REVIEW ARTICLE

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Efficacy and safety outcomes of proposed randomized controlled trials investigating hydroxychloroquine and chloroquine during the early stages of the COVID-19 pandemic

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Aims: To assess whether randomized clinical trials (RCTs) proposed to evaluate the treatment of patients with COVID-19 with hydroxychloroquine (HQ) or chloroquine early in the pandemic included plans to measure outcomes that would translate into meaningful efficacy/effectiveness and safety outcomes.

Methods: The World Health Organization International Clinical Trials Registry Platform database was searched for registers of RCTs evaluating HQ or chloroquine, alone or in combination, compared with other treatments for patients diagnosed with COVID-19. The final search was performed on 8 April 2020.

Results: Among 51 registered RCTs (median sample size 262; interquartile range: 100, 520), 34 (67%) reported a clinical outcome, 12 (24%) a surrogate outcome, and 5 (10%) a combination of clinical and surrogate outcomes as primary endpoints. Six (15%) trials included the World Health Organization scale for clinical improvement as a primary clinical outcome. Clinical improvement and mortality accounted for 45% of the unique domains among 18 clinical outcome domains of efficacy. Twenty-four (47%) RCTs did not describe plans to assess safety outcomes; when assessed, safety outcomes were determined in generic terms of total, severe or serious adverse events.

Conclusion: The RCTs investigating HQ or chloroquine during the early stages of the COVID-19 pandemic included heterogeneous and insufficient approaches to measure efficacy/effectiveness and safety relevant to patients and clinical practice. These findings provide insights to inform clinical and regulatory decisions that can be drawn about the efficacy/effectiveness and safety of these agents in patients with COVID-19. Trialists need to adapt quickly to the research progress on COVID-19, ensuring that core outcome measures are assessed in ongoing RCTs.

KEYWORDS

COVID-19, hydroxychloroquine, chloroquine, clinical trials, adverse events

1 | INTRODUCTION

On 31 December 2019, a cluster of cases of atypical pneumonia of unknown aetiology was reported in the city of Wuhan, China, and later identified as being caused by a novel coronavirus.[1] The ability of the novel severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2; hereafter referred to as COVID-19)[2] to infect human hosts and be transmitted among individuals rapidly evolved into a global pandemic with over 52.2 million confirmed cases in 235 countries as of 13 November 2020 (https://www.who.int/emergencies/diseases/novel-coronavirus-2019). Although the majority (~80%) of the COVID-19 cases develop a mild condition, a smaller percentage

(~15%) of patients require hospitalization and some develop a severe condition (~5%) that requires mechanical ventilation in the first 24 hours of hospital admission.[3] Clinical complications such as profound acute hypoxaemic respiratory failure and sepsis[4,5] have led to a total of 1 286 063 deaths worldwide (https://www.who.int/emergencies/diseases/novel-coronavirus-2019; last updated on 13 November 2020).

Worldwide, the capacity of the healthcare systems to offer care for patients diagnosed with COVID-19 depends on the capability of intensive care units (ICUs) and emergency departments (EDs) to accommodate the additional requirements brought about by the increased patient volumes during the pandemic. This is of critical relevance considering the high ICU occupancy commonly seen in many locations[6] and the long-recognized ED overcrowding and its negative consequences on patient outcomes.[7–9] Moreover, early in the pandemic, the management of patients with COVID-19 was supportive, and recovery time was estimated at around 3–6 weeks for critically ill patients.[10] In this challenging scenario, it is not surprising that there has been a frantic search for effective treatments. Early in April 2020, there were 788 entries of registered COVID-19 trials on the World Health Organization International Clinical Trials Registry Platform (WHO-ICTRP). By the end of August 2020, the WHO-ICTRP database had registered 3 times more entries.

Clinical trials provide vital evidence to establish the efficacy and safety of new interventions or new indications for existing interventions. To be informative, however, they have to be designed and implemented following standards to ensure valid and meaningful evidence.[11] Meaningful evidence involves defining outcomes comprising the potential benefits (efficacy/effectiveness) and harms (safety) of the treatments under investigation.[12] Moreover, efficacy/effectiveness outcomes should represent clinically meaningful results that directly measure how a patient feels, functions or survives.[13] Alternatively, trials may report surrogate outcomes, which may provide evidence for benefit that encourages further research. Trials assessing surrogate outcomes may be smaller, completed faster and be less expensive; however, surrogate outcomes may or may not predict clinical results and translate into meaningful evidence of efficacy/effectiveness.[13,14]

Likewise, safety outcomes are essential in defining the value of a treatment intervention for healthcare providers, patients, and health systems. Despite the importance of finding a treatment that effectively mitigates or cures patients diagnosed with COVID-19, it is critical to appropriately define and detect the potential adverse events of the treatment options under investigation. There are guidance and legal requirements for clinical trial protocols to plan the data collection of adverse events, whether applying systematic or nonsystematic assessment approaches.[12,15,16]

