Is hydroxychloroquine protective against the risk of COVID-19 infection and severe outcomes?

Study Protocol

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This is a collaboration between the following institutions as part of OpenSAFELY.org:

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- Electronic Health Records Research Group, Department of Non-communicable Disease Epidemiology, London School of Hygiene and Tropical Medicine

Introduction

Hydroxychloroquine, a derivative of chloroquine, is a commonly used 4-aminoquinoline anti-malarial drug. It is included in the WHO Essential Medicines List[1] and is also indicated for the treatment of systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), and certain dermatological conditions in the United Kingdom (UK).[2,3] Hydroxychloroquine has gained considerable attention as a candidate treatment for coronavirus disease 2019 (COVID-19) with debates around its widespread use despite little evidence of efficacy and well-documented adverse effects.[4] There is also interest in its potential use as prophylaxis against SARS-CoV-2 infection and progression to more serious disease. Following demonstrations of *in vitro* inhibition of SARS-CoV-2[5,6] and initial observational reports in humans,[7] substantial research effort has gone into testing its potential treatment and prophylactic benefit.[8] Additional research has suggested that the therapeutic effect of hydroxychloroquine for COVID-19 may be enhanced through combination with azithromycin, a macrolide antibiotic.[9]

Pharmaceutical interventions in COVID-19 may be effective at different stages of the process from infection with SARS-CoV-2, through initial pre-symptomatic viral replication to symptomatic disease, then becoming severe disease requiring oxygen to the final stages of disease often with a cytokine storm, coagulation effects and then death. Most randomised trials have looked at the use of hydroxychloroquine at later stages focusing on hospitalised patients. Its use in earlier stages has been less studied. In addition, doses used in later-stage disease treatment have often been very high, while the doses in its licensed indications has been lower.

The US Food and Drug Administration issued an Emergency Use Authorisation (EUA)[10,11] for use of hydroxychloroquine for the treatment of COVID-19 on 28 March 2020, but later cautioned against the use of the drug outside of clinical trials[12] and ultimately revoked the EUA on 15 June 2020.[13,14] Other countries have produced variable guidance on how hydroxychloroquine should be used .[15,16] The recent retraction of an influential observational study led to further questions around the efficacy and safety of hydroxychloroquine in COVID-19. The study,[17] which after publication led to ongoing clinical trials to review their safety data, was retracted on 4 June 2020 due to lack of transparency leading to serious data validity concerns. Even in light of these events, the question about the effectiveness of hydroxychloroquine for the prevention of COVID-19 remains to be properly addressed in real-world data.

A living systematic review[8] identified four randomised controlled trials (RCTs), 10 cohort studies, and nine case series assessing hydroxychloroquine as a treatment for COVID-19, but no studies evaluating prophylaxis. The authors concluded “that there is insufficient and often conflicting evidence on the benefits and harms of using hydroxychloroquine or chloroquine to treat COVID-19. As such, it is impossible to determine the balance of benefits to harms.” An RCT examining hydroxychloroquine for post-exposure prophylaxis has since failed to demonstrate a significant benefit in preventing infection, although the findings were compatible with an absolute risk reduction as much as 7% in the context of an absolute risk of about 14% in the placebo arm.[18] Interim data from the RECOVERY trial[19] in the UK showed no benefit to

treatment with hydroxychloroquine in hospitalised COVID-19 patients. The investigators halted all enrollment in the hydroxychloroquine arm of the trial. This follows substantial evidence from numerous observational studies showing no clinical benefit to hydroxychloroquine treatment in COVID-19 patients.[20–22]

The UK Medicines Agency (MHRA) on 16 June 2020 "instructed UK clinical trialists using hydroxychloroquine to treat or prevent coronavirus (COVID-19) to suspend recruitment of further participants."[23] They said, "We followed the emerging concerns about use of hydroxychloroquine in COVID-19, and took into consideration the results from two different trials, including the UK's RECOVERY trial which has provided convincing evidence of no meaningful mortality benefit in hospitalised patients with COVID-19" but it is clear that the amount of randomised evidence in trials for prophylaxis was limited at that date. On 26 June 2020, the UK MHRA released their decision to allow for continued recruitment into the COPCOV trial investigating hydroxychloroquine in prevention of COVID-19.[24]

