




BMJ Open Hydroxychloroquine plus personal protective equipment versus personal protective equipment alone for the prevention of laboratory-confirmed COVID-19 infections among healthcare workers: a multicentre, parallel-group randomised controlled trial from India

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To cite: Tirupakuzhi Vijayaraghavan BK, Jha V, Rajbhandari D, *et al*. Hydroxychloroquine plus personal protective equipment versus personal protective equipment alone for the prevention of laboratory-confirmed COVID-19 infections among healthcare workers: a multicentre, parallel-group randomised controlled trial from India. *BMJ Open* 2022;12:e059540. doi:10.1136/bmjopen-2021-059540

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (<http://dx.doi.org/10.1136/bmjopen-2021-059540>).

Received 24 November 2021
Accepted 13 May 2022



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ABSTRACT

Objectives To determine whether hydroxychloroquine when used with personal protective equipment reduces the proportion of laboratory-confirmed COVID-19 among healthcare workers in comparison to the use of personal protective equipment alone.

Design Multicentre, parallel-group, open-label randomised trial. Enrolment started on 29 June 2020 and stopped on 4 February 2021. Participants randomised in Hydroxychloroquine Prophylaxis Evaluation were followed for 6 months.

Setting 9 hospitals across India.

Participants Healthcare workers in an environment with exposure to COVID-19 were randomised in a 1:1 ratio to hydroxychloroquine plus use of personal protective equipment or personal protective equipment alone. 886 participants were screened and 416 randomised (213 hydroxychloroquine arm and 203 personal protective equipment).

Intervention Participants in intervention arm received 800 mg of hydroxychloroquine on day of randomisation and then 400 mg once a week for 12 weeks in addition to the use of personal protective equipment. In the control arm, participants continued to use personal protective equipment alone.

Main outcome Proportion of laboratory-confirmed COVID-19 in the 6 months after randomisation.

Results Participants were young (mean age 32.1 years, SD 9.1 years) with low-comorbid burden. 47.4% were female. In the 6 months after randomisation (primary analysis population=413), 11 participants assigned to the hydroxychloroquine group and 12 participants assigned to the standard practice group met the primary

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ Our trial is the largest multicentre trial evaluating hydroxychloroquine prophylaxis for COVID-19 from a low and middle-income country setting.
- ⇒ The trial tested the dose of hydroxychloroquine recommended by the Indian regulatory agencies and had the longest follow-up duration among hydroxychloroquine trials.
- ⇒ Our trial included a diverse set of participants, both in terms of balance of men and women, but also in terms of the various healthcare worker roles.
- ⇒ The trial stopped early for futility, hence limiting any conclusions.
- ⇒ Our trial did not include a placebo arm or employ blinding.

endpoint (5.2% vs 5.9%; OR 0.85, 95% CI 0.35 to 2.07, $p=0.72$). There was no heterogeneity of treatment effect in any prespecified subgroup. There were no significant differences in the secondary outcomes. The adverse event rates were 9.9% and 6.9% in the hydroxychloroquine and standard practice arms, respectively. There were no serious adverse events in either group.

Conclusions and relevance Hydroxychloroquine along with personal protective equipment was not superior to personal protective equipment alone on the proportion of laboratory-confirmed COVID-19. Definitive conclusions are precluded as the trial stopped early for futility, and hence was underpowered.

Trial registration number CTRI/2020/05/025067.

INTRODUCTION

¹There have been over 524,000,000 cases of COVID-19 with over 6.2 million deaths until 25th May 2022. In India, there have been over 500,000 deaths.^{1 2} At the onset of the pandemic, neither vaccines nor drugs providing post-exposure prophylaxis were available. Given their role, healthcare workers (HCWs), particularly those on the front lines, were identified as the group at the highest risk of acquiring the infection. In the severe acute respiratory syndrome and Middle East respiratory syndrome coronavirus outbreaks, HCWs accounted for 21.1% and 19.1% of cases, respectively.^{3 4} In data from China and Italy in the early stages of the COVID-19 pandemic, 3.8% and 9% of confirmed cases were among HCWs.^{5 6} In subsequent reports, this proportion has ranged from 7% to 15%.⁷

Early reports indicated that hydroxychloroquine (HCQ) may provide effective prophylaxis against SARS-CoV-2 infection based on its ability to reduce binding of the virus to the ACE2 receptor, prevent cellular entry of the virus and inhibit viral replication.^{8 9} This, in combination with the observation that HCQ possessed favourable pharmacokinetic characteristics and its proven track record of safety for non-COVID indications, provided sufficient justification for conducting trials evaluating HCQ for pre-exposure prophylaxis.^{10–12} However, the published trials are underpowered, or have suffered from methodological limitations or were evaluating HCQ in a different population. Importantly, none of these trials were from a lower middle-income context, where the challenges are inherently different. HCWs, particularly in India, were at a higher risk because of the limited availability of personal protective equipment (PPE), the slow

roll-out of vaccination programmes and the enormous case burden.

Early in the pandemic, the Indian Council of Medical Research (ICMR) recommended HCQ as prophylaxis for HCWs and simultaneously made a plea that 'proof of concept and pharmacokinetics studies be taken up expeditiously'.¹³ In parallel, there were also reports of adverse events¹⁴ including death following the use of HCQ as prophylaxis/treatment. There was thus an ethical and a public health imperative to rapidly evaluate its effectiveness and safety.

The HydrOxychloroquine Prophylaxis Evaluation (HOPE) trial was designed to evaluate the combination of HCQ along with PPE over the use of PPE in preventing COVID-19 infection among HCWs at risk.

METHODS

Study design and oversight

HOPE was an investigator-initiated, stratified, parallel-group, open-label, multicentre randomised controlled trial. From 29 June 2020 to 4 February 2021, we enrolled HCWs from nine hospitals across India. These centres were selected on the basis of them being designated COVID-19 centres by the Government of India or by virtue of being involved in the care of patients with confirmed COVID-19. Written informed consent was obtained from all participants.

The trial was designed and overseen by a steering committee. An independent data and safety monitoring committee monitored the trial and reviewed data at the first interim analysis for safety (321 participants followed

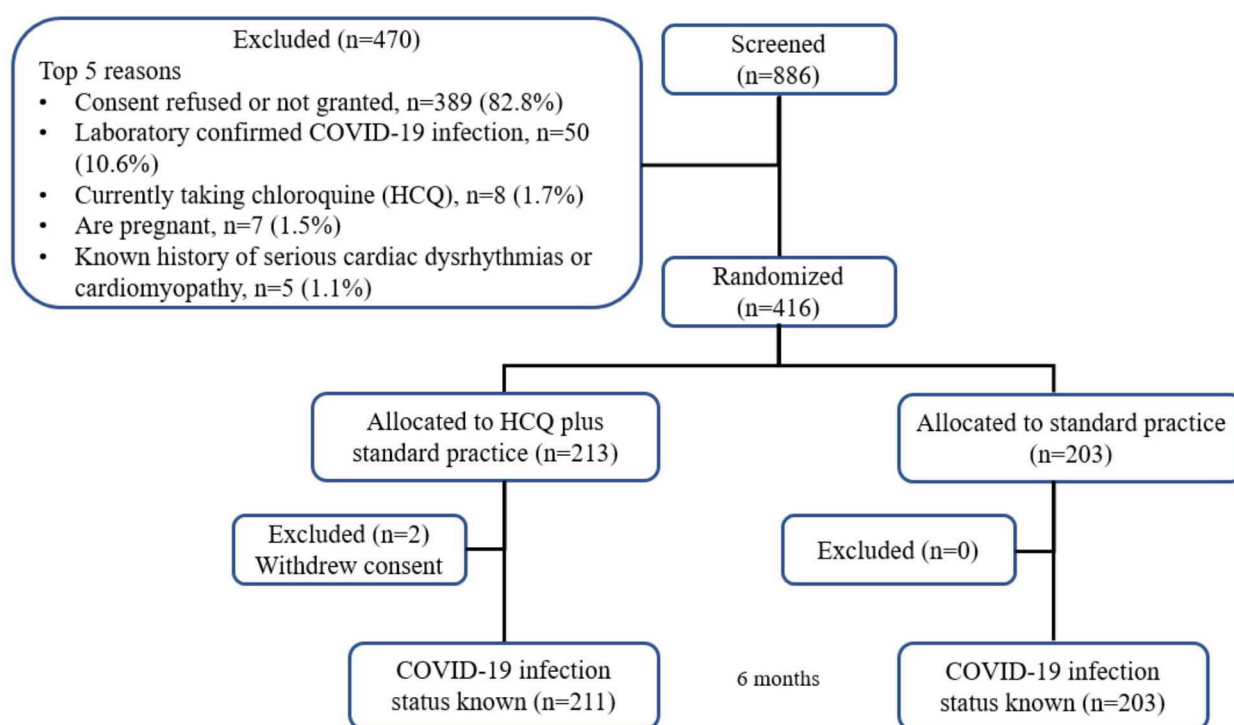


Figure 1 Consolidated Standards of Reporting Trials (CONSORT) flow diagram.