The objective of this study was to assess whether the randomized clinical trials (RCTs) of COVID-19 treatments registered on the WHO-ICTRP included definitions and data collection plans to produce evidence on meaningful efficacy, effectiveness and safety outcomes. We focused on RCTs as the highest level of evidence and those evaluating treatments with **hydroxychloroquine** (HQ) or **chloroquine**. Traditionally, these immune-suppressants have been used to treat autoimmune diseases such as rheumatoid arthritis and inflammatory bowel disease;

What is already known about this subject

- There is an urgent need for effective and safe treatments that reduce the morbidity and mortality of patients diagnosed with COVID-19.
- Chloroquine, and its derivate hydroxychloroquine (HQ), have been identified as potential therapies described in the scientific literature and social media.

What this study adds

- The results show that the initial randomized controlled trials (RCTs) proposed to investigate the efficacy/effectiveness of HQ or chloroquine include a heterogeneous set of clinical outcomes domains.
- These early planned RCTs failed to include sufficient and structured approaches to detect adverse events that are relevant to patients and to inform clinical practice.
- This study highlights 3 critical areas that can be improved to better inform clinical and regulatory decisions about the value of HQ or chloroquine in the treatment of COVID-19: the selection of efficacy/effectiveness outcomes; assessment of treatment harms and patient safety; and reducing missing and variable dosing schedules and treatment duration.

however, they have also been approved for the treatment of malaria since 1955.[17] In the context of COVID-19, these drugs received widespread support as effective treatments following demonstration of in vitro viral activity against SARS-CoV-2 and a potential viral load reduction in a case series report.[18,19] During the early stages of the pandemic, HQ and chloroquine received emergency use authorization[20] by the Food and Drug Administration in the USA and overwhelming social media and leadership support, resulting in medication shortages. Evolving research has shown that HQ and chloroquine do not reduce the mortality of patients with COVID-19.[21] Nonetheless, there is continued interest in high-quality RCTs on the efficacy and safety of these and other drugs in the treatment of patients diagnosed with COVID-19 infection.[21] Furthermore, familiarity with HQ and chloroquine have created a push for expedited clinical trials.

2 | METHODS

We downloaded the COVID-19 WHO-ICTRP database (https://www.who.int/ictrp/search/en/) on 8 April 2020, at 10:30 GMT−6. We filtered studies on the database according to the intervention (HQ or chloroquine) and the study design (randomized vs nonrandomized). All the retrieved registers were screened and reviewed for data

extraction purposes. Eligible studies were parallel RCTs evaluating either HQ or chloroquine to treat patients diagnosed with COVID-19 infection, used alone or in any combination, and compared with any other treatment option (including placebo). Uncontrolled trials and observational studies were excluded. We included trials recorded in the clinical trial registry of any country and at any recruitment status. Patients and investigators were not aware of this study at the time of their submissions.

2.1 | Data extraction and sources

One author (D.J.) extracted data using a standardized form. Quality control was performed by re-extracting data from 15% of the included trial registries. Information on the trial ID, scientific title, date of registration, recruitment status, patient population and funding sources were extracted from the WHO-ICTRP database. Information on the country where the trials were planned to be conducted was extracted primarily from the WHO-ICTRP database and completed using the data from the trial registry when appropriate.

The trial's registry was accessed and provided additional information to characterize the RCTs according to:

- Number of participants planned to be recruited;
- Age and sex of the participants planned to be recruited;
- Intervention and comparison treatments, including doses and administration schedules;
- Treatment duration;
- Efficacy/effectiveness outcomes defined as primary endpoints;
- Safety outcomes, i.e. adverse events;
- Timeframe for the assessment of the efficacy/effectiveness and safety outcomes;
- Mode of data collection of safety outcomes.

The efficacy/effectiveness outcomes were classified as clinical (e.g. improvement or recovery from respiratory symptoms) or surrogate outcomes (e.g. viral load, biomarkers). The mode of data collection of the adverse events was classified as *systematic assessment* when specific ascertaining methods to detect the occurrence of adverse events were described by the use of checklists, questionnaires, or laboratory tests at regular intervals, and as *nonsystematic assessment* when the detection methods relied on the spontaneous report of adverse events by clinicians or participants.[15]

2.2 | Data analysis

The characteristics of the RCTs were summarized according to clinical or surrogate outcomes and ascertainment methods to detect adverse events. Simple proportions were reported for dichotomous outcomes. For continuous data, means and standard deviations or medians and interquartile ranges (IQRs) were reported, as appropriate. Comparisons between continuous variables were made using t-test and reporting

the mean difference (MD) with 95% confidence intervals (CI). Finally, outcomes planned to be measured in the RCTs were compared to the primary outcome defined in the master protocol for COVID-19 studies published by WHO on 18 February 2020,[22] which comprised a composite measure of clinical improvement and/or survival measured on an ordinal scale ranging from 0, uninfected, to 8, dead.

