses

We shall perform sensitivity analyses to check the robustness of the overall estimates, excluding:

- studies with a high risk of bias (due to inadequate allocation concealment or lack of blinding)
- studies with unavailable IPD and missing data in the aggregate report
- studies funded by pharmaceutical companies

Assessment of reporting biases

If we can pool ten or more trials, we shall create and examine funnel plots to explore possible publication biases.

'Summary of findings' table

We will create a 'Summary of findings' table comparing chloroquine/hydroxychloroquine versus placebo, chloroquine/hydroxychloroquine versus antivirals, chloroquine/hydroxychloroquine versus other antimalarials and chloroquine/hydroxychloroquine versus biologics . We will assess all predefined primary outcomes. We shall use the five GRADE considerations (study limitations, consistency of effect, imprecision, indirectness, and publication bias) to assess the certainty of a body of evidence as it relates to the studies that contribute data to the meta-analysis for the prespecified outcomes (12). We will use the methods and recommendations described in the *Cochrane Handbook for Systematic Reviews of Interventions* (8) employing GRADEpro GDT software (13). We intend to justify all decisions to downgrade or upgrade the certainty of the evidence from studies using footnotes, and make comments to aid readers' understanding of the review where necessary.

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OXFORD
BRAZIL
EBM
Alliance

Appendix 1.

Search Strategy

Cochrane Library

#1 MeSH descriptor: [Coronavirus] explode all trees

#2 "COVID-19" OR (COVID) OR (Coronavirus) OR (SARS-CoV-2) OR (Coronaviruses) OR (Deltacoronavirus) OR (Deltacoronaviruses) OR "Munia coronavirus HKU13" OR (Coronavirus HKU15) OR (Coronavirus, Rabbit) OR (Rabbit Coronavirus) OR (Coronaviruses, Rabbit) OR (Rabbit Coronaviruses) OR "Bulbul coronavirus HKU11" OR "Thrush coronavirus HKU12"

#3 #1 OR #2

#4 MeSH descriptor: [Hydroxychloroquine] explode all trees

#5 MeSH descriptor: [Chloroquine] explode all trees

#6 MeSH descriptor: [Antimalarials] explode all trees

#7 (Hydroxychloroquine) OR (Oxychlorochin) OR (Oxychloroquine) OR (Hydroxychlorochin) OR (Plaquenil) OR (Hydroxychloroquine Sulfate) OR "Hydroxychloroquine Sulfate (1:1) Salt" OR (Hidroxicloroquina) OR (Hydroxychloroquine) OR (Hydroxychloroquinum) OR (Oxichlorochine) OR (Oxichloroquine) OR Chlorochin OR Cloroquina OR Cloroquine OR Chloroquine OR (Antimalarials) OR (Antimalarial Agents) OR (Agents, Antimalarial) OR (Antimalarial Drugs) OR (Drugs, Antimalarial) OR (Anti-Malarials) OR (Anti Malarials) OR "(N4-(7-Chloro-4-quinolinyl)-N1,N1-diethyl1,4-pentanediamine)" OR Hydroquin OR Axemal OR Dolquine OR Quensyl OR Quinoric OR Plaquenil OR chloraquin OR chloraquine OR chloroquine OR cloroquin OR chlorokin OR chlorokine OR chlorquin OR chlorquine OR kloroquin OR kloroquine

#8 #4 OR #5 OR #6 OR #7

#9 #3 AND #8

Embase

#1 'coronavirinae' OR 'coronavirinae'/exp OR coronavirinae OR 'corona virus'/exp OR 'corona virus' OR 'coronavirus'/exp OR coronavirus OR 'covid-19' OR covid OR 'sars-cov-2' OR coronaviruses OR deltacoronavirus OR deltacoronaviruses OR 'munia coronavirus hku13' OR 'coronavirus hku15' OR 'coronavirus, rabbit' OR 'rabbit coronavirus' OR 'coronaviruses, rabbit' OR 'rabbit coronaviruses' OR 'bulbul coronavirus hku11' OR 'thrush coronavirus hku12'