Table 1 Baseline characteristics

| Characteristics | Standard practice (PPE) (n=203) | HCQ +standard practice (PPE) (n=213) | Total (n=416) |
|---|---------------------------------|--------------------------------------|----------------------|
| Age (years) | | | |
| Mean (SD) | 31.8 (8.63) | 32.3 (9.65) | 32.1 (9.16) |
| Median (Q1; Q3) | 29.0 (25.0; 36.0) | 30.0 (25.0; 38.0) | 30.0 (25.0; 37.0) |
| Sex (%) | | | |
| Male | 106 (52.2) | 113 (53.1) | 219 (52.6) |
| Female | 97 (47.8) | 100 (46.9) | 197 (47.4) |
| Role (%) | | | |
| Nurse | 68 (33.5) | 67 (31.5) | 135 (32.5) |
| Doctor | 31 (15.3) | 34 (16.0) | 65 (15.6) |
| Allied health worker | 44 (21.7) | 46 (21.6) | 90 (21.6) |
| Ancillary worker | 60 (29.6) | 66 (31.0) | 126 (30.3) |
| Visiting doctor | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Usual place of work (%) | | | |
| ICU | 53 (26.1) | 53 (24.9) | 106 (25.5) |
| Emergency department | 18 (8.9) | 26 (12.2) | 44 (10.6) |
| Ward | 130 (64.0) | 130 (61.0) | 260 (62.5) |
| Outpatient | 2 (1.0) | 4 (1.9) | 6 (1.4) |
| Weight (kg) | | | |
| Mean (SD) | 61.7 (13.15) | 62.3 (14.02) | 62.0 (13.59) |
| Median (Q1; Q3) | 60.0 (52.0; 70.0) | 61.0 (52.0; 70.0) | 61.0 (52.0; 70.0) |
| Height (cm) | | | |
| Mean (SD) | 161.7 (12.15) | 161.7 (9.90) | 161.7 (11.04) |
| Median (Q1; Q3) | 162.0 (155.0; 169.0) | 161.0 (155.0; 169.0) | 161.0 (155.0; 169.0) |
| Smoker (%) | | | |
| No | 194 (95.6) | 205 (96.2) | 399 (95.9) |
| Yes | 9 (4.4) | 8 (3.8) | 17 (4.1) |
| Diabetes (%) | | | |
| No | 200 (98.5) | 206 (96.7) | 406 (97.6) |
| Yes | 3 (1.5) | 7 (3.3) | 10 (2.4) |
| High blood pressure or taking blood pressure medication (%) | | | |
| No | 200 (98.5) | 211 (99.1) | 411 (98.8) |
| Yes | 3 (1.5) | 2 (0.9) | 5 (1.2) |
| Chronic heart disease (%) | | | |
| No | 203 (100) | 213 (100) | 416 (100) |
| Yes | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Chronic lung disease (%) | | | |
| No | 203 (100) | 213 (100) | 416 (100) |
| Yes | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Chronic kidney disease (%) | | | |
| No | 203 (100) | 211 (99.1) | 414 (99.5) |
| Yes | 0 (0.0) | 2 (0.9) | 2 (0.5) |
| Chronic liver disease (%) | | | |
| No | 203 (100) | 213 (100) | 416 (100) |
| Yes | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| BCG (TB, tuberculosis) vaccination during childhood (%) | | | |
| No | 25 (12.3) | 35 (16.4) | 60 (14.4) |

Continued

Table 1 Continued

| Characteristics | Standard practice (PPE) (n=203) | HCQ +standard practice (PPE) (n=213) | Total (n=416) |
|--|---------------------------------|--------------------------------------|---------------|
| Yes | 152 (74.9) | 151 (70.9) | 303 (72.8) |
| Unknown | 26 (12.8) | 27 (12.7) | 53 (12.7) |
| Use of any PPE during last contact with patient with suspected or confirmed COVID-19 (%) | | | |
| No | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Yes | 203 (100) | 213 (100) | 416 (100) |

HCQ, hydroxychloroquine; ICU, intensive care unit; PPE, personal protective equipment.

up for 4 weeks). The trial was stopped on 4 February 2021 after the first interim analysis because of slow enrolment due to the commencement of the vaccination programme and a high likelihood of futility (online supplemental appendix page 7); by this time, 416 participants had been randomised and the enrolled participants were followed up for the full 6-month duration. The trial was conducted in accordance with ethical principles consistent with the Declaration of Helsinki,¹⁵ the ICH Good Clinical Practice guidelines¹⁶ and all other relevant national and regional guidelines. The trial was sponsored by The George Institute for Global Health.

The trial protocol (online supplemental appendix)¹⁷ and statistical analysis plan (online supplemental appendix)¹⁸ were published a priori. All the authors vouch for the adherence to the protocol, for the accuracy and completeness of data and for the reporting of serious adverse events.

Participants

All HCWs (medical, nursing, allied health and ancillary workers) working in an environment with direct exposure to patients with confirmed COVID-19 infection and providing written informed consent were eligible for enrolment. Direct exposure to COVID-19 was defined as participants working in the areas designated for care of patients with COVID-19 in the hospitals (emergency room, wards, intensive care units (ICU)). We excluded those that did not provide consent, had a history of laboratory-confirmed COVID-19 infection, were already on HCQ, or pregnant or breast feeding. The full list of exclusion criteria is provided in the online supplemental appendix page 4.

Randomisation and masking

We used centralised randomisation and a computer-generated allocation sequence with permuted blocks of varying sizes. Randomisation was stratified by site and by role of HCW (nurse, doctor and other). This was an unblinded study.

Trial procedures

Participants were randomised in a 1:1 ratio to receive either HCQ plus PPE or PPE alone. In the HCQ group, in addition to use of PPE, HCWs received 400 mg of HCQ twice on the day of enrolment, followed by 400 mg once a week for a total of 12 weeks. This dose was chosen based

on the recommendation issued by ICMR. All the HCWs in this arm underwent an ECG between weeks 4 and 6 and asked to report any side effects such as chest pain, palpitations or syncope.

HCWs were advised to stop the drug if they contracted COVID-19 during the intervention period, if they developed any serious adverse reactions to HCQ or if they no longer desired to continue in the trial. The trial drug would also be stopped if the corrected QT interval in the mid-trial ECG exceeded 450 ms irrespective of symptoms. For HCWs wishing to stop the drug during the intervention period, consent was sought for collecting follow-up data.

HCWs randomised to PPE alone group were asked to continue using appropriate PPE as per their institutional recommendations. They were discouraged from taking HCQ and intake of HCQ in this group was considered a protocol violation. ECG was performed in this arm only if the participant reported symptoms such as chest pain, palpitations or syncope.

Outcomes

The primary outcome was the proportion of laboratory-confirmed (by reverse transcriptase PCR or presence of antibodies) SARS-CoV-2 infection in the 6 months after randomisation. Secondary outcomes included hospitalisation due to suspected or confirmed COVID-19 infection, need for ICU or high dependency unit (HDU) admission, all-cause mortality, need for respiratory support (including O₂ therapy, non-invasive and invasive ventilation), need for kidney replacement therapy, need for vasopressors, hospital length of stay, ICU or HDU length of stay, readmission to hospital and days absent from work due to suspected or confirmed COVID-19 infection.

Data collection

Baseline data included designation of the HCW, role in the COVID-19 ward or ICU, demographics, average shift duration and comorbidities. Weekly follow-up was performed for all participants using a questionnaire either in person or over the phone. Information collected during follow-up included exposure during the week, compliance with the protocol and adverse events, if any. For the primary outcome, participants shared a copy of the laboratory report confirming the presence of COVID-19 infection. Data on hospitalisation and related

Table 2 Primary outcome and dichotomous secondary outcomes

| Outcome | Standard practice (PPE) (n=203) | HCQ +standard practice (PPE) (n=211) | Unadjusted | | Adjusted* | | P value | Risk difference (95% CI) | P value |
|---|---------------------------------|--------------------------------------|---------------------|----------|---------------------|----------|-----------------------|--------------------------|---------|
| | | | OR (95% CI) | P value† | OR (95% CI) | P value‡ | | | |
| Laboratory-confirmed COVID-19 infection within 6 months after randomisation (primary outcome) | 12 (5.9%) | 11 (5.2%) | 0.88 (0.38 to 2.03) | 0.83 | 0.85 (0.35 to 2.07) | 0.72 | −0.7% (−7.8% to 6.4%) | 0.95 | |
| Secondary outcomes | | | | | | | | | |
| Laboratory-confirmed or suspected‡ COVID-19 infection within 6 months after randomisation | 12 (5.9%) | 12 (5.7%) | 0.96 (0.42 to 2.19) | 1.00 | 0.94 (0.39 to 2.24) | 0.89 | −0.3% (−7.5% to 6.9%) | 0.98 | |
| Hospitalised due to suspected COVID-19 | 2 (0.9%) | 1 (0.5%) | 0.48 (0.04 to 5.32) | 0.62 | NA | | NA | | |
| Admitted to ICU or HDU due to suspected COVID-19 | 0 (0.0%) | 1 (0.5%) | NA | 1.00 | NA | | NA | | |
| Death from any cause | 0 (0.0%) | 0 (0.0%) | | | NA | | NA | | |
| Need for O ₂ supplementation or ventilation: | | | | | | | | | |
| Oxygen supplementation | 1 (0.5%) | 1(0.5%) | 0.96(0.06, 15.48) | 1.00 | NA | | NA | | |
| Ventilation | 0 (0.0%) | 0 (0.0%) | NA | NA | NA | | NA | | |
| Need for vasopressors | 0 (0.0%) | 0 (0.0%) | NA | NA | NA | | NA | | |
| Need for renal replacement therapy | 0 (0.0%) | 0 (0.0%) | NA | NA | NA | | NA | | |
| Readmission to hospital | 0 (0.0%) | 0 (0.0%) | NA | NA | NA | | NA | | |
| *Adjusted for role of HCW (fixed effect) and site (random effect). | | | | | | | | | |
| †Fisher's exact test p value. | | | | | | | | | |
| ‡Defined as symptoms with more than 10 days off work. | | | | | | | | | |
| HCQ, hydroxychloroquine; HCW, healthcare worker; HDU, high dependency unit; ICU, intensive care unit; NA, not applicable; PPE, personal protective equipment. | | | | | | | | | |

*Adjusted for role of HCW (fixed effect) and site (random effect).

†Fisher's exact test p value.

‡Defined as symptoms with more than 10 days off work.

HCQ, hydroxychloroquine; HCW, healthcare worker; HDU, high dependency unit; ICU, intensive care unit; NA, not applicable; PPE, personal protective equipment.

secondary outcomes were obtained from the medical records. Both groups were followed up for a total of 25 weeks from randomisation.

Statistical analysis

We estimated that the enrolment of 6950 HCWs would give us a power of 80% to detect a 25% relative reduction in the proportion of confirmed COVID-19 infections from an estimated baseline proportion of 10% and a two-sided alpha of 5%. This sample size allowed for a potential loss to follow-up of 10% and a potential non-compliance rate of 10%.

Analysis of the primary and secondary outcomes was performed in the intention-to-treat population, which included all those that were randomised. In the event that consent was withdrawn, data were included only if the participant explicitly agreed for her/his data to be used until the point she/he revoked consent.

Discrete variables are summarised as percentages and frequencies. Continuous variables are summarised as mean and SD or median and IQR. The primary outcome is analysed without imputation of missing data. To account for the stratification by site and HCW role and maximise power, the main analysis was performed using logistic regression with treatment allocation and HCW role as fixed effects and site as a random effect. The effect of the intervention is presented as OR and corresponding 95% CIs. For ease of interpretation, risk difference and 95% CI are also presented. Given the overall small number of events, no adjustment for other covariates was performed. Crude proportions by treatment arm are also reported with an unadjusted OR, 95% CIs and a Fisher's exact test *p* value.

For the dichotomous secondary outcomes, comparison of proportions is summarised by treatment arm and compared using logistic regression (similar to the primary analysis). For the continuous outcomes, hospital and ICU length of stay are analysed as the number of days alive and free of outcome. Days alive and free of outcome were censored at 175 days after randomisation calculated between randomisation and end of week 25 and will therefore have values between 0 and 175 days. These are summarised as means and SDs (or medians and quartiles) and compared between the two arms using a Mann-Whitney U test. The number of hospitalisations, ICU admissions and days off work due to COVID-19 infection were very few, hence regressions outlined in the statistical analysis plan were not carried out.