3 | RESULTS

Among 927 clinical trials registered on the WHO-ICTRP database as of 8 April 2020, 72 registrations were identified as RCTs investigating the use of HQ or chloroquine for COVID-19 infection and considered potentially eligible for this study (Figure 1). Among these 72 registered trials, 2 were duplicate entries of the same trial in more than 1 clinical trial registry, 7 trials had been cancelled and 12 entries related to trials testing prophylactic interventions. Therefore, 51 registered clinical trials were included for analysis. An updated search (conducted on 24 August 2020) revealed approximately 300 registered trials involving treatments with HQ or chloroquine that would be potentially eligible.

Table 1 summarizes the characteristics of the clinical trials planned to investigate the use of HQ or chloroquine to treat patients diagnosed with COVID-19. The RCTs proposed to test the hypothesis of whether these drugs could be beneficial for people infected with SARS-CoV2 started in February 2020 when 12 trials were registered. In the following month of March, the number of trials registered tripled. All trials planned to include adults of both sexes, and 3 trials
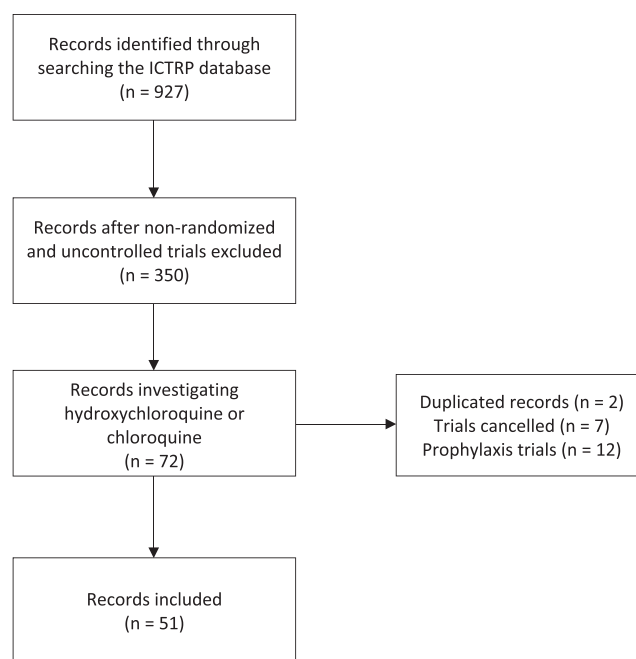

FIGURE 1 Flow diagram illustrating the selection of the clinical trial registries available on the International Clinical Trials Registry Platform (ICTRP) on 8 April 2020 at 10:30 GMT−6

TABLE 1 Characteristics of the randomized controlled trials for the treatment of COVID-19 with hydroxychloroquine or chloroquine (n = 51)

	n (%)
Month of registration	
February	12 (24)
March	33 (65)
April	6 (12)
Age groups	
Adolescents and adults	3 (6)
Adults	48 (94)
Sex	
Females	51 (100)
Males	51 (100)
Actively recruiting	24 (47)
Sample size, median (IQR)	262 (100, 520)[a]
Patient population [b]	
Inpatients	28 (55%)
Outpatients	6 (12%)
Unclear	17 (33%)
Case severity	
Mild cases	11 (22%)
Moderate cases	3 (6%)
Severe cases	10 (20%)
Critical care	2 (4%)
Not reported	
Treatment duration	
Fixed dose administration schedule (days), mean (SD)	10 (3)[c]
Variable dose administration schedule (days), mean (SD)	9 (4)[d]
Not reported	14 (27)

IQR interquartile range; SD: standard deviation.
[a]Minimum: 30, maximum: 5000;
[b]Studies could enrol >1 patient population;
[c]Among all trial registers describing at least 1 arm with a fixed dosing administration schedule of hydroxychloroquine or chloroquine (17 trials with 1 or multiple arms; 15 valid data);], minimum: 7, maximum: 14;
[d]Among all trial registers describing at least 1 arm with a variable dosing administration schedule of hydroxychloroquine or chloroquine (20 trials with 1 or multiple arms; 22 valid data), minimum: 5, maximum: 16.

(6%) also planned to include adolescents. A total of 27 registered RCTs (53%) were not yet actively recruiting patients. The trials were mainly planned to evaluate the treatments in patients hospitalized with COVID-19 (28; 55%) among a variety of severity scenarios.

