STATISTICAL ANALYSIS PLAN

Chloroquine/ hydroxychloroquine prevention of coronavirus disease (COVID-19) in the healthcare setting; a randomised, placebo-controlled prophylaxis study (COPCOV)

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1 Contents

2 Trial Overview

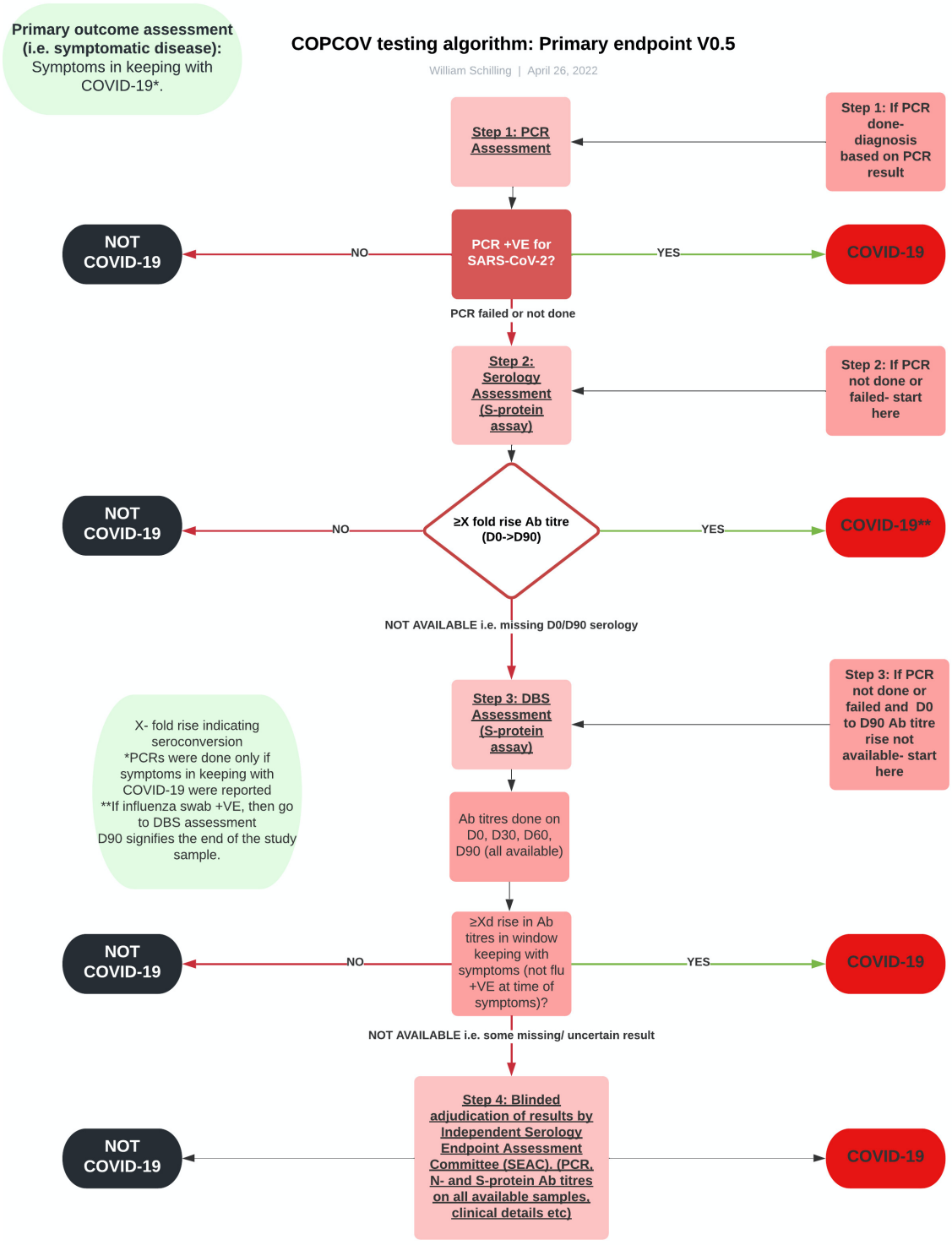
We hypothesise that chloroquine and hydroxychloroquine might slow viral replication in exposed subjects, attenuating or preventing the infection. Given the enormous experience of use in chemoprophylaxis, excellent safety and tolerability profile and its very low cost, if it proved effective then it would be a readily deployable and affordable preventive measure for high risk individuals such as healthcare workers.

2.1 Main research questions

The primary objective is to determine if prophylactic chloroquine or hydroxychloroquine prevents symptomatic COVID-19 illness. This is defined as symptoms in keeping/compatible with COVID-19 AND

laboratory evidence of infection defined as either virologically confirmed infection (a PCR positive for SARS-CoV-2), OR if the PCR is negative or not done, then serologically confirmed infection (seroconversion during the study intervention period).