Four prespecified subgroup analyses were included based on age (>35 or ≤35 years), sex (male vs female), role of HCW (doctor vs nurse vs other) and BCG vaccination status (yes vs no). The analysis for each subgroup, except for role of HCW, was performed by adding the subgroup variables as well as its interaction with the intervention as fixed effects to the main logistic regression model.

Adverse events deemed possibly, probably or definitely related to study treatment were summarised as the number and proportion of participants experiencing

at least one event and by category of events and overall number of events. Proportion of participants with adverse events was compared between the two treatment arms using the Fisher's exact test, both overall and by category.

Patient and public involvement

There was no direct patient or public involvement in the conception or design of this trial.

RESULTS

Between 29 June 2020 and 4 February 2021, a total of 886 eligible HCWs were screened; 416 were randomised. Two hundred and thirteen participants were randomly allocated to HCQ plus PPE and 203 to standard PPE alone. [Figure 1](#) shows the flow of participants in the trial. Information on trial sites and number of participants enrolled by site is provided in online supplemental table 1. All participants were followed up to 6 months with the last date of follow-up as 29 July 2021. Of the 416 participants, two were lost to follow-up and 414 were included for the analysis of the primary and key secondary outcomes.

The baseline characteristics of the included participants were comparable between the two groups ([table 1](#) and online supplemental table 7). Participants were young (mean age 32.1, SD 9.1) and healthy with low-comorbid burden. About 32.5% of the participants were nurses, 30.3% ancillary HCWs, 21.6% allied health workers and 15.6% doctors; 47.4% were female. Approximately 63% of the participants were enrolled from COVID-19 wards, 26% from ICU and 10% from the emergency room.

Vaccination started in India on 16 January 2021 and details of vaccination status of the participants are provided in online supplemental table 8.

Trial intervention

Compliance with the intervention was high (87.4%) with a total of 312 HCQ doses being missed out of the 2483 recorded doses. Details are provided in online supplemental tables 2 and 3.

Outcomes

Primary outcome

In the 6 months after randomisation, 11 participants assigned to the HCQ (8 confirmed by PCR and 3 by antibody test) and 12 participants assigned to the PPE only (10 confirmed by PCR and 2 by antibody test) groups met the primary end point of laboratory-confirmed COVID-19 (5.2% vs 5.9%; OR 0.85, 95% CI 0.35 to 2.07, *p*=0.72) ([table 2](#)). There was no significant heterogeneity in the effect of the intervention on the primary outcome in the four prespecified subgroups ([figure 2](#)).

Secondary outcomes

There were no significant differences between the intervention and control arms with respect to the key secondary outcomes ([table 2](#) and online supplemental table 4). Three participants needed hospitalisation (two in the control and one in the intervention arm) and one

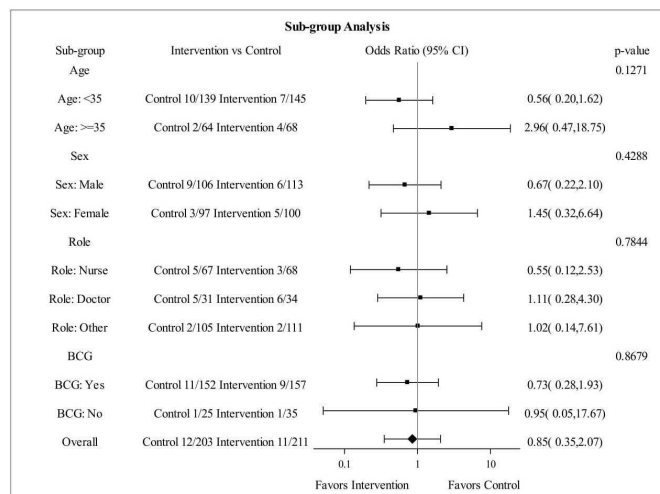


Figure 2 Forest plot for subgroup analysis of laboratory-confirmed COVID-19 infection within 6 months after randomisation. Intervention versus control: number of patients with events/total number of patients, p value is for interaction effect.

participant in either group needed supplemental oxygen therapy. There were no deaths.

Adverse events

The proportions of adverse events were 9.9% and 6.9% in the HCQ and PPE groups, respectively (risk ratio 1.43; 95% CI 0.61 to 2.23, $p=0.29$); all were minor and there were no serious adverse events (table 3 and online supplemental tables 5 and 6). ECG was performed in 172 of the

213 participants randomised to the HCQ arm and there were two participants with ECG evidence of QTc prolongation (more than 450 ms). In both these participants, the trial drug was stopped without any further adverse events.

DISCUSSION

In this trial evaluating HCQ prophylaxis among HCWs in India, the use of HCQ in addition to PPE did not result in a lower incidence of laboratory-confirmed COVID-19 as compared with PPE alone. This effect did not differ in any of the prespecified subgroups. There were also no between-group differences in any of the key secondary outcomes. There was no statistically significant difference in the proportion of adverse events between the two groups and there were no serious adverse events.

The results of our trial are consistent with previously published data from other settings. Nine published trials^{19–27} have so far evaluated the role of HCQ as a prophylactic agent. Of these, four evaluated the role of HCQ as a postexposure prophylaxis agent among contacts of patients with COVID-19,^{19–22} one evaluated the drug among migrant workers²³ and four among HCWs.^{24–27}

Rajasingham *et al*²⁴ conducted a three-arm, parallel-group trial comparing two dosing regimens of HCQ versus a placebo ($n=1483$). Neither of the dosing regimens were effective in reducing the primary outcome of COVID-19-free survival time. In contrast to HOPE, the primary outcome was a combination of laboratory-confirmed and

Table 3 Adverse events

| Characteristics | PPE only (n=203) | HCQ+PPE (n=213) | Total (n=416) | P value* | Risk ratio (95% CI) |
|--|------------------|-----------------|----------------|----------|---------------------|
| Adverse event | | | | 0.29 | |
| No | 189 (93.1%) | 192 (90.1%) | 381 (91.6%) | | |
| Yes | 14 (6.9%) | 21 (9.9%) | 35 (8.4%) | | 1.43 (0.61 to 2.23) |
| Serious adverse event | | | | | |
| No | 203/203 (100%) | 213/213 (100%) | 416/416 (100%) | | |
| Resulted in death | | | | | |
| No | 203/203 (100%) | 213/213 (100%) | 416/416 (100%) | | |
| Life threatening | | | | | |
| No | 203/203 (100%) | 213/213 (100%) | 416/416 (100%) | | |
| Requires prolonged hospitalisation | | | | | |
| No | 203/203 (100%) | 213/213 (100%) | 416/416 (100%) | | |
| Results in persistent or severe disability/incapacity | | | | | |
| No | 203/203 (100%) | 213/213 (100%) | 416/416 (100%) | | |
| Results in congenital anomaly/birth defect | | | | | |
| No | 203/203 (100%) | 213/213 (100%) | 416/416 (100%) | | |
| Is medically significant to qualify as a serious event | | | | | |
| No | 203/203 (100%) | 213/213 (100%) | 416/416 (100%) | | |
| *Fisher's exact test | | | | | |
| HCQ, hydroxychloroquine; PPE, personal protective equipment. | | | | | |

probable COVID-19 (by symptoms). Additionally, participants in the trial were enrolled through approaches on social media and not through a systematic strategy of hospital or site-level screening.

In another trial evaluating HCQ as pre-exposure prophylaxis, Abella and colleagues²⁵ randomised 132 participants. The dosing regimen in this trial was 600 mg of oral HCQ or placebo daily for a period of 8 weeks. The trial included participants with a negative PCR at baseline and retested at 4 and 8 weeks. The trial was stopped after 132 participants were enrolled (planned n=200) due to low event rates and a signal for futility.

Two other trials evaluating the role of HCQ among HCWs have been published as preprints.^{26 27} In a single-centre placebo-controlled trial from Mexico, investigators enrolled 130 participants and found no difference in the primary outcome. In another phase II trial from Pakistan, the investigators enrolled 200 participants into one of four arms—three treatment arms with different dosages of HCQ and one control arm. Participants were followed up to 12 weeks and the study found no difference in the rate of COVID-19 positivity.

To date, none of the trials have provided a definitive answer on the effectiveness of HCQ as a prophylactic agent. Based on the observed event rate at the interim analysis of HOPE, the Data Safety Monitoring Committee estimated that 10000 participants would be needed in each arm to have a 90% power to detect a 30% relative reduction in the primary outcome. Based on these numbers, the availability of vaccines and the perceived loss of clinical equipoise, the question on the effectiveness of HCQ as prophylaxis is likely to remain unanswered.

Our trial has important strengths. HOPE is the largest multicentre trial of HCQ prophylaxis from a lower middle-income country. A high proportion of eligible HCWs received the trial intervention as planned, very few enrolled participants were lost to follow-up and we incorporated a mid-trial ECG in the HCQ arm for safety. Most participating centres had limited formal research infrastructure or experience and HOPE served to create research capacity at these sites. Our trial was conducted to the highest methodological standards, was overseen by a trial steering committee and supervised by an independent data monitoring committee. We had prespecified stopping rules for harm and our trial protocol and statistical analysis plan were published a priori. We had high compliance with the treatment protocol, 99.3% follow-up for the primary outcome and the longest follow-up period among HCQ prophylaxis trials. Our trial had nearly equal proportions of men and women and was diverse in its inclusion of different HCW roles, thereby enhancing generalisability.

Our trial had limitations. Given the slow enrolment, the declining enthusiasm for HCQ and the roll-out of vaccination, we were unable to complete the trial to the planned sample size and hence were underpowered at the time of stopping. We did not include a placebo arm or employ blinding; however, bias was mitigated by the

choice of an objective primary end point. We did not perform a baseline PCR or antibody testing and relied on participant history to rule out prior COVID-19. Our screening to randomisation ratio of 0.46 is on the lower side with refusal of consent being the main reason for non-inclusion.

In conclusion, HCQ in addition to PPE was not associated with a lower incidence of COVID-19 as compared with PPE alone. However definitive inferences are precluded by the limited statistical power.

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Funding The trial was funded by Wesley Medical Research, Australia (grant number: 2020-02).

Disclaimer The funder had no role in the conception, design, conduct, analysis or the decision to publish.

Competing interests OJ reports being a member of the WHO R&D Blueprint Safety Monitoring Team, ACT Accelerator—R&D Digital Health working group and COVID-19 Clinical Research Coalition data sharing working group.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not required.