The proposed dosing schedule and treatment duration varied among the trials (Table 2). Seventeen trials reported at least 1 arm with a fixed dosing administration schedule of HQ or chloroquine ranging from a daily amount of 200 to 1200 mg. One trial planned to administer 1 single dose of HQ (200 mg) combined with other drugs. Considering the dosing schedule of all treatment arms of either HQ or chloroquine, maximum treatment duration ranged from 7 to 14 days. Twenty trials reported at least 1 arm with a variable dosing administration schedule of HQ or chloroquine. Considering all treatment arms

with a variable dosing schedule, treatment duration varied from 5 to 16 days. Fourteen registered trials did not report information on the treatment duration. One trial (2%) reported plans to monitor adherence and 2 trials (4%) reported funding support from sources with potential commercial interest (data not shown).

Forty-five of the RCTs (90%) were planned to be conducted in a single country (Table S1) with a median sample size of 262 (IQR: 100, 520). Among the trials planned to be implemented in a single country, China was the main location (16; 32%) followed by the USA (5; 10%). Five (10%) of the registered RCTs were designed to be conducted in multiple countries; 1 trial did not provide information on the location where the RCT was planned to be implemented. Overall, the proposed clinical trials anticipate recruiting a total of 37 303 participants, among outpatients and inpatients, to be randomized to receive a variety of experimental and comparison treatments with HQ, chloroquine or other agents in diverse combinations and dose schedules (Table S2). Only 14 (27%) of the registered trials reported the number of patients being recruited to the treatment and comparison arms; among these trials, a total of 1138 patients would receive HQ or chloroquine alone or in combination with other drugs (data not shown).

Table 3 summarizes the type of outcomes described in the registry of the RCTs and the related assessment timeframe. One-third of the clinical trials included in their registry information a surrogate outcome to be measured as a primary endpoint; the remaining trials (34; 67%) described plans to assess 1 clinical outcome as a primary endpoint. The timeframe of outcome assessment varied substantially among the designs of the RCTs. Trials planning to measure only clinical efficacy/effectiveness outcomes described timeframes of assessment ranging from 5 to 120 days (median 15; IQR: 15, 28). Trials planning to measure only surrogate outcomes defined timeframes of assessment ranging from 3 to 56 days (median 15; IQR: 15, 28). The RCTs planning to evaluate a clinical outcome were compared with trials planning to assess a surrogate outcome; however, no statistical difference in timeframes for outcome assessment was identified (MD 6.3; 95% CI: −10.51 to 23.12; P = .45). Among all 51 registered RCTs describing at least 1 clinical or surrogate efficacy/effectiveness outcome, 13 (26%) did not report a timeframe for outcome assessment.

The WHO scale for clinical improvement was described in the outcome assessment plans of 6 (15%) RCTs, and 16 (41%) trials mentioned clinical improvement among the primary outcomes without using the WHO scale or without detailing how it was planned to be measured. Overall, 18 different clinical outcomes were described among trials with at least 1 clinical efficacy/effectiveness outcome defined in the trial registration (Table S3). Clinical improvement and mortality accounted for 45% of the unique clinical outcome domains proposed to assess the efficacy/effectiveness of HQ or chloroquine treatment in patients diagnosed with COVID-19. Twenty-one different surrogate outcomes were identified in the registered RCTs planning to measure at least 1 surrogate outcome, with viral load and virological clearance accounting for 36% of the surrogate outcomes.

Twenty-four (47%) of the registered RCTs did not describe plans to assess a single safety outcome. Among the trials including a description of at least 1 safety outcome (n = 28), most (25; 89%)

TABLE 2 Dosing administration schedules described in randomized controlled trials (RCTs) planning to assess the effects of hydroxychloroquine (HQ) or chloroquine in the treatment of COVID-19

RCTs reporting fixed dosing schedules (n = 19)