Overview of primary endpoint ascertainment:



The quantitative rise in antibody titres, as well as the exact cut-offs for negative and positive serology, as well as the PCR thresholds, will be determined in advance of final signature of this document and

made available, as well as how to deal with uncertain results. Likewise, symptoms which are in keeping with COVID-19 will be defined in this document in advance of final sign-off, with how to deal with uncertain symptoms.

The secondary objectives include determining if chloroquine/ hydroxychloroquine:

- Attenuates the clinical severity of COVID-19 infection
- Prevents asymptomatic COVID-19
- Prevents and attenuates severity of symptomatic all-cause acute respiratory illnesses (ARI)

The study is a double-blind, randomised, placebo-controlled trial that will be conducted in healthcare settings, and those at risk of developing COVID-19 (henceforth the study population). After obtaining fully informed consent, we will recruit members of the study population who can be followed up reliably for up to 5 months. In Asia they will be randomised to receive either chloroquine or placebo (1:1 randomisation). In Europe and Africa they will be randomised to receive either hydroxychloroquine or placebo (1:1 randomisation).

A loading dose of 10mg base/kg (four 155mg tablets of base for a 60kg subject), followed by 155mg base daily (250mg chloroquine phosphate salt or 200mg of hydroxychloroquine sulphate) will be taken for 90 days. Subsequent episodes of symptomatic respiratory illness, including symptomatic COVID-19, clinical outcomes, and asymptomatic infection with the virus causing COVID-19 will be recorded during the follow-up period.

If participants are diagnosed with COVID-19 during the period of prophylaxis, they will continue their prophylaxis unless advised to do so by their healthcare professional or the study team. They will be followed up for at least 28 days from the start of illness (up until a maximum of 60 days if not recovered at 28 days).

The procedures for identifying a case and the subsequent isolation and management will follow local and national guidelines; this study will not interfere in the usual local investigation and management of COVID-19 cases. Chloroquine and hydroxychloroquine have very few drug-drug interactions and should not interfere with the management of pneumonia.

3 Statistical Analysis Considerations

3.1 General Analysis Approach

The main analysis for the primary outcome will be on the intention-to-treat (ITT) population. In this analysis, participants will be analysed according to the arm of randomisation irrespective of the treatment that was actually given and participant adherence to study drug.

If there is substantial non-adherence to randomised treatment arm (for example, participants in the placebo group self-administering chloroquine/ hydroxychloroquine, or multiple missed doses in the chloroquine/ hydroxychloroquine arm), principled methods of handling missing data such as inverse probability weighting or multiple imputation procedures will be used to account for potential post-randomisation confounding.

These ITT analyses will be followed by the per protocol (PP) analysis.

A per protocol (PP) analysis will be conducted to adjust for non-compliance to study protocols. Under an assumption of no post-randomisation confounding, this is a form of sensitivity analysis of the intention to treat analysis. In the PP analysis, participants who did not take their study drug (as reported during the study on the CRF), and any major protocol violations will be excluded. A careful expert discussion will take place prior to database lock to clearly define the most appropriate per protocol populations. The identification of the appropriate per protocol population will consider the possible missing data scenarios without looking at the data. The agreed per protocol population will be detailed in this plan prior to the signing off this document.

Inclusion in the per protocol analysis will require validation of the clinical data for each patient. Participants who did not receive the allocated study drug or who missed a significant number of doses, as defined as a major protocol deviation (>25%) in the study's SOP, will be excluded from the per protocol analysis.

Secondary endpoints will be analysed first in the ITT population, as for the main primary outcome. Data analysis will mainly be performed using R, Stata 15.0 or higher, StataCorp, 4905 Lakeway Drive College Station, Texas 77845 USA, Graphpad and other relevant software.

3.1.1 Missing data

Missing data will be imputed using appropriate methods of handling missing data. The Kaplan-Meier/ survival analysis will be the main strategy for handling missing outcome data such that outcomes with missing data will be censored at the last timepoint of follow-up.

The inverse probability weighting approach may also be utilised to account for potential post-randomisation imbalance that may confound the relationship between treatment and the primary outcome.

4 Study objectives and endpoints

4.1 Primary objective

- To determine if chloroquine/ hydroxychloroquine prophylaxis prevents symptomatic COVID-19 infection in the study population.

4.1.1 Primary endpoint

- The proportions of symptomatic COVID-19 infections will be compared between the chloroquine or hydroxychloroquine and placebo groups.