Ethics approval This study involves human participants and was approved by The George Institute Ethics Committee (reference number: 08-2020). Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. Deidentified patient data will be made available beginning 6 months after publication of the study and ending at 2 years. All requests for data sharing must be accompanied by a formal request, a study proposal with clear statement of aims and hypotheses and a statistical analysis plan. All applications will be assessed by the HOPE Management Committee. Applications from investigators with suitable academic capability to conduct the proposed work will be given consideration. Any proposal will require approval from the ethics committee which approved the conduct of this trial prior to sharing of any patient data. If a proposal is approved, a signed data transfer agreement will be required before data sharing.

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Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Tirupakuzhi Vijayaraghavan BK, Jha V et al. Hydroxychloroquine plus standard personal protective equipment versus standard personal protective equipment alone for the prevention of laboratory confirmed COVID-19 infections among healthcare workers: A multi-centre parallel group randomized controlled trial from India.

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Trial sponsor, committees, funding bodies

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The George Institute for Global Health, India

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Independent Data Monitoring and Safety Committee

Rinaldo Bellomo (Chair), Jeyaraj Pandian, Niveditha Devasenapathy, Amritendu Battacharya (Statistician)

Funding Body

Wesley Medical Research, Australia

Site Investigators and research staff

Site personnel are listed in alphabetical order. Sites were chosen based on them being identified as COVID-hospitals by the Government of India or by virtue of them treating patients with COVID-19. The primary investigator at each site is marked with *.

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Acknowledgements

We would like to thank all the health care workers for agreeing to participate in the HOPE trial; all research and pharmacy staff at the participating hospitals; the regulatory authorities and the funding sources.

Study Participants

Inclusion criteria

1. Health Care Worker (medical, nursing, allied health, ancillary worker, visiting doctor) currently working in an environment with direct exposure to patients with confirmed COVID-19 infection.

Exclusion criteria

1. HCW refused/did not grant consent
2. HCW has a laboratory confirmed COVID-19 infection
3. HCW is currently taking chloroquine or HCQ
4. HCW is pregnant
5. HCW is currently breast feeding
6. HCW has a known history of QT prolongation
7. HCW is currently taking any of the medications that are contra indicated in combination with HCQ:
 - Anti-arrhythmic (Amiodarone),
 - Systemic Antimicrobials (Azithromycin, Fluconazole, Itraconazole, Ketoconazole, Ciproflxacin, Ofloxacin, Levofloxacin, Efavirenz),
 - Antipsychotics/ Antidepressants (Olanzapine, Fluoxetine),
 - Prokinetics/antimetics/H2 blockers (Cisapride, Domeridone, Famotidine),
 - Cardiac medications (Ranolazine, Ivabradine)
8. HCW has a history of serious cardiac dysrhythmias or cardiomyopathy
9. HCW has maculopathy of the eye (contra-indicated in the use of HCQ)
10. HCW is immunocompromised due to a disease or therapy

Outcome definitions

Primary outcome

The proportion of laboratory confirmed COVID-19 (by reverse transcriptase polymerase chain reaction or presence of antibodies) cases within 6 months of randomisation

Secondary outcomes (all censored at 6 months after randomisation)

- 1) hospitalization due to suspected COVID-19 disease
- 2) ICU or HDU admission due to suspected COVID-19
- 3) all-cause mortality
- 4) need for mechanical ventilation (O2 therapy, non-invasive or invasive)
- 5) need for vasopressors
- 6) need for renal replacement therapy
- 7) hospital length of stay
- 8) ICU or HDU length of stay
- 9) readmission to hospital
- 10) days absent from work due to suspected or confirmed COVID-19

Criteria for discontinuation of trial medication and withdrawal

The procedure for handling withdrawal of consent from a patient followed national regulations.

Discontinuation and withdrawal at the choice of the patient or the proxy

The health care worker (HCW) could withdraw his/her consent or proxy consent at any time without further explanations and without consequences for further treatment. In these instances, the investigator asked the HCW if they allowed continued data registration and follow-up until week 25. Already collected data until the time of withdrawal were used according to national regulations.

If the HCW was withdrawn after one or more doses of trial medication were administered, and the HCW allowed continued data registration, the HCW remained in the ITT population. If the HCW was withdrawn after one or more doses of trial medication were administered, and the HCW did not allow continued data registration, the HCW remained in the ITT population but with missing data from the time of withdrawal.

Discontinuation and withdrawal at the choice of the investigator

A HCW could have the intervention stopped by the clinician or investigator at any time if:

- The HCW experienced intolerable adverse reactions or events (including SARs or suspected unexpected serious adverse reactions (SUSARs)) suspected to be related to the trial intervention.
- The clinicians in conjunction with the coordinating investigator decided it to be in the best interest of the participating HCW.

In these HCWs, the collection of data and the follow-up continued, and the HCW remained in the ITT population.

Recommendations of the Data Safety Monitoring Committee (DSMC)

The trial management committee, under the advisement of the DSMC, communicated the decision to the site investigators to stop any further trial enrollment with effect from 5th of February, 2021. The details of the letter are as below.

Letter from DSMC:



FACULTY OF
MEDICINE,
DENTISTRY
& HEALTH
SCIENCES

February 5th, 2021

To: Bala Venkatesh

Management Committee

HOPE study

Dear Prof Venkatesh,

Re: Interim analysis of the HOPE trial "A randomized controlled trial of hydroxychloroquine compared with standard practice for the prevention of COVID-19 infections among health care workers exposed to SARS-CoV2"

The Data Safety Monitoring Committee have had the opportunity to view and analyze the data obtained for the interim analysis of this trial as planned.

The trial has been very well conducted with successful randomization and balanced baseline features as well as an acceptable degree of protocol delivery and compliance. We congratulate the investigators for such work.

The incidence of the primary outcome and the major secondary outcomes, however, is much lower than predicted. Thus, we estimate that to have a 90% power to identify a 30% reduction in the primary outcome, approximately 10,000 patients would have to be randomized to each group. Accordingly, we advise the Management Committee to consider stopping the trial on the basis of futility.

Yours sincerely,

A handwritten signature in black ink, appearing to be "R Bellomo".

Prof Rinaldo Bellomo AO, MD, PhD, FRACP, FCICM

Chair, Data Safety Monitoring Committee

(on behalf of the full DSMC)

Trial population**Definition of the Intention to Treat (ITT) population**

The ITT population was defined as all randomized health care workers for whom there was consent for the use of data.

Supplementary Table 1: List of sites and enrollments

| S. No. | Name of the Institution | State | City | Number of participants enrolled (N=416) |
|--------|--|---------------|-------------|---|
| 1. | Apollo Hospital, Greams Road | Tamil Nadu | Chennai | 62 |
| 2. | Kasturba Medical College | Karnataka | Manipal | 100 |
| 3. | Apollo Hospitals International | Gujarat | Gandhinagar | 60 |
| 4. | Apollo Hospitals, Jubilee Hills | Telangana | Hyderabad | 0 |
| 5. | Apollo Speciality Hospitals | Tamil Nadu | Madurai | 36 |
| 6. | NephroPlus Network | Telangana | Hyderabad | 1 |
| 7. | Christian Hospital | Odisha | Nabarangpur | 43 |
| 8. | Jawahar Lal Nehru Medical College, Aligarh Muslim University | Uttar Pradesh | Aligarh | 94 |
| 9. | Apollo Indraprastha | Delhi | New Delhi | 20 |

Supplementary Table 2. Protocol violations

| | HCQ + standard practice (PPE) arm, weeks 1-12 (N=213) |
|--|---|
| Stopped taking HCQ, numPT (%) | 44 [€] (20.66%) |
| Missed HCQ doses, numVIOL/numDOSE (%) | 312/2483 [*] (12.56%) |

[€] includes 6 subjects who never took a follow-up HCQ dose.

^{*} 209 subjects over 12 weeks should have received 2508 doses. Two subjects withdrew consent after weeks 6 and 7, respectively, and two subjects who had QT prolongation were advised to stop HCQ after follow-up visits 5 and 6, respectively. 213 subjects should have received 2532 (=209*12+6+7+5+6) doses, but receipt of dose information is missing for 49 doses, resulting in a total of 2483 expected doses.

numPT: number of patients

numVIOL: number of violations

Supplementary Table 2a. Additional details of participants that stopped taking HCQ

| Number of weeks at which drug was stopped | Number of participants (total n=44) |
|---|-------------------------------------|
| <3 weeks | 17 [*] |
| 3-6 weeks | 13 |
| 7-10 weeks | 14 |

^{*} includes 6 subjects that never took a follow-up HCQ dose

Supplementary Table 3: Compliance to study treatment

| | Standard practice (PPE) (N=203) | HCQ + standard practice (PPE) (N=213) |
|---|---------------------------------|---------------------------------------|
| Number of weeks that HCW worked in an area/ward with COVID-19 patients and did not use PPE (up to 25 weeks after randomization) | | |
| N, Mean (SD) | 176, 0 (0.08) | 186, 0 (0.07) |
| Median [Q1 – Q3] | 0 (0; 0) | 0 (0; 0) |
| Min, Max | 0.0; 1.0 | 0.0; 1.0 |
| Number of weeks that HCWs reported taking HCQ during weeks 1-12 (up to 12 weeks after randomization or COVID-19 infection, whichever is earlier) | | |
| N, Mean (SD) | 9, 1.00 (0.00) | 207, 10.48 (3.16) |
| Median [Q1 – Q3] | 1.00 (1.00; | 12.00 (11.00; |
| Min, Max | 1.0; 1.0 | 1.0; 12.0 |
| Number of weeks that HCWs reported taking HCQ during weeks 13-25 | | |
| N, Mean (SD) | 7, 1.00 (0.00) | 25, 3.00 (3.64) |
| Median [Q1 – Q3] | 1.00 (1.00; | 1.00 (1.00; 2.00) |
| Min, Max | 1.0; 1.0 | 1.0; 11.0 |
| ECG performed once between weeks 4 to 6 after randomization for HCWs in HCQ + standard practice (PPE) arm | NA | 172/213 (80.8%) |

Supplementary Table 4. Secondary outcomes – continuous

| Outcome | Standard practice (PPE) (N=203) | HCQ + standard practice (PPE) (N=211) | Mann-Whitney U test p- value |
|---|--|--|-------------------------------------|
| Days alive and free of hospital (up to 175 days) | | | |
| Mean (SD) | 174.92 (0.84) | 174.97 (0.41) | |
| Median [Q1 - Q3] | 175 (175-175) | 175 (175-175) | 0.54 |
| Days alive and free of ICU or HDU (up to 175 days) | | | |
| Mean (SD) | 175.00 (0) | 174.97 (0.41) | |
| Median [Q1 - Q3] | 175 (175-175) | 175 (175-175) | 0.33 |
| Days alive, have not lost job and not absent from work due to suspected or confirmed COVID-19 (up to 175 days) | | | |
| Mean (SD) | 174.19 (3.46) | 174.24 (3.23) | |
| Median [Q1 - Q3] | 175 (175-175) | 175 (175-175) | 0.93 |