Randomised clinical trials (RCTs) remain the gold standard to study the effect of drugs on clinical outcomes. As we await the completion and full reporting of ongoing clinical trials, real-world evidence regarding any protective effect of hydroxychloroquine for COVID-19 can be generated through the analysis of observational data. The routine use of hydroxychloroquine in UK primary care settings for the treatment of RA and SLE presents an opportunity to examine whether those already on hydroxychloroquine at the start of the outbreak in the UK showed lower risk of COVID-19 outcomes. The aim of this project is to evaluate whether hydroxychloroquine use prior to the COVID-19 outbreak in the UK provided protection against COVID-19 infection, or severe outcomes among those with COVID-19. We will use data from the new OpenSAFELY platform of linked national electronic health records and registry data representing 40% of the UK population, which provides the size and detailed clinical information needed to perform these analyses. The OpenSAFELY platform has been used for two studies thus far related to factors associated with COVID-19-related mortality[25] and to the effects of inhaled corticosteroids.[26]

Objectives

The specific objectives of the study are:

Primary Objectives

1. Estimate the effect of HCQ compared to no HCQ use on the risk of COVID-19 ONS death in a population with RA or SLE, adjusted for confounding variables.

Secondary Objectives

2. Estimate the effect of HCQ compared to no HCQ use on the risk of non-COVID-19 ONS death in a population with RA or SLE, adjusted for confounding variables.

Exploratory Objectives

1. For the outcome of COVID-19 ONS death, estimate whether any effect of HCQ use varies by exposure to co-prescribed medications (e.g., other DMARD, macrolide antibiotics, NSAIDs, steroids, biologics). (pending data availability/sufficient power).
2. Estimate the effect of HCQ compared to no HCQ use on the risk of testing positive for COVID-19 in a population with RA or SLE, adjusted for confounding variables. (depending on data availability/completeness)

Methods

Data Source

We will use data from general practice (GP) records, obtained from the GP software provider The Phoenix Partnership (TPP), linked to outcomes data as described below. The data will be accessed, linked and analysed through OpenSAFELY.org - a new data analytics platform created to address urgent questions relating to the epidemiology and treatment of COVID-19 in England, hosted by TPP. OpenSAFELY provides a secure software interface that allows NHS records to be pseudonymised, linked and analysed in near real-time; the GP patient data held on OpenSAFELY never leaves TPP's secure environment; other datasets are linked to it.

The research dataset analysed through OpenSAFELY is based on GP records retrieved from the TPP SystmOne electronic health record system. These data include diagnoses, medicines, physiological parameters, such as body mass index and vital signs, prior investigations, such as blood test results, and basic socio-demographics for almost 24 million individuals – approximately 40% of the English population. Data extracted by TPP SystmOne have previously been used in medical research, as part of the ResearchOne dataset. These records were subsequently linked to data from a number of other organisations who were directed under the Health Service (Control of Patient Information) Regulations 2002 to make their data available for COVID-19 research with the openSAFELY initiative. Currently, linkage is possible to: (1) the NHSE/NHSX Emergency Care Data Set (ECDS), which contains data on emergency attendance at A&E clinics across England; (2) the NHSE/NHSX Second Generation Surveillance System (SGSS) data on SARS-COV-2 test results; (3) the Intensive Care National Audit & Research Centre (ICNARC) Case Mix Programme, containing data on COVID-19 related Intensive Treatment Units (ITU) admissions; (4) the NHSE/NHSX COVID-19 Patient Notification System (CPNS) data on deaths among COVID-19 inpatients occurring in hospitals; and (5) Office for National Statistics (ONS) death data, which includes information on all deaths, including those due to non-COVID-19 causes as well as those occurring outside the hospital setting.

All data is held in a secure research environment hosted by TPP, which is a Tier 3 data centre, accredited to NHS Digital standards for centrally hosted clinical systems (ISO 27001 standard and IG Toolkit version 2).