#2 'hydroxychloroquine' OR 'hydroxychloroquine'/exp OR hydroxychloroquine OR '7 chloro 4 [4 [ethyl (2 hydroxyethyl) amino] 1 methylbutylamino] quinoline'/exp OR '7 chloro 4 [4 [ethyl (2 hydroxyethyl) amino] 1 methylbutylamino] quinoline' OR '7 chloro 4 [4 [ethyl (2 hydroxyethyl) amino] 1 methylbutylamino] quinoline diphosphate'/exp OR '7 chloro 4 [4 [ethyl (2 hydroxyethyl) amino] 1 methylbutylamino] quinoline diphosphate' OR 'chloroquinol'/exp OR chloroquinol OR 'ercoquin'/exp OR ercoquin OR 'hydrochloroquine'/exp OR hydrochloroquine OR 'hydrocloroquine'/exp OR hydrocloroquine OR 'oxychloroquine'/exp OR oxychloroquine OR 'quensyl'/exp OR quensyl OR 'sn 8137'/exp OR 'sn 8137' OR oxychlorochin OR hydroxychlorochin OR plaquenil OR 'hydroxychloroquine sulfate' OR 'hydroxychloroquine sulfate (1:1) salt' OR hidroxicloroquina OR hydroxychloroquinum OR oxichlorochine OR oxichloroquine OR 'chloroquine' OR 'chloroquine'/exp OR chloroquine OR '4 (4 diethylamino 1 methylbutylamino) 7 chlorchinolin diphosphate' OR '4 (4 diethylamino 1 methylbutylamino) 7 chlorchinolin sulfate' OR '4 (4 diethylamino 1 methylbutylamino) 7 chlorchinolin sulfate' OR '4 (4 diethylamino 1 methylbutylamino) 7 chloroquinoline' OR '7 chloro 4 (4 diethylamino 1 methylbutylamino) quinoline' OR '7 chloro 4 (4 diethylamino 1 methylbutylamino) quinoline diphosphate' OR '7 chloro 4 (4 diethylamino 1 methylbutylamino) quinoline' OR 'a-cq' OR amokin OR amokine OR anoclor OR aralan OR aralen OR 'aralen hydrochloride' OR 'aralen phosphate' OR aralene OR arechin OR arechine OR arequine OR arthrochin OR arthrochine OR arthroquine OR artrichin OR artrichine OR artriquine OR avloclor OR avoclor OR bemaphata OR bemaphate OR bemasulph OR bipiquin OR cadiquin OR chemochin OR chemochine OR chingamine OR chingaminum OR

chloraquine OR chlorochin OR chlorochine OR chlorofoz OR chloroquin OR 'chloroquin phosphate' OR 'chloroquine diphosphate' OR 'chloroquine disulfate' OR 'chloroquine disulphate' OR 'chloroquine hydrochloride' OR 'chloroquine phosphate' OR 'chloroquine streuli' OR 'chloroquine sulfate' OR 'chloroquine sulphate' OR chloroquinesulphate OR 'chloroquini diphosphas' OR 'chloroquinum diphosphoricum' OR chlorquin OR chlorquine OR choloquine OR 'choroquine sulfate' OR 'choroquine sulphate' OR cidanchin OR 'clo-kit junior' OR clorichina OR clorichine OR cloriquine OR clorochina OR delagil OR delagyl OR dichinalex OR diclokin OR diquinalex OR diroquine OR emquin OR genocin OR gontochin OR gontochine OR gontoquine OR heliopar OR imagon OR iroquine OR klorokin OR klorokine OR klorokinfosfat OR lagaquin OR malaquin OR malarex OR malarivon OR malaviron OR maliaquine OR maquine OR mesylith OR mexaquin OR mirquin OR nivachine OR nivaquin OR nivaquine OR 'nivaquine (b)' OR 'nivaquine b' OR 'nivaquine dp' OR 'nivaquine forte' OR 'p roquine' OR quinachlor OR quingamine OR repal OR resochen OR resochene OR resochin OR 'resochin junior' OR resochina OR resochine OR resochinon OR resoquina OR resoquine OR reumachlor OR roquine OR 'rp 3377' OR rp3377 OR sanoquin OR sanoquine OR silbesan OR siragan OR sirajan OR 'sn 7618' OR sn7618 OR solprina OR solprine OR tresochin OR tresochine OR tresoquine OR trochin OR trochine OR troquine OR 'w 7618' OR w7618 OR 'win 244' OR win244 OR 'antimalarial agent'/exp OR 'antimalarial agent' OR 'anti malaria drug'/exp OR 'anti malaria drug' OR 'antimalaria agent'/exp OR 'antimalaria agent' OR 'antimalaria drug'/exp OR 'antimalaria drug' OR 'antimalaria drug, synthetic'/exp OR 'antimalaria drug, synthetic' OR 'antimalarial'/exp OR antimalarial OR 'antimalarial drug'/exp OR 'antimalarial drug' OR 'antimalarials'/exp OR antimalarials OR 'antipaludean agent'/exp OR 'antipaludean agent' OR 'antiplasmodic agent'/exp OR 'antiplasmodic agent' OR 'synthetic antimalaria agent'/exp OR 'synthetic antimalaria agent'