Supplementary Table 5: Adverse events listing*

| Record | AE_ Description | AE_ Date | OUTCOME |
|---------|---|------------|--|
| 8433057 | ECG DONE AT 4-6TH WEEK SHOWED PROLONGATION OF QT INTERVAL. DRUG STOPPED AS PER PROTOCOL. PARTICIPANT IS DOING WELL. | 30/11/2020 | Participant was followed to end of trial and is doing well |
| 8434065 | ECG SHOWED SHOWED QT PROLONGATION. HCQ WAS STOPPED SUBSEQUENTLY FOR THE PATIENT. NO SYMPTOMS. | 5/12/2020 | Participant was followed to end of trial and is doing well |
| 8434100 | THE PARTICIPANT REPORTED MILD BLURRING OF VISION ASSOCIATED WITH HEADACHE AND FATIGUE. | 24/11/2020 | Resolved spontaneously |
| 8434100 | THE PARTICIPANT REPORTED NAUSEA AND CRAMPING ABDOMINAL PAIN FOR A FEW HOURS AFTER TAKING HCQ. | 1/12/2020 | Resolved spontaneously |
| 8434100 | THE PARTICIPANT REPORTED NAUSEA AND ONE EPISODE OF BILIOUS, NON BLOOD STAINED VOMITING. | 8/12/2020 | Resolved spontaneously |
| 8436004 | ACIDITY | 20/03/2021 | Resolved with Treatment |
| 8436005 | ACIDITY | 26/02/2021 | Resolved with Treatment |
| 8436010 | GASTRIC PROBLEM: ACIDITY | 15/01/2021 | Resolved with Treatment |
| 8436010 | CHEST PAIN | 8/01/2021 | Resolved with Treatment |
| 8436010 | GAS | 12/01/2021 | Resolved with Treatment |
| 8436012 | GASTRIC PROBLEM: ACIDITY | 8/01/2021 | Resolved with Treatment |
| 8436012 | ACIDITY | 23/01/2021 | Resolved with Treatment |
| 8436012 | GASTRIC- ACIDITY | 15/03/2021 | Resolved with Treatment |
| 8436014 | ACIDITY | 31/12/2020 | Resolved with Treatment |
| 8436014 | ACIDITY | 9/01/2021 | Resolved with Treatment |
| 8436015 | GASTRIC PROBLEM | 13/02/2021 | Resolved with Treatment |
| 8436015 | ACIDITY | 5/03/2021 | Resolved with Treatment |
| 8436017 | ACIDITY | 8/02/2021 | Resolved with Treatment |
| 8436018 | ACIDITY | 20/03/2021 | Resolved with Treatment |
| 8436019 | ACIDITY | 13/03/2021 | Resolved with Treatment |
| 8436021 | ACIDITY | 28/12/2020 | Resolved with Treatment |
| 8436022 | ACIDITY | 17/01/2021 | Resolved with Treatment |
| 8436027 | ACIDITY | 13/03/2021 | Resolved with Treatment |
| 8436028 | ACIDITY | 18/03/2021 | Resolved with Treatment |

Supplementary Table 5: Adverse events listing (Continued)

| Record | AE_ Description | AE_ Date | OUTCOME |
|----------|----------------------|------------|-------------------------|
| 8436029 | ACIDITY | 16/01/2021 | Resolved with Treatment |
| 8436029 | GAS | 25/01/2021 | Resolved with Treatment |
| 8436029 | ACIDITY | 27/02/2021 | Resolved with Treatment |
| 8436034 | ACIDITY | 8/03/2021 | Resolved with Treatment |
| 8436035 | ACIDITY | 9/04/2021 | Resolved with Treatment |
| 8436038 | ACIDITY | 18/01/2021 | Resolved with Treatment |
| 8436038 | ACIDITY | 25/03/2021 | Resolved with Treatment |
| 8436039 | GAS | 12/11/2020 | Resolved with Treatment |
| 8436041 | ACIDITY | 20/01/2021 | Resolved with Treatment |
| 8436044 | ACIDITY | 14/05/2021 | Resolved with Treatment |
| 8436048 | GAS | 5/02/2021 | Resolved with |
| 8436049 | ACIDITY | 11/01/2021 | Resolved with Treatment |
| 84360843 | ACIDITY | 24/01/2021 | Resolved with Treatment |
| 84360843 | ACIDITY | 20/02/2021 | Resolved with Treatment |
| 84360843 | ACIDITY | 1/05/2021 | Resolved with Treatment |
| 8436054 | ACIDITY | 17/01/2021 | Resolved with Treatment |
| 8436056 | GAS | 17/01/2021 | Resolved with Treatment |
| 8436056 | ACIDITY | 24/01/2021 | Resolved with Treatment |
| 8436057 | ACIDITY | 13/03/2021 | Resolved with Treatment |
| 8436058 | GAS | 30/05/2021 | Resolved with Treatment |
| 8436058 | ACIDITY | 13/03/2021 | Resolved with Treatment |
| 694007 | ANXIETY, PALPITATION | 5/12/2020 | Resolved spontaneously |
| 694056 | MILD GASTRIC ISSUES | 20/01/2021 | Resolved spontaneously |
| 694059 | MILD GASTRIC ISSUES | 14/01/2021 | Resolved spontaneously |
| 694066 | MILD GASTRIC ISSUES | 14/01/2021 | Resolved spontaneously |
| 667788 | MILD GASTRIC ISSUES | 14/01/2021 | Resolved spontaneously |
| 667788 | MILD GASTRIC ISSUES | 21/01/2021 | Resolved spontaneously |

*Table represents all adverse events (a participant could have had more than one adverse event)

Supplementary Table 6. Comparison of adverse events by category between the intervention and control arm*

| AE_Description | AE_EVENT | PPE Only (N=203) | PPE+HCQ (N=213) | P-value [€] | Risk ratio (95% CI) |
|-------------------|----------------|------------------|-----------------|----------------------|---------------------|
| Cardiac | No, numPT (%) | 202 (99.5%) | 212 (99.5%) | 1 | 0.95 (0.06, 15.55) |
| | Yes, numPT (%) | 1 (0.5%) | 1 (0.5%) | | |
| Gastro-Intestinal | No, numPT (%) | 189 (93.1%) | 195 (91.5%) | 0.59 | 1.23 (0.56, 2.14) |
| | Yes, numPT (%) | 14 (6.9%) | 18 (8.5%) | | |
| Headache | No, numPT (%) | 203 (100%) | 212 (99.5%) | 1 | - |
| | Yes, numPT (%) | 0 (0%) | 1 (0.5%) | | |
| QT Prolongation | No, numPT (%) | 203 (100%) | 211 (99.1%) | 0.5 | - |
| | Yes, numPT (%) | 0 (0%) | 2 (0.9%) | | |

[€] Fishers' exact test p-value.

*Table represents information by adverse event category at the participant level

Supplementary Table 7: Use of PPE during last contact with suspected or confirmed COVID-19 patient at baseline

| Outcome | Standard PPE (N=203) | HCQ + standard PPE (N=213) | Total (N=416) |
|------------------------|----------------------|----------------------------|-----------------|
| Surgical mask | 131/203 (64.5%) | 145/213 (68.1%) | 276/416 (66.3%) |
| N95 mask or similar | 194/203 (95.6%) | 201/213 (94.4%) | 395/416 (95.0%) |
| Gown | 71/203 (35.0%) | 83/213 (39.0%) | 154/416 (37.0%) |
| Jumpsuit | 135/203 (66.5%) | 131/213 (61.5%) | 266/416 (63.9%) |
| Head covering | 174/203 (85.7%) | 172/213 (80.8%) | 346/416 (83.2%) |
| Gloves | 201/203 (99.0%) | 207/213 (97.2%) | 408/416 (98.1%) |
| Booties or shoe covers | 174/203 (85.7%) | 173/213 (81.2%) | 347/416 (83.4%) |
| Eye protection | 127/203 (62.6%) | 138/213 (64.8%) | 265/416 (63.7%) |
| Face shield | 166/203 (81.8%) | 182/213 (85.4%) | 348/416 (83.7%) |
| Breathing apparatus | 28/203 (13.8%) | 28/213 (13.1%) | 56/416 (13.5%) |

Supplementary Table 8: Vaccination status of trial participants

| Vaccination done (post- randomisation) | Standard practice (PPE) | HCQ + standard practice (PPE) | Total |
|---|--------------------------------|--------------------------------------|-----------------|
| No | 46/181 (25.5) | 42/189 (22.2) | 88/370 (23.7%) |
| Yes | 135/181 (74.5) | 147/189 (77.8) | 282/370(76.3%) |
| Vaccination type | | | |
| Covishield | 116/135 (85.9%) | 126/147 (85.7%) | 242/282 (85.8%) |
| Covaxin | 18/135 (13.3%) | 20/147 (13.6%) | 38/282 (13.5%) |
| Sputnik V | 1/135 (0.7%) | 1/147 (0.7%) | 2/282 (0.7%) |

Vaccination started on 16th January 2021. By this time, 46 participants had completed the study and information on vaccination was available only for the 370 participants that were still in follow-up.

HOPE Protocol

Version: 3.0

Dated: 03June2020



HOPE - HydOxychloroquine Prophylaxis Evaluation

HOPE Study

A randomized controlled trial of hydroxychloroquine (HCQ) compared to standard practice for the prevention of COVID-19 infections among healthcare workers (HCW) exposed to SARS-CoV2

Protocol Number: TGI-IN4673

Version Number: 3.0

Date: 03 June 2020



Confidentiality statement: This entire protocol is the intellectual property of the investigators and cannot be used without express written permission.