Study Design and Population

We will use a population-based cohort design to address our research questions. From the raw data, we will select individuals using the following inclusion and exclusion criteria:

Inclusion Criteria

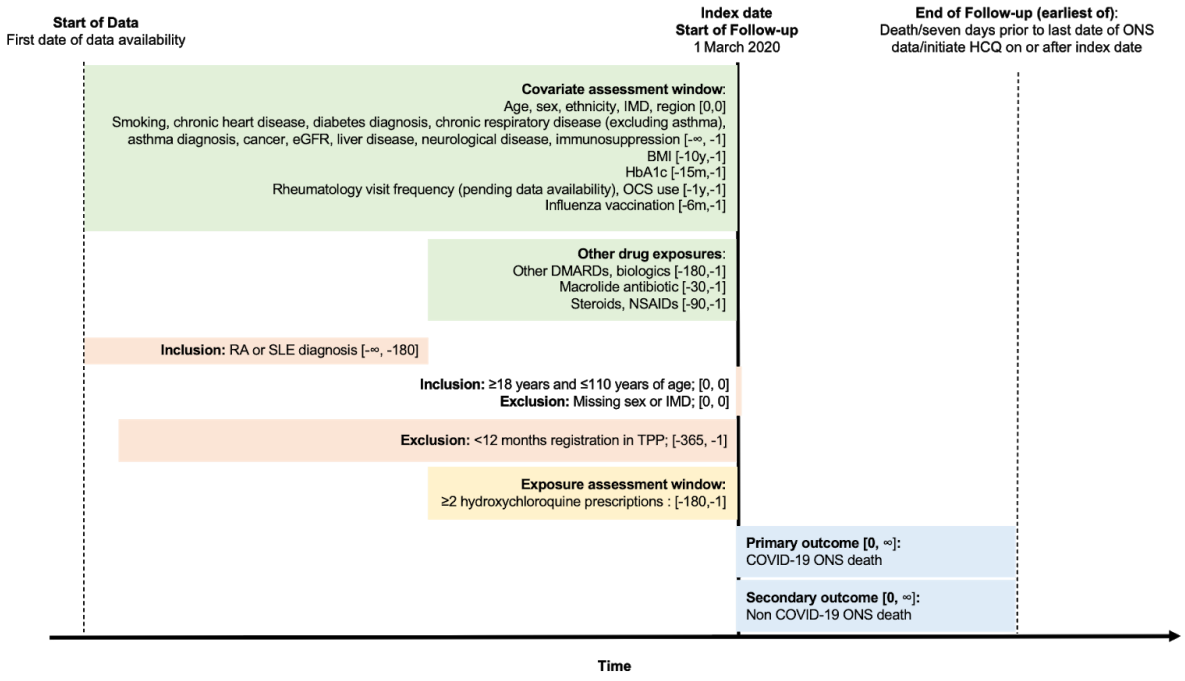
1. Ever diagnosed with RA or SLE before 1 September 2019
2. ≥18 and ≤110 years of age on 1 March 2020

Exclusion Criteria

1. Any prescription of chloroquine phosphate or chloroquine sulfate between 1 September 2019 and 1 March 2020
2. Less than 12 months of registration in a TPP practice as of 1 March 2020, which could preclude adequate ascertainment of confounding variables
3. Missing sex or index of multiple deprivation (IMD).

A graphical illustration of the study design is provided in Figure 1.

Figure 1. Illustration of the Study Design



Study Measures

Discussions and decisions on every measure have been documented before implementing the final underlying code to complete the analysis. Detailed information on compilation and sources for every individual codelist is available at https://codelists.opensafely.org/ and the lists are available for inspection and re-use by the broader research community.

Exposure

The exposure of interest is use of HCQ compared to no use of HCQ in a population of patients with diagnosed RA or SLE prior to 1 March 2020, to capture usage in pre-COVID-19 conditions. This date was chosen due to reports of substantial early and over-ordering of medicines and appeals by the NHS not to extend prescription durations in March[27]. Therefore prescribing patterns from March may not represent usual usage e.g. with respect to levels of adherence.

After applying inclusion and exclusion criteria as listed above, all individuals at this stage will belong to one of the following groups (Table 1). Links are provided to codelists for these variables.

Table 1. Operational Definition for the Drug Exposure of Interest

Variable	Variable level	Category	Definition	Timeframe
Drug Exposure	0	No HCQ (comparator group)		180 days prior to 1 March 2020
	1	HCQ	Two or more prescriptions for: ● Hydroxychloroquine Sulfate (1001030C0) OpenCodelist (HCQ)	

In RA, treatment patterns tend to be like the following:

1. First line for people with mild disease typically HCQ only.
2. If disease progresses, typically start on methotrexate (MTX) or sulfasalazine (SSZ).
3. Common to initiate or build up to triple combination therapy (MTX+SSZ+HCQ).
4. If disease isn't controlled on these 'traditional or non-biologic DMARDs', then biologics are added. Usually in combination to the non-biologic DMARDs rather than switching to biologic monotherapy. MTX is typically co-prescribed with biologics unless prior

problems with it (side effects or inefficacy). Thus, of patients on biologics, it would be not uncommon for them also to be on HCQ.