4.1.2 Secondary objectives and endpoints

- To determine if chloroquine/hydroxychloroquine prophylaxis attenuates the severity of COVID-19 infections.
- In all participants, the severity of infection will be compared between the two groups using a predefined severity score
- To determine if chloroquine/hydroxychloroquine prophylaxis prevents asymptomatic COVID-19 infection.
    - The proportions of asymptomatic cases of COVID-19 will be determined by comparing acute and convalescent serology in the two groups.
- To determine if chloroquine/hydroxychloroquine prophylaxis prevents and attenuates all-cause symptomatic acute respiratory illnesses.
    - The proportions and severity of symptomatic acute respiratory illnesses will be compared between the chloroquine/hydroxychloroquine and placebo groups.

4.1.3 Tertiary objective and endpoint

- To characterise genetic and baseline biochemical markers associated with symptomatic COVID-19, respiratory illness and disease severity
- Genetic loci and levels of biochemical components will be correlated with frequency of COVID-19, ARI and disease severity.
- To assess the impact of chloroquine or hydroxychloroquine prophylaxis on work and behaviour during the pandemic.

- The days lost to work, and the relationship between the subjective assessment of well-being and the decision to self-isolate when unwell (i.e. not go to work) will be examined in relation to the infection and treatment arm.
-
- To perform health economic analyses to assess the impact of chloroquine or hydroxychloroquine prophylaxis on costs and quality of life measures.
- The trial will collect data on use of health care resources and health related quality of life (EQ-5D-3L) to determine the effects between treatment groups.

Study design

The study is a double-blind, randomised, placebo-controlled trial that will be conducted in the study population. We will recruit participants, who can be followed reliably for up to 5 months. 40,000 participants were planned to be recruited and we predicted an average of 400-800 participants per site in 50-100 sites.

The participants will be randomised in Asia to receive either chloroquine or placebo (1:1 randomisation), and in Europe and Africa, to hydroxychloroquine or placebo (1:1 randomisation). The randomisation list will be prepared by the trial statistician using block randomisation and sent to the drug companies for drug packaging. The randomisation procedure will be stratified by site.

4.2 Determination of sample size

The sample size calculations were based on an assumption of 3% incidence of symptomatic COVID-19 during the trial period. Expert opinion considers that if chloroquine/ hydroxychloroquine is effective, it may decrease symptomatic COVID-19 by approximately 23%, and therefore, the chloroquine/ hydroxychloroquine arm would have a 2.31% incidence of COVID-19 diagnosis. A 95% confidence interval with 80% power would require 8,520 subjects randomised to each arm. We aimed to enrol 10,000 subjects in each arm in the two trials which allows for a 20% LTFU, withdrawal rate, protocol deviation and non-adherence. Thus 20,000 would be randomised in Asia and 20,000 in Europe/Africa.