HOPE Study Protocol | Version 3.0, 03 June 2020
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1. Study Synopsis

| | |
|-----------------------------|--|
| Study Title | A randomized controlled trial of hydroxychloroquine (HCQ) compared to standard practice for the prevention of COVID-19 infections among healthcare workers (HCW) exposed to SARS-CoV2 |
| Short Title | HOPE - <u>H</u> ydro <u>Q</u> xychloroquine <u>P</u> rophylaxis <u>E</u> valuation. |
| Protocol Number | Version 3.0, 03 June 2020 |
| Study Design | Multi-centre, open, phase III, randomized controlled trial of standard practice vs. standard practice plus HCQ |
| Primary outcome | Proportion of laboratory confirmed COVID-19 infections at 6 months after randomisation |
| Secondary outcomes | <ol style="list-style-type: none"> 1. Hospitalization due to suspected COVID-19 infection 2. admission with suspected or confirmed COVID-19 to a HDU or ICU 3. all-cause mortality 4. need for ventilation (O2 therapy, non-invasive or invasive) 5. need for vasopressors 6. need for renal replacement therapy 7. duration of hospitalization 8. duration of ICU or HDU stay 9. readmission to hospital 10. days off work |
| Intervention | HCW will be randomised to either receive 400mg of HCQ twice on the day of enrollment followed by 400mg once a week plus standard practice (use of PPE) or standard practice (use of PPE) for 12 weeks and followed up at 6 months |
| Planned sample size | 6,950 HCWs |
| Planned study period | 12 months |
| Inclusion criteria | Health Care Worker (medical, nursing, allied health, ancillary worker, visiting doctor) currently working in an environment with direct exposure to patients with confirmed COVID-19 infection |
| Exclusion criteria | <ol style="list-style-type: none"> 1. HCW refused/did not grant consent 2. HCW has a laboratory confirmed of COVID-19 infection 3. HCW is currently taking chloroquine or HCQ 4. HCW is pregnant 5. HCW is breast feeding 6. HCW has known QT prolongation 7. HCW is currently taking any of the medications that are contra indicated in combination with HCQ: <ul style="list-style-type: none"> • Antiarrhythmics (Amiodarone), • Systemic Antimicrobials (Azithromycin, Fluconazole, Itraconazole, Ketoconazole, Ciprofloxacin, Ofloxacin, Levofloxacin, Efavirenz), • Antipsychotics/ Antidepressants (Olanzapine, Fluoxetine) • Prokinetics/antimetics/H2 blockers (Cisapride, Domperidone, Famotidine), • Cardiac medications (Ranolazine, Ivabradine) 8. HCW has history of serious cardiac dysrhythmias or cardiomyopathy 9. HCW has maculopathy of the eye (a contra-indication to HCQ) 10. HCW is immunocompromised due to a disease or therapy |
| Randomisation | Web-based randomisation system available 24/7. Eligible HCWs will be randomized in a 1:1 ratio to standard practice plus HCQ or standard practice only. |

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2. Administrative information

2.1. Chief Investigators

Prof. Vivekanand Jha, Director, The George Institute for Global Health, New Delhi, India

Dr. Bharath Kumar Tirupakuzhi Vijayaraghavan, Consultant, Critical Care, Apollo Hospitals, Chennai, India

2.2. Study Sponsor / Trial Coordinating Centre

Sponsor: The George Institute for Global Health, New Delhi, India

2.3. HOPE Management Committee

Indian investigators:

Dr. Arpita Ghosh, Senior Research Fellow, The George Institute for Global Health, New Delhi, India

Dr. Oommen John, Senior Research Fellow, The George Institute for Global Health, New Delhi, India

Prof. Bala Venkatesh, Professorial Fellow, The George Institute for Global Health, Australia and Adjunct Prof. St. Johns Medical College and Research Institute, Bangalore, India

Prof. Sheila Myatra, Anaesthesiology and Intensive Care, Tata Memorial Hospital and Research Institute, Mumbai, India

Dr Rohina Joshi, The George Institute for Global Health, India and Australia

International co-investigators:

Dr Naomi Hammond, Senior Research Fellow, The George Institute for Global Health, Australia

Dr Lachlan Donaldson, Research Fellow, The George Institute for Global Health, Australia

Dorrilyn Rajbhandari, Senior Project Manager, The George Institute for Global Health, Australia

2.4. Trial Funding

The George Institute for Global Health has received support from Wesley Medical Research, Australia and is the trial funding body for sites in India. Additional funding will be sought.

2.5. Role of the funding bodies

The study will be designed and conducted, and the results analysed, presented and published by the investigators independent of any funding agencies.

2.6. Trial Registration

The protocol has been registered on the following clinical trial registry: CTRI/2020/05/025067

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3. Introduction

3.1. Background

In December 2019, a novel strain of the coronavirus (now labelled SARS CoV-2) emerged from Wuhan (Hubei province), China and resulted in a cluster of cases of respiratory illness with several patients proceeding onto severe acute respiratory failure. The disease which has now been labelled COVID-19 has rapidly spread and as of 27th March 2020, involves 200 countries (or territories) with 1812734 cases and 113675 deaths globally.¹ The World Health Organization (WHO) declared the disease a Pandemic on the 11th of March, 2020.²

In India, after an initial period of isolated reports (mostly imported cases), there has been a steep increase in the number of cases to over 35043 by the 1st of May with 1147 deaths.^{3,3} From initial reports, it appears that about 15-20% of affected patients need hospitalization and/or intensive care^{4,5} with conflicting reports of the case fatality rate (anywhere between 0.15-15.8%).⁶

Healthcare workers (HCWs) who are at the frontlines of the battle against COVID-19 are at very high risk of acquiring infection. In published data from China⁴, 3.8% of confirmed cases were healthcare workers and in Italy about 9%⁷. In the previous Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS) coronavirus infections, HCWs accounted for 21.1% and 19.1% of cases respectively.^{8,9} Based on epidemiological modelling from the data reported from China⁵ with 10-15% of patients requiring hospitalization and 5% requiring intensive care, this could translate into hundreds of thousands of patients needing hospital care in India. This will potentially put thousands of HCWs at risk.

Whilst equipment capacity and health care systems can be boosted during pandemics, HCWs cannot be urgently manufactured. Presently, health care workers are every country's most valuable resource.

There is no proven effective prophylaxis, treatment or vaccine. The availability of personal protective equipment (PPE) for HCWs, a key factor for HCW safety, is also a concern as shortages have been described in many regions protecting the HCWs is likely to be particularly challenging because of the limited isolation facilities, limited personal protective equipment (PPE), and higher patient density per ward. This poses the problems of increasing the case burden, loss of trained healthcare personnel that are vital for patient care and additionally the massive loss of morale among the entire healthcare community. There are reports that there is severe shortage of PPEs,¹⁰ which makes it imperative to find alternate strategies that provide protection against this infection.

Given the large population and the relatively low testing rates, there will continue to be a pool of infected community members whom will contribute to ongoing new infections even after the peak of the pandemic is over. There are now reports confirming that over 10% of patients admitted with severe respiratory illness to hospitals had no travel history.¹¹

Although several groups around the world are racing to develop a vaccine, most estimates suggest it will take over a year to develop one. Currently, there are no proven therapies for COVID-19.¹² There are in-vitro data that confirm efficient inhibition of SARS-CoV2 by both Chloroquine and Hydroxychloroquine (HCQ)^{13,14} and several trials are now underway for investigating the effectiveness of these drugs in patients with confirmed COVID-19. We note that the WHO has started a mega-trial of four different treatment approaches, but only for treatment of patients with COVID-19 infection.¹⁵ Both drugs have been in use for several years (for malaria and for rheumatoid arthritis respectively) and have a proven track record of safety.

Recently, the Indian Council of Medical Research (ICMR) has recommended the use of HCQ for prophylaxis of HCW, but have made a plea that "proof of concept and pharmacokinetics studies be taken up expeditiously" and said that "new evidence will guide any change in the recommendation". UK has prohibited its use outside of clinical trials. Furthermore, there have been recent reports of adverse events¹⁶ including death following the use of HCQ as prophylaxis/treatment for this condition. There is

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an ethical and a public health imperative to generate definitive clinical trial evidence for the efficacy and safety of this approach in HCW.

To answer this question, we propose a randomized controlled trial of HCQ among healthcare workers exposed to confirmed COVID-19 patients. We hypothesise that the use of HCQ as a prophylactic agent amongst frontline healthcare workers will reduce the incidence of new COVID-19 infections. The primary outcome of interest will be the proportion HCWs that develop a confirmed COVID-19 infection, while being on prophylaxis. We also propose to align our study with similar studies being led globally to ensure a coordinated meta-analysis.

3.2. Rationale

Healthcare workers involved in the care of hospitalized COVID-19 patients are at high risk, even with the conscientious use of personal protective equipment. These risks are further amplified in those taking care of patients in the intensive care unit (ICU), where procedures that are part of patient's care (such as nebulizations, intubation, non-invasive ventilation, cardio-pulmonary resuscitation etc.) dramatically increase the risk of aerosol generation and the potential for HCW infection. The loss of a part of or significant portions of the healthcare workforce will seriously impede efforts at controlling the pandemic and will likely result in collapse of the entire healthcare system.

There is biological plausibility that hydroxychloroquine (HCQ) will provide effective prophylaxis against SARS-CoV-2 infection based on its ability to reduce binding of the virus to the ACE2 receptor, prevent cellular entry of the virus and inhibit viral replication. HCQ has many favourable pharmacokinetic characteristics such as high oral bioavailability, a very large volume of distribution, a long terminal half-life, and is concentrated in tissues including the lung. Chloroquine and hydroxychloroquine have both shown in-vitro effect against the virus (both in the previous SARS epidemic and now for SARS-CoV2). Both drugs have been in use for a several years and extended duration use has shown to be safe. Chloroquine continues to be used as chemoprophylaxis by travellers visiting regions where malaria is endemic and hydroxychloroquine is part of the standard therapy for conditions such as SLE and Rheumatoid Arthritis. Both drugs are inexpensive and relatively easily available across the country.

Rationale for HCQ prophylaxis dosage and duration

There are no human studies of HCQ prophylaxis against COVID-19. However, there is an advisory recommendation from the Indian Council of Medical Research for HCW to take a loading dose of 400mg taken twice on Day 1 followed by 400mg once a week for 7 weeks. Based on the current number of cases in India and the International trajectories of COVID -19 cases we anticipate HCW will be exposed for longer than 7 weeks. Therefore a 12-week prophylaxis duration has been chosen for this study. There is reasonable safety data on use of HCQ for longer than 12 weeks and therefore is a safe duration for this trial.

Only a robust, well designed and implemented RCT would provide reliable estimates of benefit and provide data on adverse events (AEs) and serious adverse events (SAEs).

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4. Study Design

4.1 Aim

To conduct a multicentre randomised, controlled trial (RCT) to determine whether hydroxychloroquine (HCQ) in addition to standard practice reduces the proportion of HCWs developing symptomatic and laboratory confirmed COVID-19 infections as compared to standard practice alone.

4.2 Hypothesis

The HOPE study will test the hypothesis that a weekly dose of 400mg of oral HCQ for 12 weeks (following a HCQ loading dose, 400mg twice on the day of enrolment) in addition to standard practice (using PPE) is superior to standard practice (using PPE) alone at reducing the risk of acquiring laboratory-confirmed COVID-19 infection in frontline healthcare professionals caring for or in contact with patients with known or suspected COVID-19 disease.