Given these treatment patterns, we will extract information on exposures to other DMARDs, including biologics (pending data availability), and explore confounding and interaction with these other medication exposures.

Follow up and Outcomes

The primary outcome is COVID-19 death from ONS. Individuals will be followed from 1 March 2020, considered the start of risk for experiencing the outcomes due to the dynamics of the coronavirus outbreak in the UK. Individuals who do not experience the outcome of interest will be censored at the earliest of:

- Seven days prior to the last date of ONS data availability (to account for a week lag of data availability)
- Death due to other causes recorded in ONS
- Initiate DMARD on or after 1 March 2020

Table 3. Operational Definition for the Primary Outcome Variable

Variable	Definition	Timeframe
COVID-19 Death	Death information from ONS will be used to capture deaths occurring in and out of hospitals with laboratory confirmed or suspected COVID-19. ICD-10 codes will be used to identify COVID-19 related deaths in ONS: ● U07.1 COVID-19, virus identified (assigned to a disease diagnosis of COVID-19 confirmed by laboratory testing) ● U07.2 COVID-19, virus not identified (assigned to a clinical or epidemiological diagnosis of COVID-19 where laboratory confirmation is inconclusive or not available)	On or after 1 March 2020 until seven days prior to the end of data availability (to account for week lag in data completeness)

	Both U07.1 and U07.2 may be used for mortality coding as cause of death[28].	

Covariates

The covariates of interest were chosen following discussion with practising clinicians to identify potentially important determinants of the exposure and outcomes of interest. The covariates which were pre-specified as potentially important confounding variables are listed below. Definitions and code lists are available at https://codelists.opensafely.org/ and are available for inspection and re-use by the broader research community.

Unless otherwise specified, variables were created using diagnostic codes present ever in a patients' medical record.

- Age on 1 March 2020
- Sex
- Ethnicity
- Index of Multiple Deprivation
- Geographic region (STP, n~35)
- BMI, ascertained from weight measurements within the last 10 years, restricted to those taken when the patient was over 16 years old
- Smoking, most recent code prior to 1 March 2020
- Chronic heart disease
- Diabetes, categorised as controlled (HbA1c <58 mmol/mol), uncontrolled (HbA1c ≥58 mmol/mol) or HbA1c not measured in the 15 months prior to 1 March 2020
- Hypertension, defined as diagnosed hypertension
- Chronic respiratory disease (excluding asthma)
- Current asthma, categorised as ≥2 prescriptions of OCS prednisolone in the 6 months prior to 1 March 2020
- Cancer, any
    - https://codelists.opensafely.org/codelist/opensafely/cancer-excluding-lung-and-haematological/
    - https://codelists.opensafely.org/codelist/opensafely/lung-cancer/
    - https://codelists.opensafely.org/codelist/opensafely/haematological-cancer/
- Kidney function, as measured by eGFR
- Liver disease
- Neurological disease, any
    - http://codelists.opensafely.org/codelist/opensafely/stroke-updated/
    - http://codelists.opensafely.org/codelist/opensafely/dementia/
- Immunosuppression, any
  https://codelists.opensafely.org/codelist/opensafely/permanent-immunosuppresion/
  https://codelists.opensafely.org/codelist/opensafely/temporary-immunosuppresion/
- Flu vaccination status, between 1 Sep 2019 and 29 Feb 2020