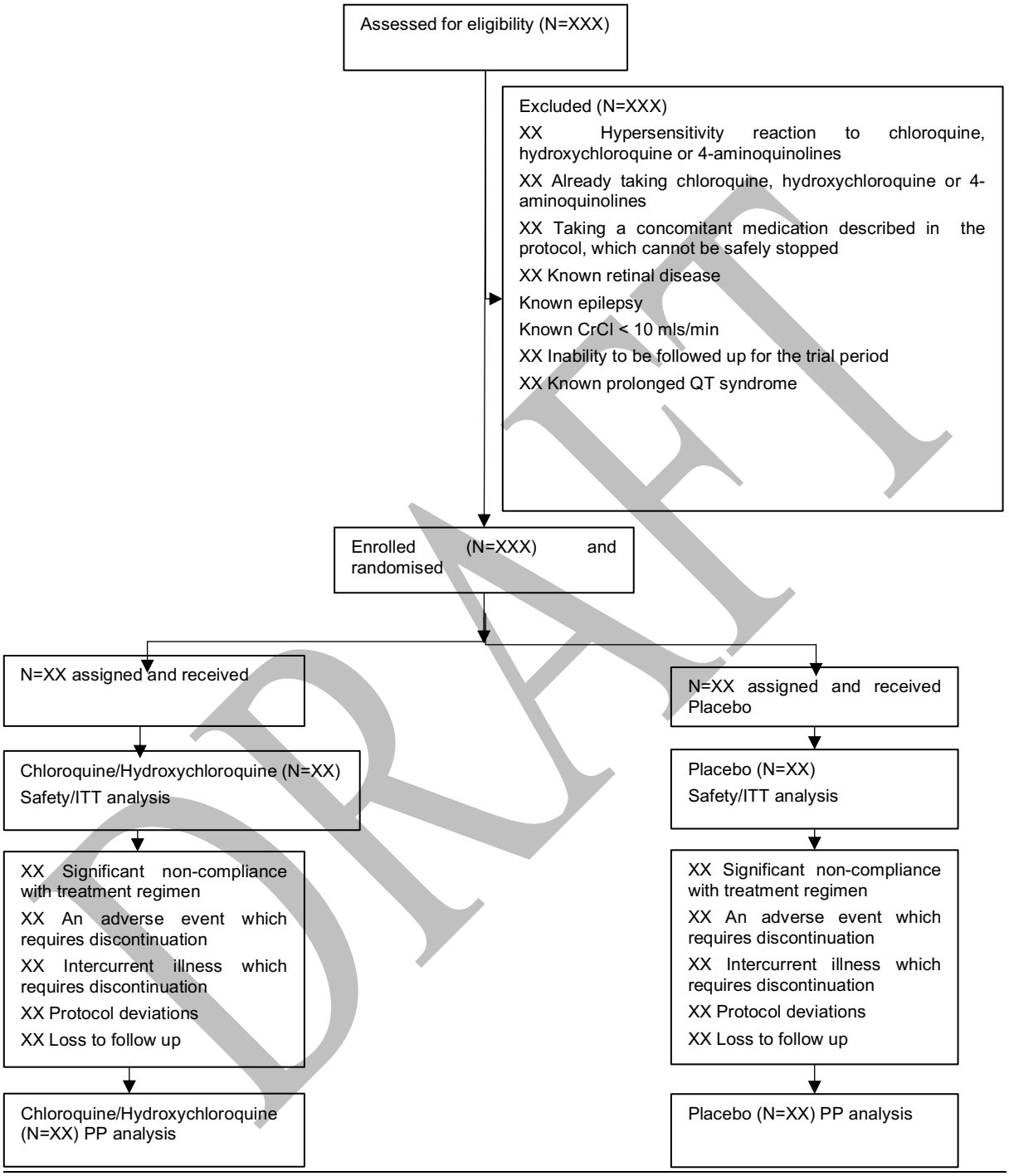
With repeated waves of COVID-19 during the study the sample size calculations have been updated during the study. The possibility of pooling data from chloroquine/ hydroxychloroquine arms (same mechanism of action) as well as with other similar studies, has justified continuation, although the original 40,000 was not feasible due to practical reasons.

5 Data Analysis

5.1 Trial Profile

The number of patients who will be screened, reasons for non-enrolment, number of patients randomised, number of patients lost to follow up and the number of patients assessed for the primary endpoint will be summarised in a CONSORT flow diagram, as shown in Figure 1, below.

Figure 1 Consort Trial Profile by Arms



5.2 Demographics and other baseline characteristics

The following baseline characteristics will be described by study arm as shown in table 1 (below). Skewed continuous variables such as age will be summarised using median with interquartile range (IQR). Continuous variables such as weight, height and temperature will be summarised using the mean with the standard deviation. Categorical variables such as sex, presence of fever, at baseline will be summarised using frequencies and percentages.

Table XXX. Baseline Characteristics of participants by study arm

Characteristics		**Chloroquine/Hydroxychloroquine (N=XX)**	**Placebo (N=XX)**
Age (years), med (IQR)		XX.X (XX.X-XX.X)	XX.X (XX.X-XX.X)
Sex	Male, n (%)	XX (XX.X)	XX (XX.X)
Temperature C, mean (SD)		XX (XX.X)	XX (XX.X)
Temperature ≥37·5°C	N (%)	XX (XX.X)	XX (XX.X)
Weight (kg), mean (SD)		XX.X (XX.X)	XX.X (XX.X)
Height (cm), mean (SD)		XX.X (XX.X)	XX.X (XX.X)
BMI **kg**/m^2			
Occupation	Doctor, n (%)	XX (XX.X)	XX (XX.X)
	Nurse, n (%)	XX (XX.X)	XX (XX.X)
	Healthcare assistant, n (%)	XX (XX.X)	XX (XX.X)
	Occupational therapist, n (%)		
	Physiotherapist, n (%)		
	Pharmacist, n (%)	XX (XX.X)	XX (XX.X)
	Dietician, n (%)	XX (XX.X)	XX (XX.X)
	Cleaner, n (%)	XX (XX.X)	XX (XX.X)
	Social Worker, n (%)		
	Other (health worker), n (%)	XX (XX.X)	XX (XX.X)
	Other (non-health worker), n (%)	XX (XX.X)	XX (XX.X)
Smoker	Yes, n (%)	XX (XX.X)	XX (XX.X)
COVID-19 in Household	Yes, n (%)	XX (XX.X)	XX (XX.X)
	No, n (%)	XX (XX.X)	XX (XX.X)
	Unknown, n (%)	XX (XX.X)	XX (XX.X)
Place of work for healthcare workers	Outpatients, n (%)	XX (XX.X)	XX (XX.X)