#3 #1 AND #2

#4 #3 AND [embase]/lim NOT ([embase]/lim AND [medline]/lim)

LILACS

#1 MH:"Coronavirus" OR MH:B04.820.504.540.150$ OR (Coronavirus) OR "COVID-19" OR (COVID) OR (SARS-CoV-2) OR (Deltacoronavirus) OR (Coronaviruses)

#2 MH:"Hydroxychloroquine" OR MH:"Hidroxicloroquina" OR MH:D03.633.100.810.050.180.350$ OR (Hydroxychloroquine) OR (Hidroxicloroquina) OR (Hydroxychlorochin) OR (Hydroxychloroquine Sulfate) OR "Hydroxychloroquine Sulfate (1:1) Salt" OR (Oxychlorochin) OR (Oxychloroquine) OR (Plaquenil) OR (Oxicloroquina) OR MH:"Cloroquina" OR MH:"Chloroquine" OR MH:D03.633.100.810.050.180$ OR (Cloroquina) OR (Chloroquine) OR (Aralen) OR (Arechine) OR (Arequin) OR (Chingamin) OR (Chlorochin) OR (Chloroquine Sulfate) OR (Chloroquine Sulphate) OR (Khingamin) OR (Nivaquine) OR (Sulfate, Chloroquine) OR (Sulphate, Chloroquine) OR MH:"Antimaláricos" OR MH:"Antimalarials" OR MH:D27.505.954.122.250.100.085$ OR (Antimaláricos) OR (Antimalarials) OR (Agents, Antimalarial) OR (Anti Malarials) OR (Anti-Malarials) OR (Antimalarial Agents) OR (Antimalarial Drugs) OR (Drugs, Antimalarial)

#3 #1 AND #2

#4 in [Lilacs]

MEDLINE (via PubMed)

#1 "Coronavirus"[Mesh] OR "COVID-19" OR (COVID) OR (Coronavirus) OR (SARS-CoV-2) OR (Coronaviruses) OR (Deltacoronavirus) OR (Deltacoronaviruses) OR "Munia coronavirus HKU13" OR (Coronavirus HKU15) OR (Coronavirus, Rabbit) OR (Rabbit Coronavirus) OR (Coronaviruses, Rabbit) OR (Rabbit Coronaviruses) OR "Bulbul coronavirus HKU11" OR "Thrush coronavirus HKU12"

#2 "Hydroxychloroquine"[Mesh] OR (Hydroxychloroquine) OR (Oxychlorochin) OR (Oxychloroquine) OR (Hydroxychlorochin) OR (Plaquenil) OR (Hydroxychloroquine Sulfate) OR

"Hydroxychloroquine Sulfate (1:1) Salt" OR (Hidroxicloroquina) OR (Hydroxychloroquine) OR (Hydroxychloroquinum) OR (Oxichlorochine) OR (Oxichloroquine) OR "Chloroquine"[Mesh] OR Chlorochin OR Cloroquina OR Cloroquine OR Chloroquine OR "Antimalarials"[Mesh] OR (Antimalarials) OR (Antimalarial Agents) OR (Agents, Antimalarial) OR (Antimalarial Drugs) OR (Drugs, Antimalarial) OR (Anti-Malarials) OR (Anti Malarials) OR "(N4-(7-Chloro-4-quinolinyl)-N1,N1-diethyl-1,4pentanediamine)" OR Hydroquin OR Axemal OR Dolquine OR Quensyl OR Quinoric

#3 #1 AND #2

Opengrey

#1 "COVID-19" OR (COVID) OR (Coronavirus) OR (SARS-CoV-2) OR (Coronaviruses) OR (Deltacoronavirus) OR (Deltacoronaviruses)

ClinicalTrials.gov

#1 "COVID-19" OR (COVID) OR (Coronavirus) OR (SARS-CoV-2) OR (Coronaviruses) OR (Deltacoronavirus) OR (Deltacoronaviruses)

#2 Hydroxychloroquine OR Oxychlorochin OR Oxychloroquine OR Hydroxychlorochin OR Plaquenil OR Chlorochin OR Cloroquina OR Cloroquine OR chloroquine OR Antimalarials OR Antimalarial

#3 #1 AND #2

WHO-ICTRP

#1 "COVID-19" OR (COVID) OR (Coronavirus) OR (SARS-CoV-2) OR (Coronaviruses) OR (Deltacoronavirus) OR (Deltacoronaviruses)

#2 Hydroxychloroquine OR Oxychlorochin OR Oxychloroquine OR Hydroxychlorochin OR Plaquenil OR Chlorochin OR Cloroquina OR Cloroquine OR chloroquine OR Antimalarials OR Antimalarial

#3 #1 AND #2