Trial ID	Intervention and comparison groups	Fixed dose schedule	Total amount/daily	Treatment duration
ChiCTR2000030054	1. HQ; 2. Chloroquine; 3. Standard care	HQ: 200 mg 2×/d	400 mg	14 d
ChiCTR2000029992	1. HQ; 2. Chloroquine; 3. Standard care	HQ: 200 mg 2×/d	400 mg	14 d
ChiCTR2000029740	1. HQ; 2. Standard care	HQ: 200 mg 2×/d	400 mg	14 d
EUCTR2020-001270-29-GB	1. HQ; 2. Standard care	HQ: 200 mg (frequency NR)	200 mg	NR
EUCTR2020-001010-38-NO & NCT04316377	1. HQ; 2. Standard care	HQ: 200 mg (frequency NR)	200 mg	NR
EUCTR2020-000936-23-FR	1. HQ; 2. Lopinavir/ritonavir; 3. Remdesivir	HQ: 200 mg (frequency NR)	200 mg	NR
ISRCTN86534580	1. HQ; 2. Standard care	HQ: 200 mg 2×/d	400 mg	7 d
NCT04307693	1. HQ; 2. Lopinavir/ritonavir	HQ: 400 mg 2×/d	800 mg	7–10 d
NCT04315896	1. HQ; 2. Placebo	HQ: 200 mg 2×/d	400 mg	10 d
NCT04322123	1. HQ; 2. HQ + azythromycin	HQ: 400 mg 2×/d	800 mg	7 d
NCT04261517	1. HQ; 2. Standard care	HQ: 400 mg 2×/d	800 mg	7 d
NCT04321278	1. HQ; 2. HQ + azythromycin	HQ: 400 mg 2×/d	800 mg	10 d
NCT04324463	1. Chloroquine + azithromycin; 2. Standard care	Chloroquine: 500 mg 2×/d	1000 mg	7 d
NCT04330586	1. HQ + ciclesonide; 2. Ciclesonide	HQ: 400 mg 1×/d	400 mg	10 d
NCT04331470	1. HQ + Lopinavir/ritonavir; 2. Levamisole + budesonide/Formoterol	HQ: 200 mg single dose	200 mg	Single dose
NCT04329923	1. HQ for 14 d; 2. HQ for 7 d	1. 600 mg 2×/d; 2. 600 mg 1×/d	1. 1200 mg; 2. 600 mg	1. 14 d; 2. 7 d
NCT04333628	1. Chloroquine dose A; 2. Chloroquine dose B; 3. Standard care	1. Chloroquine: 125 mg 1×/d 2. Chloroquine 500 mg 2×/d	1. 125 mg 2. 1000 mg	7 d
NCT04332835	1. HQ + azithromycin; 2. Convalescent plasma + HQ + azithromycin	400 mg 2×/d	800 mg	10 d

RCTs reporting variable dosing schedules (n = 20)

Trial ID	Intervention and comparison groups	Loading dose	Maintenance dose	Treatment duration
ChiCTR2000030054	1. Hydroxychloroquine (HQ); 2. Chloroquine; 3. Standard care	Chloroquine: 100 mg for 2 d (frequency NR)	500 mg for 12 d (frequency NR)	14 d
ChiCTR2000029992	1. HQ; 2. Chloroquine; 3. Standard care	Chloroquine: 100 mg for 2 d (frequency NR)	500 mg for 12 d (frequency NR)	14 d
ChiCTR2000029899	1. HQ; 2. Chloroquine	HQ: 1200 mg on d 1 (600 mg loading dose + 600 mg after 6 hours); chloroquine: 1000 mg for 3 d (500 mg 2×/d for 3 d)	HQ: 200 mg 2×/d for 5 d; chloroquine: 250 mg 2×/d for 2 d	HQ: 6 d; chloroquine: 5 d
ChiCTR2000029898	1. HQ; 2. Chloroquine	HQ: 1200 mg on d 1 (600 mg loading dose + 600 mg after 6 hours);	HQ: 200 mg 2×/d for 5 d; chloroquine: 250 mg 2×/d for 2 d	HQ: 6 d; chloroquine: 5 d

TABLE 2 (Continued)

RCTs reporting variable dosing schedules (*n* = 20)

Trial ID	Intervention and comparison groups	Loading dose	Maintenance dose	Treatment duration
		chloroquine: 1000 mg for 3 d (500 mg 2×/d for 3 d)		
ACTRN12620000445976	1. HQ; 2. Lopinavir/ritonavir 3. Lopinavir/ritonavir + HQ; 4. Standard care.	HQ: 1600 mg on d 1 (800 mg orally 2×/d)	400 mg 2×/d for 6 d	7 d
IRCT20100228003449N29	1. HQ + Lopinavir/ritonavir; 2. Sofosbuvir/ledipasvir + HQ + Lopinavir/ritonavir	HQ: 800 mg on d 1 (400 mg orally 2×/d)	200 mg 2×/d for at least 5 d	5 d
ISRCTN50189673	1. HQ; 2. Lopinavir/ritonavir; 3. Dexamethasone; 4. Azithromycin	HQ: 2000 mg on d 1 (800 mg orally loading dose, 800 mg after 6 hours, 400 mg after 12 hours of the loading dose)	400 mg 2×/d for 9 d	10 d
NCT04315948	1. HQ; 2. Remdesivir; 3. Lopinavir/ ritonavir; 4. Lopinavir/ritonavir + interferon β-1a; 5. Standard of care	HQ: 800 mg on d 1 (400 mg 2×/d)	400 mg 1×/d for 9 d	10 d
NCT04321616	1. HQ; 2. Remdesivir; 3. Standard of care	HQ: 1600 mg on d 1 (800 mg 2×/d)	400 mg 2×/d for 10 d	11 d
NCT04323631	1. HQ; 2. Standard care	HQ: 800 mg on d 1 (400 mg 2×/d)	200 mg 2×/d for 9 d	10 d
NCT04329611	1. HQ; 2. Placebo	HQ: 800 mg on d 1 (400 mg 2×/d)	200 mg 2×/d for 4 d	5 d
NCT04325893	1. HQ; 2. Placebo	HQ: 800 mg on d 1 (400 mg 2×/d)	200 mg 2×/d for 8 d	9 d
NCT04324463	1. Chloroquine + azithromycin; 2. Standard care	Chloroquine: 500 mg 2×/d for 2 d	500 mg 1×/d for 5 d	7 d
NCT04329832	1. HQ; 2. Azithromycin	HQ: 800 mg on d 1 (400 mg 2×/d) 200 mg orally 2×/d for 4 d	200 mg 2×/d for 4 d	5 d
NCT04328012	1. HQ; 2. Lopinavir/ritonavir; 3. Losartan; 4. Placebo	HQ: 800 mg on d 1 (400 mg 2×/d)	200 mg 2×/d for 5 d and up to 14 d if supply available	5–14 d
NCT04328272	1. HQ; 2. Azithromycin; 3. Placebo	HQ: 1200 mg on d 1 (600 mg loading dose + 600 mg after 6 hours)	400 mg 2×/d for 6 d	7 d
NCT04332094	1. HQ + azithromycin; 2. Tocilizumab + HQ + azithromycin	HQ: 800 mg on d 1 (400 mg 2×/d)	200 mg 2×/d for 6 d	7 d
NCT04328493	1. Chloroquine; 2. Standard care	Chloroquine: 1200 mg on d 1 (schedule NR)	300 mg 1×/d for 9 d	10 d
NCT04332991	1. HQ; 2. Placebo	HQ: 800 mg on d 1 (400 mg 2×/d)	200 mg 2×/d for 4 d	5 d
NCT04333914	1. Chloroquine; 2. Nivolumab; 3. Tocilizumab; 4. Standard care	Chloroquine: 200 mg 2×/d for 2 d	200 2×/d for 14 d	16 d