	Intensive Care Unit, n (%)	XX (XX.X)	XX (XX.X)
	Medical Ward, n (%)	XX (XX.X)	XX (XX.X)
	Accident and Emergency, n (%)	XX (XX.X)	XX (XX.X)
	Paediatrics, n (%)		
	Other, n (%)	XX (XX.X)	XX (XX.X)
Existing co-morbidities	Yes, n (%)	XX (XX.X)	XX (XX.X)
Chronic pulmonary disease (not asthma)	Yes, n (%)	XX (XX.X)	XX (XX.X)
Asthma (physician diagnosed)	Yes, n (%)	XX (XX.X)	XX (XX.X)
Chronic kidney disease	Yes, n (%)	XX (XX.X)	XX (XX.X)
Liver disease	Yes, n (%)	XX (XX.X)	XX (XX.X)
AIDS / HIV	Yes, n (%)	XX (XX.X)	XX (XX.X)
Diabetes	Yes, n (%)	XX (XX.X)	XX (XX.X)
Hypertension	Yes, n (%)	XX (XX.X)	XX (XX.X)
Cancer	Yes, n (%)	XX (XX.X)	XX (XX.X)
Condition requiring immunosuppressive	Yes, n (%)	XX (XX.X)	XX (XX.X)
Ischaemic heart disease	Yes, n (%)	XX (XX.X)	XX (XX.X)
High Cholesterol	Yes, n (%)	XX (XX.X)	XX (XX.X)
Other	Yes, n (%)	XX (XX.X)	XX (XX.X)
Baseline symptoms			
Fever	Yes, n (%)	XX (XX.X)	XX (XX.X)
Cough	Yes, n (%)	XX (XX.X)	XX (XX.X)
Sore throat	Yes, n (%)	XX (XX.X)	XX (XX.X)
Rhinorrhoea	Yes, n (%)	XX (XX.X)	XX (XX.X)
Wheezing	Yes, n (%)	XX (XX.X)	XX (XX.X)
Anosmia	Yes, n (%)	XX (XX.X)	XX (XX.X)
Chest pain	Yes, n (%)	XX (XX.X)	XX (XX.X)
Myalgia	Yes, n (%)	XX (XX.X)	XX (XX.X)
Arthralgia	Yes, n (%)	XX (XX.X)	XX (XX.X)

Shortness of breath on exertion	Yes, n (%)	XX (XX.X)	XX (XX.X)
Shortness of breath at rest	Yes, n (%)	XX (XX.X)	XX (XX.X)
Fatigue/ malaise	Yes, n (%)	XX (XX.X)	XX (XX.X)
Itching	Yes, n (%)	XX (XX.X)	XX (XX.X)
Headache	Yes, n (%)	XX (XX.X)	XX (XX.X)
Dizziness	Yes, n (%)	XX (XX.X)	XX (XX.X)
Visual Disturbance	Yes, n (%)	XX (XX.X)	XX (XX.X)
Abdominal pain	Yes, n (%)	XX (XX.X)	XX (XX.X)
Anorexia	Yes, n (%)	XX (XX.X)	XX (XX.X)
Nausea	Yes, n (%)	XX (XX.X)	XX (XX.X)
Vomiting	Yes, n (%)	XX (XX.X)	XX (XX.X)
Diarrhoea	Yes, n (%)	XX (XX.X)	XX (XX.X)
Rash	Yes, n (%)	XX (XX.X)	XX (XX.X)
Other	Yes, n (%)	XX (XX.X)	XX (XX.X)

5.3 Comparisons of incidence rates of symptomatic COVID-19 infections between the chloroquine or hydroxychloroquine and placebo groups

A mixed effects Negative Binomial model will be used to model the incidence of symptomatic COVID-19 infection to obtain incidence rate ratios comparing the chloroquine/ hydroxychloroquine arm with the placebo. Repeated measures will be taken into account in the mixed effects model. Incidence rate ratios and the corresponding 95% confidence intervals will be obtained and reported.

As much as possible graphical methods will be used to show trends in the incidence of symptomatic COVID-19 over time and by arm. If the Negative Binomial models fail to converge, as is the characteristic of these models when the outcome is rare, a Binomial regression model will be considered to model the risk/ odds of symptomatic COVID-19 infection to obtain risk differences/ odds ratios as appropriate comparing the chloroquine/ hydroxychloroquine arm with placebo.

Survival methods will be used to estimate the time to COVID-19 infection and also as a method of handling missing data in case of dropouts. In this approach, participants without outcomes will be censored at their longest observed time. Cumulative risk curves will be compared using the logrank test. In the survival approach, participants in which study drugs are discontinued and/ or endpoints are not available due to other reasons (such as withdrawal from the study, loss to follow up) will be censored or treated as competing risks, as appropriate, from the moment of occurrence of one of these events in the ITT analyses.