- NSAIDs, ≥2 prescriptions in the 6 months prior to 1 March 2020
- Other drugs
    - Other DMARD, ≥2 prescriptions in the 6 months prior to 1 March 2020 for primary analysis; ≥1 prescription in the 3 months prior to 1 March 2020 for sensitivity analysis
        - The following medicines are considered Disease Modifying Anti-Rheumatic Drugs or "DMARDs": Azathioprine, Mercaptopurine, Sulfasalazine, Hydroxychloroquine, Ciclosporin, Penicillamine, Leflunomide and Mycophenolate mofetil, methotrexate (Github Codelist)
    - Macrolide antibiotics (i.e., azithromycin, clarithromycin), ≥1 prescription in the 30 days prior to 1 March 2020
    - Biologics for RA, ≥2 prescriptions in the 6 months prior to 1 March 2020 for primary analysis; ≥1 prescription in the 3 months prior to 1 March 2020 for sensitivity analysis
        - Anti-TNF: etanercept, adalimumab, infliximab, certolizumab, golimumab
        - Anti-IL6: tocilizumab**,** sarilumab
        - Anti-B cell therapies: rituximab
        - Anti-IL1: anakinra
        - T-cells: abatacept
        - JAK inhibitors: tofacitinib, baricitinib
    - Biologics for SLE, ≥2 prescriptions in the 6 months prior to 1 March 2020 for primary analysis; ≥1 prescription in the 3 months prior to 1 March 2020 for sensitivity analysis
        - Anti-BLyS (B cell): rituximab, belimumab

Variables to be considered if they become available:

- Number of rheum visits in the year prior to 1 March 2020

Missing Data

In the primary analysis, those with missing BMI will be assumed non-obese and those with missing smoking information will be assumed to be non-smokers on the assumption that both obesity and smoking would be more likely to be recorded if present.

We anticipate ~25% missing data on ethnicity from prior work, in which multiple imputation did not alter conclusions from complete case analyses. Thus, primary models will not be adjusted for ethnicity. However, we will additionally adjust for ethnicity in the fully adjusted model among those who have recorded ethnicity and compare results.

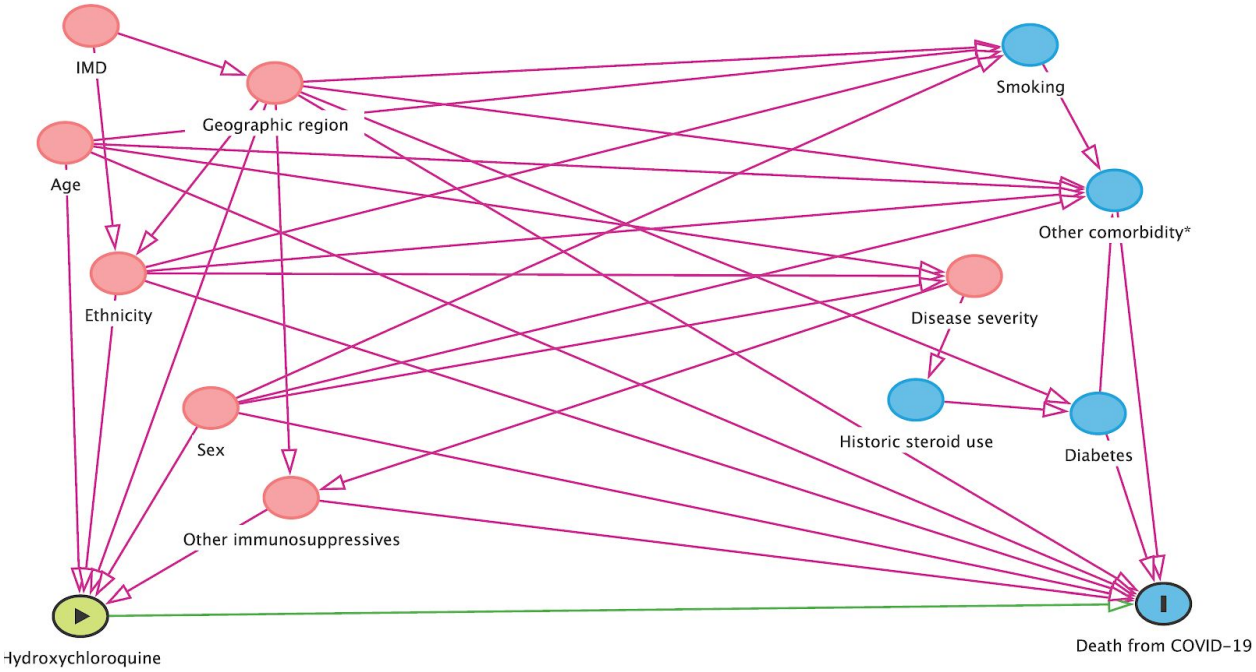
Statistical Analysis

Primary and Secondary Objectives

As a first step, flowcharts showing the number of patients meeting each inclusion and exclusion criteria will be generated. The characteristics of patients will be summarised using descriptive statistics, stratified by exposure status.