4.3 Design

This is a, multi-centre, open, phase III, randomized controlled trial of HCQ prophylaxis+ standard practice vs. standard practice alone.

5. Study Outcomes

5.1 Primary Outcome

The proportion of laboratory confirmed COVID-19 cases within 6 months of randomisation

5.2 Secondary Outcome:

- 1) hospitalization due to suspected COVID-19 disease
- 2) ICU or HDU admission due to suspected COVID-19
- 3) all-cause mortality
- 4) need for mechanical ventilation (O2 therapy, non-invasive or invasive)
- 5) need for vasopressors
- 6) need for renal replacement therapy
- 7) hospital length of stay
- 8) ICU or HDU length of stay
- 9) readmission to hospital
- 10) days absent from work due to suspected or confirmed COVID-19

6. Study Participants

6.1. Study Setting

This study will be conducted in public and private hospitals across India. These centres will be selected on the basis of them being designated centres for COVID-19 patients by the Government of India or involved in the care of patients with confirmed COVID-19 infection.

6.2. Inclusion criteria

1. Health Care Worker (medical, nursing, allied health, ancillary worker, visiting doctor) currently working in an environment with direct exposure to patients with confirmed COVID-19 infection.

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6.3. Exclusion criteria:

1. HCW refused/did not grant consent
2. HCW has a laboratory confirmed COVID-19 infection
3. HCW is currently taking chloroquine or HCQ
4. HCW is pregnant
5. HCW is currently breast feeding
6. HCW has a known history of QT prolongation
7. HCW is currently taking any of the medications that are contra indicated in combination with HCQ:
 - Anti-arrhythmic (Amiodarone),
 - Systemic Antimicrobials (Azithromycin, Fluconazole, Itraconazole, Ketoconazole, Ciproflxacin, Ofloxacin, Levofloxacin, Efavirenz),
 - Antipsychotics/ Antidepressants (Olanzapine, Fluoxetine),
 - Prokinetics/antimetotics/H2 blockers (Cisapride, Domperidone, Famotidine),
 - Cardiac medications (Ranolazine, Ivabradine)
8. HCW has a history of serious cardiac dysrhythmias or cardiomyopathy
9. HCW has maculopathy of the eye (contra-indicated in the use of HCQ)
10. HCW is immunocompromised due to a disease or therapy

7. Study interventions

7.1. Participant recruitment

Potential participants will be identified by research staff in each of the sites and will be approached to consent to participate in the study. The recruitment period is expected to be 6 months.

7.2. Randomisation

Randomisation will be conducted through a password-protected, secure website using a central, computer-based randomisation program. Randomisation will be stratified by participating institution and by the role of HCW – nursing, medical and other. Participants will be randomised 1:1 to either standard practice only or HCQ plus standard practice.

Following successful randomisation, each participant will be assigned a unique ‘participant study number’.

7.3. Study treatment regimen

7.3.1 Standard practice (use of PPE only) (control arm)

Standard practice will be defined as the use of personal protective equipment (PPE) as per the recommendations of the institution employing the HCW. The recommendation of the participating institutions will be ascertained by obtaining any policies or guidelines relating to the use of PPE when caring for or exposed to COVID-19 patients. This definition is pragmatic in nature, due to the context of an ongoing pandemic at the time of the trial and given that time is of the essence.

HCWs randomised to ‘standard practice’ will continue to use PPE whilst at work as per their institutional recommendations. They will be discouraged from taking HCQ. Participant will be asked weekly if they have taken HCQ and this will be reported as a protocol deviation.

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7.3.2. HCQ and standard practice (use of PPE) (intervention arm)

HCWs will receive 400mg of HCQ twice on the day of enrollment, followed by 400mg once a week for a total of 12 weeks. The HCQ on the day of enrolment will be given as two doses of 400mg, one dose under supervision by the research staff at site, the other dose will be given to the HCW to take later. Study drug (HCQ) will be provided on a weekly basis for 12 weeks by the site study team and will require the HCW to attend to receive the weekly dose.

All HCW in the HCQ plus standard practice arm will be required to have an ECG performed once between weeks 4 to 6. An ECG should be performed if the HCW reports experiencing side effects such as chest pain, syncope and/or palpitations.

HCWs randomized to 'HCQ plus standard practice' will continue to use PPE whilst at work as per their institutional recommendations, however they will receive HCQ weekly as prophylaxis against contracting COVID-19 infection.

7.4. Premature cessation of study assigned treatment

For HCWs assigned to the HCQ plus standard practice arm, study drug will be suspended if the HCW contracts COVID-19 during the 12 weeks treatment period.

Study drug may also be permanently stopped in the following circumstances:

1. Request to stop the study drug by the participant. Consent to collect follow-up data will be sought.
2. Adverse or serious adverse reaction to HCQ.

Regardless of whether the full study treatment regime is continued or not, the follow-up schedule should continue unchanged for all randomised participants.

7.5. Blinding

This is an unblinded study: study assigned treatment will be known to the research team and participant. Bias will be mitigated through an objective end point (laboratory confirmed COVID-19 infection).

7.6. Safety considerations

7.6.1. Management of potential risks to participants

HCQ has a favorable adverse effect profile and has been in use for Rheumatoid arthritis and systemic lupus erythematosus for several years. Most adverse effects are minor and usually restricted to nausea, stomach cramps, headache and diarrhoea. However, all AEs and SAEs will be recorded and reported to the Ethics Committee, Sponsor and the required regulatory bodies.

In accordance with the Indian Council of Medical Research recommendations and as a safety strategy, an ECG will be performed once between weeks 4 to 6 weeks for all HCWs randomized to receive HCQ. An ECG will be performed if the HCW reports cardiovascular symptoms such as chest pain, syncope and/or palpitations. If the ECG report indicates QT prolongation (QT Interval is >45ms) and /or is abnormal the HCQ will be ceased and the participant referred to a cardiologist.

7.6.2. Precautions and adverse reactions

HCQ is a registered product with the Central Drugs Standard Control Organization (CDSCO). The researchers must be aware of the precautions and potential adverse reactions for HCQ that are detailed in Product Information for India. Participants will be monitored for the known side effects of HCQ including ECG monitoring for abnormal prolongation of the QT interval (QT Interval >450ms).

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8. Study Assessments

8.1. Participating site information

Data describing institutional recommendations for HCWs on the use of PPE when caring for or exposed to COVID-19 patients will be collected prior to recruitment commencing at all sites.

8.2. Screening

Potential participants will be approached by the research team who will screen them for eligibility and request consent.

A screening log will be kept to monitor recruitment.

8.3. Randomisation

Once consent is obtained, the participants demographics will be entered into a web-based randomisation system. Each eligibility criterion will be answered with a Yes / No response and only participants meeting all criteria will proceed to randomisation.

8.4. Baseline

At baseline, information will be collected on designation, role in COVID ward (nursing, medical, allied health, ancillary worker, visiting doctor), demographics, average shift duration, and comorbidities.

8.5. Weekly questionnaire

Each participant will complete a questionnaire either by phone interview or in person. Information will be obtained about the amount of exposure during the past week, confirmation of compliance with standard process and HCQ administration or not. This will continue for a total of 25 weeks unless the participant tests positive to COVID-19.

8.6. Electrocardiograph

Each participant in the HCQ plus standard practice arm will have an ECG performed once between weeks 4 to 6 following randomisation. The ECG will be assessed for QT interval prolongation (QT interval is >450ms) and HCQ will be ceased if the report is abnormal. An ECG may be performed if the HCW reports cardiovascular symptoms such as chest pain, syncope and/or palpitations.

8.7. Definition of COVID-19 diagnosis

COVID-19 diagnosis is defined as a positive laboratory confirmed COVID-19 infection.

8.8. COVID-19 and Follow up at 6 months.

When a participant test indicates COVID-19 positive then administration of HCQ ceases and the information is collected at the end of 6 months on hospitalisation, admission to HDU or ICU, the need for ventilation (O2 therapy, non-invasive and invasive), Inotropes and renal replacement therapy and the amount of time off work.

9. Safety Monitoring and reporting

9.1. Safety Reporting:

9.1.1. Definition of Serious Adverse Events:

A serious adverse event is any untoward medical occurrence that:

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- results in death
- is life-threatening
- requires inpatient hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability/ incapacity
- consists of a congenital anomaly or birth defect

Other 'important medical events' may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences.

Definitions:

| | |
|---|---|
| Adverse Event (AE) | Any untoward medical occurrence in a participant to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product. |
| Adverse Reaction (AR) | <p>An untoward and unintended response in a participant to an investigational medicinal product which is related to any dose administered to that participant.</p> <p>The phrase "response to an investigational medicinal product" means that a causal relationship between a trial medication and an AE is at least a reasonable possibility, i.e. the relationship cannot be ruled out i.e. the relationship is definitely, probably, possibly or unlikely to be related (see below).</p> <p>All cases judged by either the reporting medically qualified professional or the Sponsor as having a reasonable suspected causal relationship to the trial medication qualify as adverse reactions.</p> |
| Serious Adverse Event (SAE) | <p>A serious adverse event is any untoward medical occurrence that:</p> <ul style="list-style-type: none"> • results in death • is life-threatening • requires inpatient hospitalisation or prolongation of existing hospitalisation • results in persistent or significant disability/incapacity • consists of a congenital anomaly or birth defect. <p>Other 'important medical events' may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences.</p> <p>NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.</p> |
| Serious Adverse Reaction (SAR) | This is an adverse event that is both serious and is considered a drug reaction. |
| Suspected Unexpected Serious Adverse Reaction (SUSAR) | <p>A SUSAR is a SAR that is:</p> <ul style="list-style-type: none"> • not listed in the summary of product characteristics (SmPC) for that product or |

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| | |
|--------------|--|
| | <ul style="list-style-type: none"> • has not been described in the published literature before |
| Expectedness | An expected AR or SAR is a drug reaction that is listed in the SmPC and or has been described in the published literature before |

NB: to avoid confusion or misunderstanding of the difference between the terms “serious” and “severe”, the following note of clarification is provided: “Severe” is often used to describe intensity of a specific event, which may be of relatively minor medical significance. “Seriousness” is the regulatory definition supplied above.

9.1.2. Causality

The relationship of each adverse event to the trial medication must be determined by a medically qualified individual according to the following definitions:

- Definitely related
- Probably related
- Possibly related
- Unlikely to be related
- Not related

9.1.3. Procedures for Recording Adverse Events

All AEs occurring during the trial/ or until 28 days after the trial finishes, that are observed by the Investigator or reported by the participant, will be recorded on the CRF, whether or not attributed to trial medication.