Table XX Comparisons of incidence rate of symptomatic COVID-19 infections between the chloroquine or hydroxychloroquine and placebo groups

n/N, (%)		**IRR (XX% CI, p-value)**
Chloroquine/ hydroxychloroquine (N=XX)	Placebo (N=XX)	
XX/XXX (XX.X)	XX/XXX (XX.X)	XX.X (XX.X - XX.X, 0.XXX)

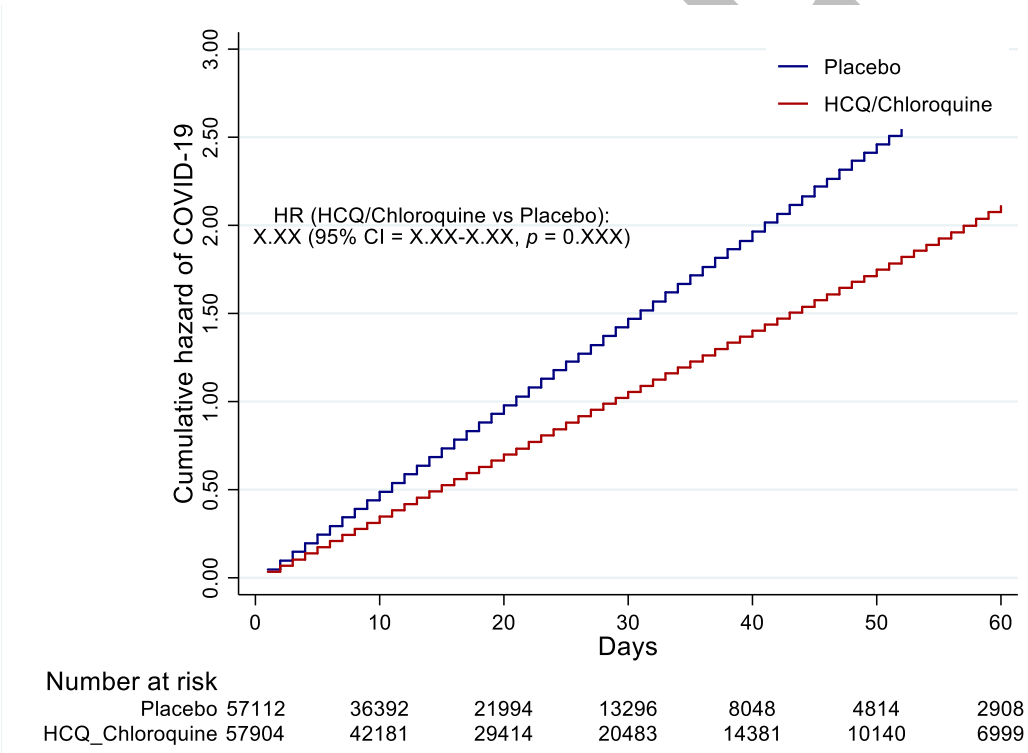


Figure XXX The Kaplan-Meier curves of cumulative hazard of developing COVID-19 in the Chloroquine/ hydroxychloroquine (HCQ) or Placebo (DUMMY Figure)

5.4 Safety Chloroquine/hydroxychloroquine

The table below summaries the adverse events

Table XX Adverse events during follow up.