Time to death due to COVID-19 as registered by ONS, will be displayed in Kaplan-Meier plots with time in study as the timescale. Cox regression will be used to estimate hazard ratios and 95% confidence intervals for the association between hydroxychloroquine and the outcome. Univariable and age/sex-adjusted models, as well as models using a minimal adjustment set of confounders identified by a directed acyclic graph (DAG) (Figure 2), will be presented. The DAG and resulting minimal adjustment set hinges on the assumption that other immunosuppressives are captured accurately and comprehensively, which eliminates the need to additionally adjust for disease severity.

Figure 2. Directed acyclic graph



Minimally adjusted set: age, sex, ethnicity, geographic region, other immunosuppressives

**Other comorbidities associated with death from COVID-19 but not exposure include: heart disease, lung disease, kidney disease, liver disease, BMI, hypertension, cancer, stroke, dementia, and respiratory disease*

Graphical methods and tests based on Schoenfeld residuals will be used to explore violations of the proportional hazards assumption. Post-hoc models including other adjustments, or removing some adjustment variables may be fit; however, these will be clearly marked as post-hoc exploratory work in the presentation of any results. *A priori* we will determine whether the association between HCQ exposure and death varies by age and exposure to other DMARDs,

macrolide antibiotics, steroids, NSAIDs, or biologics (pending data availability). There are no other pre-specified interactions between the treatment exposure of interest and the clinical variables; however, if an effect is found we will explore whether this varies according to calendar time (pre and post lockdown in the UK, 23 March 2020). This investigation would depend on having a sufficient number of cases in our study population pre-lockdown.

If we detect a non-null association, we will investigate this further through the use of a negative control outcome, as we hypothesise that any effect of HCQ on COVID-19 outcomes may be specific to COVID-19 and may not be expected to be seen with other outcomes. Hydroxychloroquine use is not anticipated to have a marked effect on the risk of dying from non-COVID-19 causes. However, general frailty and disease severity, likely would increase the risk of dying from non-COVID-19 causes. If any association observed is due to confounding - that is, people who receive hydroxychloroquine are sicker or healthier than those who do not - we would expect to be able to observe a similar association with risk of non-COVID-19 death. Analyses will therefore be repeated using non-COVID-19 death over the same time-period as a negative control outcome.

Sensitivity Analyses

We will also conduct a number of sensitivity analyses to evaluate the robustness of our results. This is anticipated to include:

1. **Exposure windows.** In primary analysis, exposure is defined by two or more prescriptions of hydroxychloroquine in the six months prior to 1 Mar 2020. In sensitivity analysis, we will tighten the exposure ascertainment window to 3 months and define exposure by at least one prescription.
2. **Separate populations.** Primary analyses include a cohort of individuals with RA or SLE. Pending sufficient power (i.e. number of outcomes in each population, we will analyse individuals with RA and SLE separately.
3. **Quantitative bias analysis.** For any non-null association, with 95% confidence intervals wholly above or below 1 in the primary analysis, we will conduct a quantitative bias analysis. This will estimate how strong unmeasured confounding would need to be in order to explain the association. We will use Ding and Vanderweele's e-value formulae, alongside probabilistic bias analysis, to estimate how strongly associated one or more unmeasured confounders would need to be with exposure and outcome to fully explain the observed association.
4. **Additional adjustments**. We will supplement the fully adjusted models in primary analysis with models additionally adjusted for other covariates of interest, including comorbidities associated with the outcome, anti-inflammatory medications, and vaccination status.

Exploratory Analyses

Patients switching to a treatment regimen including a monoclonal antibody are likely to stop hydroxychloroquine and other DMARDs (apart from methotrexate). The OpenSAFELY platform is currently in discussions to link in data that would allow us to capture prescribed biologics for this analysis. Pending data availability and sufficient power, we will explore interactions between hydroxychloroquine and monoclonal antibodies, and tocilizumab alone if possible. We anticipate we may only be able to capture prescriptions for monoclonal antibodies in a six month window, which aligns with the exposure ascertainment window for hydroxychloroquine.