The following information will be recorded: description, date of onset and end date, severity, assessment of relatedness to trial medication, other suspect drug or device and action taken. Follow-up information should be provided as necessary.

The severity of events will be assessed following the Common Toxicity Criteria v5.0: 1 = mild, 2 = moderate, 3 = severe, 4 = very severe.

AEs considered related to the trial medication as judged by a medically qualified investigator or the Sponsor will be followed either until resolution, or the event is considered stable.

It will be left to the Investigator’s clinical judgment to decide whether or not an AE is of sufficient severity to require the participant’s removal from treatment. A participant may also voluntarily withdraw from treatment due to what he or she perceives as an intolerable AE. If either of these occurs, the participant must undergo an end of trial assessment and be given appropriate care under medical supervision until symptoms cease, or the condition becomes stable.

9.1.4. Reporting

All SAEs, including SARs and SUSARs, detected by site investigator should be reported to the co-principal investigators and the local ethics committee within 24hrs.

The co-principal investigators will also report these to the Sponsor within 24hrs of becoming aware of the event.

9.2. Data Safety Monitoring Committee

An independent Data Safety and Monitoring Committee with a fully constituted DSMC charter will be formed to oversee the progress of the trial and to conduct interim analyses. In order to address safety concerns, at least one formal interim analysis will be conducted after 90 days of enrolment. The purpose of this interim analysis is to test for the difference in outcomes between the two study groups, to check for potential safety issues as well as assess early efficacy. Any additional reviews of the data or may be performed at the discretion of the Independent Data Monitoring Committee.

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10. Ethics and dissemination

10.1. Ethical principles

The study will be conducted in accordance with ethical principles consistent with the Declaration of Helsinki¹⁹ and all relevant national and local guidelines on the ethical conduct of research.²⁰⁻²¹

10.2. Human Research Ethics Committee

Ethics Committee Approval:

All participating sites and investigators will obtain local EC approval and other approvals as necessary.

10.3. Informed consent procedures

Consent:

All eligible participants will be approached for participation in the trial by a member of the site research team.

To obtain informed consent, study personnel will follow the following steps:

- Present information on the study in a simple and understandable manner;
- Answer questions in a simple and understandable manner;
- Allow the potential participant an opportunity to reflect and discuss study participation with their family, friends, or family physician if desired;
- Confirm that the participant understands the risks and benefits of participating in the study and that their participation is voluntary;
- Complete and obtain signatures for informed consent form and obtain contact information from the participant.

10.4. Confidentiality and privacy

All participant information pertaining to the study will be stored in a computer database maintaining confidentiality in accordance with local legislation regarding privacy and use of health data. When archiving or processing data pertaining to the investigator and/or to study participants, the coordinating centre will take all appropriate measures to safeguard and prevent access to this data by any unauthorised third party.

The site Principal Investigator will maintain the confidentiality of all study documentation and take measures to prevent accidental or premature destruction of these documents. The site Principal Investigator must notify the coordinating centre prior to destroying any study documents following study completion or discontinuation. If the site Principal Investigator's situation is such that archiving can no longer be ensured by him/her, the site Principal Investigator will inform the coordinating centre and the relevant records will be transferred to a mutually agreed designee.

If any site Principal Investigator retires, relocates, or otherwise withdraws from conducting the study, the responsibility for maintaining records may be transferred to the coordinating centre, or other site Principal Investigator. The coordinating centre must be notified of and agree to the change. All associated documentation must also be updated.

11. Data collection and management

Data management will be provided by The George Institute for Global Health, India. The principle means of data collection and data processing will be electronic via a password protected website (electronic Case Report Form - eCRF). All computerised forms will be electronically signed by the authorised study

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staff and all changes made following the electronic signing will have an electronic audit trail with a signature and date.

The relevant study participant data will be collected on paper during interviews with the participants by the site research staff, either in person or by telephone call. Participants will be contacted via telephone weekly for 25 weeks after randomisation by a member of the research team at each site to determine treatment compliance and COVID-19 status. Any paper CRFs and participants logs will be kept at the participating sites in secure locked cabinets or other enclosures that are accessible only to study personnel.

A comprehensive guide to data collection with definitions and rationale will be provided together with a paper version of the case report form (CRF). A comprehensive guide to accessing the data entry forms on the website and entering all follow-up data will be provided in the Data Completion Manual and Operations Manual. All of these documents will also be available in PDF format as required to assist the site research staff to ensure high-quality data collection and data entry.

11.1. Record retention

All paper study records, including consent documentation, paper CRFs (if used) and electronic records will be kept following the completion of the study: 15 years and otherwise as per local regulations in other jurisdictions.

12. Quality control and quality assurance monitoring

12.1. Responsibilities of the investigator

The site Principal Investigator agrees to perform the clinical trial in accordance with this clinical trial protocol, ICH guideline for Good Clinical Practice and all applicable regulatory requirements. The site Principal Investigator is required to ensure compliance with all procedures required by the clinical trial protocol and with all study procedures provided by the central or regional coordinating centre.

The site Principal Investigator agrees to provide reliable data and all information requested by the clinical trial protocol in an accurate, legible and timely manner according to instructions provided.

12.2. Responsibilities of the Coordinating centre

The central coordinating centre, The George Institute for Global Health - India, is responsible for taking all reasonable steps to ensure the proper conduct of the clinical trial protocol. The coordinating centre has multiple measures in place for data quality control. These measures include:

- i. on-site training of research and clinical personnel
- ii. standard operating procedures to guide storage and administration of the study drug
- iii. ongoing assessment of quality metrics
- iv. ongoing review of missing data and outliers
- v. availability of Coordinating Centre personnel and the Principal Investigators 24/7 to answer study-related questions

12.2.1. Site Initiation

Prior to initiation of the study at each participating site, the central or regional coordinating centre will be responsible for providing adequate training to the site Principal Investigator and study personnel. The training will cover all aspects of the study protocol and procedures and will include practical training on the use of the web-based randomisation system, electronic CRF website and study materials. The site initiation visit will be conducted by teleconference, videoconference or face-to-face meeting at the participating site. Written and electronic materials will be supplied for study staff and for the education of clinical ICU staff at each participating site.

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12.2.2 Monitoring during the study

A study monitor from the central or regional coordinating centre will ensure that the study is conducted according to the protocol, Good Clinical Practice guidelines and relevant regional regulatory requirements. The main duty of the study monitor is to help the investigator and the coordinating centre maintain a high level of ethical, scientific, technical and regulatory quality in all aspects of the trial.

The site Principal Investigator and study personnel will be available to discuss the study. These monitoring visits by phone or in person will include, but will not be limited to, review of the following aspects:

1. Adherence to the protocol including consistency with inclusion and exclusion criteria
2. HCW recruitment
3. Adverse event documentation and reporting
4. Compliance with the study assigned administration method
5. Compliance with regulations

The central coordinating centre team will conduct regular remote monitoring on the web-based database by applying validation and consistency rules and with regular data cleaning to ensure the integrity of the study data.

12.2.3. Site Close out

At completion of the trial, ensure secure facilities for the storage of study data as required by local regulations.

12.3. Management of protocol deviations

A protocol deviation is an unanticipated or unintentional departure from the expected conduct of an approved study that is not consistent with the current research protocol or consent document. A protocol deviation may be an omission, addition or change in any procedure described in the protocol.

The site investigator should not implement any deviation from or changes to the protocol without agreement by the study management committee and documented approval from the HREC / IRB of the amendment, except where necessary to eliminate an immediate hazard(s) to trial participants. In the event of an emergency intended to eliminate an apparent immediate hazard to participants the investigator may implement or omit any process as deemed appropriate.

Substantive deviations from the protocol must be documented and promptly reported to the study management committee and the HREC / IRB (if applicable). The report should summarise the event and action taken.

12.4. Access to data and documents

The study may be audited by government regulatory authorities, local HREC / IRBs or qualified representatives of The George Institute for Global Health as permitted by regulations. Therefore, access to other study related files, must be made available at all study sites for monitoring and audit purposes during the course of the study and after its completion.

Participants will be assigned a unique 'participant study number' and will not be identified by name in the study database. The site research staff will securely keep a list of participants and their corresponding study number, and confidentiality of information will be preserved. The confidentiality of the participant will be maintained unless disclosure is required by regulations.

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13. Statistical methods

13.1. Sample size:

6,950 HCWs will be enrolled to detect a 25% relative reduction, or 2.5% absolute risk reduction, in the infection rate from an estimated baseline infection rate of 10%, with 80% power. This sample size allows for a potential loss to follow-up rate of 10% and a potential non-compliance rate of 10% in both the treatment and control arms.

Based on the premise that there are a minimum of 300-400 HCWs exposed to COVID-19 patients at each of the hospitals treating these patients, we will plan to recruit about 15-25 hospitals across the country. The investigators have strong collaborations with both public and private hospitals across the length and breadth of India and therefore achieving the sample size is feasible. As the study population will be drawn from a broad cohort of hospitals, the results are generalizable.

13.2. Statistical analysis plan

Categorical variables will be reported as numbers and percentages and continuous variables as mean/SD or median/IQR based on the distribution of data. For the primary comparison of symptomatic and confirmed COVID-19 disease between the groups, we will apply a chi-square test. We will develop a multivariable logistic regression model to adjust for differences in key baseline covariates (if any). For all secondary outcome measures, appropriate statistical tests will be employed.

A formal statistical analysis plan will be agreed upon and placed in the public domain before the study database is locked for the analysis of the primary outcome. The trial protocol will be written up for a formal publication in a peer reviewed journal. The trial will also be registered on the Indian clinical trials registry and on clinicaltrials.gov

13.3. Interim analysis

In order to address safety concerns, at least one formal interim analysis will be conducted at 90 days (where 25% of planned recruitment) has been completed and followed up for 4 weeks. The purpose of this interim analysis is to assess safety and efficacy according to a pre-specified DSMC Charter.

14. Publications and reports

The study will be conducted in the name of the 'HOPE Study Investigators'. Central project coordination and data management will be provided by The George Institute for Global Health, Delhi, India.

Authorship of publications arising from the study will be the management committee with full credit assigned to all collaborating Institutions, investigators and site research staff. Responsibility for the content of manuscripts will rest with the writing committee, and, where listed, the chair of the writing committee will be listed first with subsequent members listed alphabetically.

It is expected that findings will be disseminated via publication in high-quality peer reviewed journals in the medical literature. Study findings will also be presented at regional, national, international intensive care conferences, and results via social media and mainstream media platforms.

Funding bodies will be acknowledged in all publications.

14.1. Public Access

The protocol and statistical analysis plan will be made public prior to data analysis of the principal study. The participant level dataset will be made available at a time approved by the Management Committee.

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