Adverse events	**Chloroquine/ hydroxychloroquine**		**Placebo**	
Number of subjects	XX		XX	
AEs results in subject not going to work	XX/XXX (XX.X)		XX/XXX (XX.X)	
AEs interfering with quality of life	XX/XXX (XX.X)		XX/XXX (XX.X)	
Serious adverse events (SAEs), n/N, (%)	XX/XXX (XX.X)		XX/XXX (XX.X)	
Deaths, n/N, (%)	XX/XXX (XX.X)		XX/XXX (XX.X)	
Possible, probable or definite drug related SAEs, n/N, (%)	XX/XXX (XX.X)		XX/XXX (XX.X)	
Grading of adverse events, n/N, (%)	2	3-4	2	3-4
Symptoms, n/N (%)	**X/XX (X.X)**	**X/XX (X.X)**	**X/XX (X.X)**	**X/XX (X.X)**
XXXXXXX	X/XX (X.X)	X/XX (X.X)	X/XX (X.X)	X/XX (X.X)
XXXXXXX	X/XX (X.X)	X/XX (X.X)	X/XX (X.X)	X/XX (X.X)
XXXXXXX	X/XX (X.X)	X/XX (X.X)	X/XX (X.X)	X/XX (X.X)
XXXXXXX	X/XX (X.X)	X/XX (X.X)	X/XX (X.X)	X/XX (X.X)
XXXXXXX	X/XX (X.X)	X/XX (X.X)	X/XX (X.X)	X/XX (X.X)
XXXXXXX	X/XX (X.X)	X/XX (X.X)	X/XX (X.X)	X/XX (X.X)
XXXXXXX	X/XX (X.X)	X/XX (X.X)	X/XX (X.X)	X/XX (X.X)
XXXXXXX	X/XX (X.X)	X/XX (X.X)	X/XX (X.X)	X/XX (X.X)
XXXXXXX	X/XX (X.X)	X/XX (X.X)	X/XX (X.X)	X/XX (X.X)
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XXXXXXX	X/XX (X.X)	X/XX (X.X)	X/XX (X.X)	X/XX (X.X)
XXXXXXX	X/XX (X.X)	X/XX (X.X)	X/XX (X.X)	X/XX (X.X)
XXXXXXX	X/XX (X.X)	X/XX (X.X)	X/XX (X.X)	X/XX (X.X)
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XXXXXXX	X/XX (X.X)	X/XX (X.X)	X/XX (X.X)	X/XX (X.X)
XXXXXXX	X/XX (X.X)	X/XX (X.X)	X/XX (X.X)	X/XX (X.X)
XXXXXXX	X/XX (X.X)	X/XX (X.X)	X/XX (X.X)	X/XX (X.X)
XXXXXXX	X/XX (X.X)	X/XX (X.X)	X/XX (X.X)	X/XX (X.X)

6 Meta-Analysis

A number of other studies have also published results on the use of chloroquine/ hydroxychloroquine vs placebo in order to determine if chloroquine or hydroxychloroquine prophylaxis prevents symptomatic COVID-19 infection.

However, the majority of previous studies were small and not powered to show some desired detectable difference between the chloroquine/ hydroxychloroquine vs placebo. The manuscript from our study will present the results of the trial primary outcome and also include a meta-analysis section of the previous studies plus this trial. The resulting manuscript will firstly focus on the results of this trial (COPCOV) and then combine these results with other trial results in a Meta-Analysis. This approach will help to provide stronger evidence of the expected outcome in the population. Since the results of meta-analyses are also key findings, these will also be summarised in the abstract along with the main trial findings for the primary outcome. A systematic review will be done in order to search for the relevant randomised trials with similar design and analysis approach to be included in the meta-analysis. The relevant search engines such as Medline will be utilised. The number and proportion of participants with a success outcome will be presented for each study by arm. In addition, the measure of effect such as risk ratio/odds ratio or risk difference with corresponding 95% confidence intervals will be presented in a meta-analysis forest plot. The I^2 statistic will be used to show the percentage of total variation across studies resulting from trial heterogeneity rather than chance, with the p value of significance included.

7 Secondary objectives and endpoints

7.1 Comparison of severity and duration of COVID between the chloroquine/ hydroxychloroquine and placebo using a severity score.

A continuous severity score will be used to assess the severity of COVID-19, specifically taking into account the duration of illness. It has been adapted from the WHO COVID-19 Therapeutic Trial Synopsis guidelines (February, 2020).[1]

Each trial participant will be scored with a number varying from zero to 10^9 (death due to COVID-19). Participants who remain well throughout the trial, are ill due to other reasons than COVID-19 or have asymptomatic COVID-19 infection will be assigned a score of zero implying that they all have tied ranks equal to 1 (Group 0).

We will use a rank-based mixed model approach to analyse these scores, stratified by site (hospital) [1]. For site *i*, the Wilcoxon-Mann-Whitney estimate of the site-specific effect is denoted θ_i. We will use an ANOVA F test of the null hypothesis that $\theta_1=\theta_2=\ldots=\theta_N=1/2$ where N is the total number of sites [1] .

[1] https://www.who.int/blueprint/priority-diseases/key-action/novel-coronavirus/en/

7.1.1 Severity score table

Outpatient		
Group	**Score/day**	**Definition**
1	1	Feels unwell (reported on app but no specific symptoms)
2	5	Sore throat, runny nose, myalgia (not significantly limiting mobility), oral temperature ≥ 38°C
3	25	Cough
4	250	Only able to leave chair/bed for short periods (~15mins) due to severe symptoms
5	500	Shortness of breath on exertion
6	1,000	Shortness of breath at rest

Inpatient: hospitalised on clinical grounds (not for control/ isolation reasons)*		
Group	**Score/day**	**Definition**
7	10^4	Not requiring supplemental oxygen
8	10^5	SpO_2 < 94% (RA) or requiring** supplemental oxygen via face mask or nasal prongs
9	10^6	SpO_2 < 90% (RA) or requiring** supplemental high-flow oxygen or non-invasive ventilation
10	10^7	Requiring** intubation and mechanical ventilation
11	10^8	Ventilation and additional organ support (vasopressors, renal replacement therapy) or ECMO criteria met
12	10^{10}	Death