HQ: hydroxychloroquine; NR: not reported.

TABLE 3 Efficacy and safety outcomes described in randomized controlled trials planning to assess the effects of hydroxychloroquine or chloroquine in the treatment of COVID-19 (n = 51)

	n (%)
Efficacy/effectiveness outcomes	
Clinical outcome	34 (67)
Surrogate outcome	12 (24)
Clinical and surrogate outcome	5 (10)
Clinical outcomes (n = 39) [a]	
WHO ordinal scale for clinical improvement	6 (15)
Mortality/survival	8 (21)
Clinical improvement	16 (41)
Safety outcomes	
None	24 (47)
Mode of data collection (n = 28)	
Systematic assessment	1 (4)
Unclear	2 (7)
Not reported	25 (89)
Timeframe of outcome assessment (days)	
Clinical outcome (n = 34), median (IQR) [b]	15 (15, 28)
Surrogate outcome (n = 12), median (IQR) [c]	14 (14, 23)
Safety outcome (n = 28), median (IQR) [d]	28 (14, 30)

[a]One trial could describe more than 1 primary outcome;
[b]data not reported for 8 trials;
[c]data not reported for 4 trials;
[d]data not reported for 14.
IQR, interquartile range

did not report the method to be implemented for the detection of adverse events. The timeframe for the assessment of safety outcomes was not defined in 13 (46%) of the trials reporting plans to measure at least 1 safety outcome. The timeframe for the assessment of the safety outcomes ranged from 7 to 120 days (median 28; IQR: 14, 30). The timeframe of safety outcome assessment was planned to be longer in comparison with the assessment of clinical outcomes (MD −9.8; 95% CI: −26.08 to 6.56; P = .23). The generic terminologies total, severe and serious adverse events accounted for 41% of the unique domains reported in at least 2 registered trial (Table S4). Twenty-five different domains were reported by only 1 clinical trial in which the assessment of at least 1 safety outcome was described.

4 | DISCUSSION

Clinical trials are study designs central to the regulatory and commercialization process of therapeutic interventions such as pharmaceutical agents and devices. Regulatory decisions informed by clinical trials data often represents a certificate of clinical efficacy/effectiveness and safety to new medicines or new indications of existing medicines.[23] Given the potential severity of the COVID-19 infection, the need to find a mitigating or curative treatment is beyond urgent.

Several candidate compounds addressing different disease processes (e.g. antibiotics, antivirals, immune suppressants, anticoagulants, oxygen delivery) have been proposed and are now undergoing clinical trials. Both HQ and chloroquine have been popular potential therapies described in the scientific literature and social media, and evidence for their efficacy/effectiveness and safety are desperately needed. Nevertheless, a recent evaluation of the 3 published HQ trials found important methodological weaknesses and suboptimal reporting of key information.[24]

In this study, we found that early RCTs proposed to evaluate the clinical efficacy/effectiveness and safety of HQ or chloroquine in the treatment of patients diagnosed with COVID-19 are designed to collect data that vary substantially in terms of the outcome domain used to determine the evidence base upon which these drugs will be judged. Moreover, data on safety outcomes are overlooked or only superficially included among the outcomes planned to be measured in these trials. Finally, essential information related to dosing schedules, treatment duration and timeframe of outcome assessment were frequently missing in the description of the RCTs. Overall, this analysis yielded 3 major areas of concern.