* Patient must be hospitalised due to illness severity (the opinion of the admitting physician is such that the patient cannot be safely managed out of hospital) and not for public health control/isolation reasons or legislation

** Either receipt of supplemental oxygen via this route OR in the opinion of the treating physician this was required but not administered (e.g. due to resource constraints)

The least severe symptomatic group (Group 1) is given a baseline score of 1 per day of symptoms (arbitrary choice, this does not influence the statistical analysis which is rank based). Each ordinal grouping, from Groups 2-12, is then assigned a relative increase in severity. For example, Group 2 is considered 5x worse than Group 1, whereas Group 5 is considered 100x worse than Group 2.

Scores are calculated on a daily basis (the average of the participants' two half-daily self-ratings via the mobile application). The final score of a symptomatic participant is defined as the sum of the scores for the period of symptoms associated with COVID-19.

By performing daily scoring with scores that are linear on a logarithmic scale, we can use the duration of symptoms to rank severity between participants, safeguarding that the most significant symptoms will dominate the final score.

For example, a participant who feels unwell for 3 days but no specific symptoms (Group 1), followed by 2 days of shortness of breath on exertion (Group 5) and then 4 days of cough (Group 3) would have a total score of 1x3 + 500x2 + 25x4 = 1003.

7.2 Determining if chloroquine or hydroxychloroquine prophylaxis prevents asymptomatic COVID-19 infection.

The number of asymptomatic cases of COVID-19 will be determined by comparing baseline and end of trial serology between chloroquine/ hydroxychloroquine and the placebo arms (as defined in section **2.1**). The proportions will be obtained and risk differences along with the 95% confidence intervals will be calculated and reported.

Table XX Comparison of incidence rates of asymptomatic cases of COVID-19 with acute and convalescent serology between chloroquine or hydroxychloroquine and the placebo

n/N, (%)		**IRR** **(XX% CI, p-value)**
Chloroquine/ Hydroxychloroquine (N=XX)	Placebo (N=XX)	
XX/XXX (XX.X)	XX/XXX (XX.X)	XX.X (XX.X - XX.X, 0.XXX)

7.3 Determining if chloroquine/ hydroxychloroquine prophylaxis prevents all-cause symptomatic acute respiratory illnesses.

The number and severity of symptomatic acute respiratory illnesses will be compared between the chloroquine/ hydroxychloroquine and placebo groups. The proportions will be obtained and risk differences along with the 95% confidence intervals will be calculated and reported to assess the difference in the proportions of symptomatic acute respiratory illnesses. Number will be assessed as per the methodology of **5.3**. Severity will be assessed as per the methodology of **6.1**. Subgroup analyses will occur for symptomatic acute respiratory illnesses excluding those with SARS-CoV-2 detected and in other individual respiratory viruses.

The severity of the symptomatic acute respiratory illnesses will be summarised as frequencies and percentages. The Poisson distribution will be used to calculate the incidence rates of severe symptomatic acute respiratory illnesses. The incidence rate ratios and the corresponding 95% confidence intervals will be obtained and used to compare the incidence rates of severe symptomatic acute respiratory illnesses between chloroquine/ hydroxychloroquine and the placebo. Tests of significance will be performed at 5% significance level.

Table XX: Comparison the proportion of symptomatic acute respiratory between the chloroquine or hydroxychloroquine and placebo groups.

n/N, (%)		**IRR** **(XX% CI, p-value)**
Chloroquine/Hydroxychloroquine (N=XX)	Placebo (N=XX)	
XX/XXX (XX.X)	XX/XXX (XX.X)	XX.X (XX.X - XX.X, 0.XXX)

7.4 Tertiary objective and endpoint

- To characterise genetic and baseline biochemical markers associated with symptomatic COVID-19, respiratory illness and disease severity
- Genetic loci and levels of biochemical components will be correlated with frequency of COVID-19, ARI and disease severity.

- To assess the impact of chloroquine or hydroxychloroquine prophylaxis on work and behaviour during the pandemic.
- The days lost to work, and the relationship between the subjective assessment of well-being and the decision to self-isolate when unwell (i.e. not go to work) will be examined in relation to the infection and treatment arm.

- To perform health economic analyses to assess the impact of chloroquine or hydroxychloroquine prophylaxis on costs and quality of life measures.
- The trial will collect data on use of health care resources and health related quality of life (EQ-5D-3L) to determine the effects between treatment groups.

8 References

[1] Boos, Dennis D., and Cavell Brownie. "A rank-based mixed model approach to multisite clinical trials." *Biometrics* (1992): 61-72.