4.1 | Selection of efficacy/effectiveness outcomes

The outcomes measured in clinical trials are critical in providing meaningful data and in allowing comparison among the results of other RCTs and different interventions.[25] Although most of the evaluated RCTs specified at least 1 clinical outcome as a primary endpoint, the outcome domains varied widely. For example, while half of the registered trials described plans to assess all-cause mortality/mortality and clinical status/recovery to evaluate the efficacy/effectiveness of the drugs, the remaining trials defined over 15 different outcome domains. Ideally, the results of RCTs are subsequently combined in systematic reviews and meta-analysis, which are vital to inform all healthcare providers and health decision-makers. This may be particularly true during the COVID-19 pandemic, as many of the existing trials are small, and a definitive, mega-trial trial may not emerge from the list identified. In the presence of highly heterogeneous outcomes, the development of systematic reviews and meta-analysis is likely to be less informative if not precluded.

During the early stages of the COVID-19 pandemic, core outcomes of relevance to be measured in studies including adult hospitalized patients diagnosed with COVID-19 were proposed by different groups (http://www.comet-initiative.org/Studies/Details/1538). The core outcomes comprised mortality and respiratory support, outcome domains included in some, but not all the RCTs planned to evaluate the effect of HQ or chloroquine in patients diagnosed with COVID-19. On 18 February 2020, the WHO published a protocol for COVID-19 therapeutic trials recognizing that consistency among outcome measures and time points is vital for interpretation and combination of results across trials.[22] This document informed a consensus exercise that culminated in the development of a minimal common outcome measure set for COVID-19 clinical research, published on 12 June 2020.[26] Several RCTs registered up to April 2020 did not plan to assess the domains

proposed in the WHO protocol from February. Similarly, a *posthoc* comparison of the outcomes included in the RCT registries against the minimal common outcome measure set for COVID-19 clinical research proposed by the WHO[26] shows that none of the trials described measuring all the 3 proposed core outcome measure set: viral burden, survival and clinical progression. More concerning is that several of the clinical trials registered in the WHO-ICTRP database included only surrogate outcomes to estimate the efficacy/effectiveness of the drugs. There are several examples where positive results in trials measuring surrogate outcomes were not replicated in efficacy/effectiveness trials where clinical outcomes were measured.[14,27]

To increase research usefulness and relevance to patients and the health system, any investigation on drugs that might potentially treat patients diagnosed with COVID-19 needs to include a minimal standardized set of clinical outcomes of efficacy/effectiveness. This set of outcomes will be continually informed by the evolving research on the clinical characteristics of this new disease. Trialists should move quickly to adapt any planned and ongoing RCT to the clinical research progress on COVID-19, particularly ensuring that the minimal outcome measure set viral burden, survival, and clinical progression is determined. Ultimately, the strain on the health system's capacity will only abate when we identify treatments that improve clinical outcomes for patients, such as reducing intubation rates and subsequent deterioration. The development of a safe, effective and widely available vaccine will be the long-term solution to the COVID-19 pandemic.

4.2 | Inadequate assessment of treatment harms and patient safety

Chloroquine, and its derivate HQ, have been approved by the Food and Drug Administration since 1955.[17] These are antimalarial drugs and are also important in the treatment of immune-mediated diseases such as lupus erythematosus and rheumatoid arthritis.[28] Both drugs can induce irreversible retinal damage, cardiomyopathy and QTc prolongation, severe hypoglycaemia and dermatologic adverse events.[17] The severity of these adverse effects range from mild to severe; occasionally, these agents have been found to cause death.

Since we can anticipate a set of adverse events that is highly relevant to patients and clinical practice, the proposal of RCTs should contain plans to systematically assess fully defined adverse events according to appropriate timeframes.[12,16,29] For instance, QTc prolongation and drug-induced arrhythmias such as torsades de pointes, are of concern in critically ill patients with COVID-19[30] and should be carefully ascertained. Monitoring QTc through electrocardiographic tracings regularly would represent a systematic approach to the problem, even if monitoring is required to be performed remotely for safety reasons. The systematic assessment of adverse events can improve the accuracy of estimates within trials[31] while also minimizing bias.[32] Finally, the assessment of defined anticipated adverse events, together with their seriousness, severity and duration, would be more informative than the mere documentation of generic events.

In this study, we showed that retinopathy, cardiac and dermatological adverse events, and hypoglycaemia were planned to be assessed in a single clinical trial among the 51 trials that had been registered to evaluate the treatment with HQ or chloroquine for patients diagnosed with COVID-19. Outcomes of safety were not included among the outcomes defined in several of the proposed trials (24, 47%), while the remaining RCTs reported a nonspecific approach for observing safety outcomes. Based on these results, and the fact the many adverse effects are rare in small clinical trials, we are concerned that the evidence on the harms of these investigational drugs to patients diagnosed with COVID-19 may be likely to be incomplete and biased.

4.3 | Missing information

The comprehensive and prospective registration of clinical trials has been internationally supported since 2004 as a way to reduce the selective publication of studies and the selective reporting of outcomes.[33] Since the early years of clinical trial registration, ensuring that the registered data are complete and accurate has been a challenging objective of multiple enforcement mechanisms, including legal requirements.[29,33] Remarkably, approximately 1/3 of the registered RCTs included in this study had at least 1 piece of missing information, either related to treatment dose, duration, timeframes of outcome assessment or the lack of definition of a safety outcome. This is of particular concern amid the current pandemic scenario where the rush to test any potential helpful drug may pose a risk that low-quality evidence may be used to support clinical decisions with unpredictable impacts on patients and the health system.

4.4 | Limitations

We reviewed the information provided by all clinical trials focused on HQ and chloroquine for patients diagnosed with COVID-19 available in the WHO-ICTRP database up to 8 April 2020, at 10:30 GMT −6. We chose the WHO-ICTRP because it compiles data from ClinicalTrials.gov and 10 primary registries (https://www.who.int/ictrp/en/). In the scenario of the COVID-19 pandemic, we judged that this approach would provide an improved overview of clinical trials being planned in different countries. Nevertheless, as we did not search the primary registries directly, it is possible that some potentially eligible registered RCTs could have been missed. Also, the data analysed in this study are limited to the information provided in the record of the clinical trials' registry. A minority of the clinical trials provided access to the full study protocol; therefore, the data collected and analysed in this study may be incomplete if authors have deliberately left information missing on the publicly available record of the planned trials. Nevertheless, if the trial registries are incomplete for low-quality designs or deliberate actions, this represents a risk to the strength of the evidence that will ultimately be available to inform decisions.

Similar to any analysis of secondary data, the findings reported may be impacted by the heterogeneity of the primary information extracted from the trial registry. For instance, the patient population and case severity varied among the RCTs from mild cases treated in the community (outpatients) to severe cases requiring hospitalization. Nevertheless, since this analysis was focused on whether the planned outcomes represented clinical or surrogate results, variability in the patient population and the severity of the disease probably have no impact our findings and conclusions.

Finally, as the development of research on COVID-19 is evolving rapidly, additional RCTs exist that were planned but registered after the study timeline; these trials were not included in the present analysis. Our analysis focused on the clinical research proposed during the early phase of the COVID-19 pandemic. Since this work was completed, approximately 300 additional trials have been registered. It will be important to analyse the progress of the research on potential treatments for COVID-19, and such work needs to be developed in line with the rapidly evolving scenario that characterizes this pandemic. For instance, the largest RCTs evaluating the value of HQ and chloroquine to treat patients with COVID-19 have now halted these treatment arms (e.g. the WHO Solidarity, RECOVERY and ORCHID trials), which will certainly impact the trials that continue to study these drugs in a variety of treatment combinations.

5 | CONCLUSION

Early in the COVID-19 pandemic, an impressive number of RCTs were planned to evaluate the clinical efficacy/effectiveness and safety of HQ or chloroquine in the treatment of patients diagnosed with COVID-19. Outcome domains described in these clinical trials were highly heterogeneous and included both clinical and/or surrogate measures. Moreover, despite HQ and chloroquine being known to induce cardiovascular and other adverse events that can be irreversible and potentially life-threatening, the registered RCTs did not describe systematic assessment methods to accurately detect adverse events. The pandemic scenario is demanding researchers to register, plan and deploy RCTs at an incredibly rapid pace. The present analysis supports the need for improvements in the design of ongoing and future RCTs. Ultimately, finding safe and effective treatments is required to decrease the burden on patients, providers and health care systems worldwide created by patients diagnosed with COVID-19.

COMPETING INTERESTS

There are no competing interests to declare.

CONTRIBUTORS

Dr Junqueira led the research conceptualization, data curation, formal analysis, investigation, methodology, project administration and visualization. She wrote the original draft and worked with Dr Rowe on reviewing and editing the final manuscript. Dr Rowe led the funding acquisition and worked with Dr Junqueira on the research conceptualization, analysis, and reviewing and editing the final manuscript.

TRANSPARENCY

Dr Junqueira and Dr Rowe (the manuscript's guarantors) affirm that the manuscript is an honest, accurate and transparent account of the study being reported.

DATA SHARING

The data used for analysis are in the public domain. Nevertheless, the full dataset analysed can be requested from the authors.

NOMENCLATURE OF TARGETS AND LIGANDS

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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