OpenSAFELY has conducted linkage to national SGSS COVID-19 testing data, but the data have not yet been used in analysis. Pending confirmation of accurate and complete testing data (as will be done in separate protocols), we will explore using SGSS COVID-19 testing data as an outcome, whereby we estimate associations between HCQ and testing positive for COVID-19, adjusting for the confounders listed above. If these analyses are conducted, we will include a negative control outcome of testing negative for COVID-19.

Table 4. Operational Definition for Secondary Outcome

Variable	Definition	Timeframe
Testing positive for COVID-19	Testing data from SGSS will be using to identify individuals who test positive for COVID-19 SGSS Summary Variables needed are, among those with any positive test: ● First and last positive ● First and last negative ● Number of tests Among those without any positive test: ● First and last negative ● Number of tests	On or after 1 March 2020

It should be noted that more sensitivity analyses may be added based on the initial results of analyses. These will be clearly marked as post-hoc analyses in any reporting of the results.

Table Shells

Note: Table shells are presented for primary objectives only. The tables will be adapted and repeated for secondary objectives as required. Figures are not included as shells.

Figure 1: Flowchart of Patients

Table 1: Descriptive Characteristics

		Total	No HCQ	HCQ
Total				
Age	18-<40			
	40-<50			
	50-<60			
	60-<70			
	70-<80			
	80+			
Gender	Female			
	Male			
BMI	<18.5			
	18.5-24.9			
	25-29.9			

	30-34.9			
	35-39.9			
	Missing			
Ethnicity	White			
	Mixed			
	Asian or Asian British			
	Black			
	Other			
	Missing			
IMD	1 (least deprived)			
	2			
	3			
	4			
	5 (most deprived)			
Smoking	Never			
	Current			
	Former			

	Missing			
Comorbidities	Neurological disease			
	Hypertension			
	Chronic Heart Disease			
	Liver Disease			
	Diabetes			
	Cancer			
	Immunosuppression			
	Kidney function, measured by eGFR			
	Chronic Respiratory Disease (excl. Asthma)			
	Current asthma			
Health seeking behaviour	Influenza vaccination status			
	Number of rheumatology visits in previous year			
Exposure to other medications	Other DMARD			
	Biologics			
	Azithromycin			

	NSAIDs			

Figure 2: Kaplan-Meier Plot of Time to COVID-19 death, stratified by exposure group

[Note: Including number under follow-up at each time-point, for each treatment category]

Table 2: Hazard Ratios (HRs) and 95% confidence intervals (CI) for COVID-19 death

			Crude	Age/Sex Adjusted	DAG Adjusted	DAG+other Adjustments
	Events	**Rate per 1000 PY**	**HR (95% CI)**	**HR (95% CI)**	**HR (95% CI)**	**HR (95% CI)**
No HCQ			1.00	1.00	1.00	1.00
HCQ						

Figure 3: Forest Plots of Hazard Ratios (HRs) and 95% confidence intervals (CI) for COVID-19 death

*Figure 2, Figure 3, and Table 2 will be repeated for *a priori* interactions between HCQ use and:

1. other DMARD
2. macrolide antibiotics

3. NSAIDs
4. steroids
5. biologics

Strengths and Limitations

The strengths of this study will include the size of the source population: OpenSAFELY represents one of the largest EHR databases in the world. This will allow analyses to have as high power as is possible during this stage of the pandemic. Outcomes are being recorded and analysed in near real-time, which will allow the number of outcome events to be maximised and, again, ensuring analyses are as well powered as possible. The richness of the EHR will allow us to characterise patients' medical history with a relatively high degree of accuracy, as we will not be relying on data being collected during the pandemic to characterise comorbidities. This should allow us to better control for confounding by indication compared to studies conducted solely in the hospital setting. Other strengths will include the pre-specified objectives and analysis plan, which will clearly allow readers to see which hypotheses and analyses were planned in advance. Finally, all source code that is used both to define the study population and run the analysis will be made publicly available for other researchers to both re-use and scrutinize.

However, there are also limitations which should be borne in mind when interpreting any results. Notably these limitations would tend to apply to any study addressing this question using observational data, and are not unique to this study. Firstly, although we will attempt to reduce confounding by indication by choosing a restricted study population, as well as adjusting for potentially important confounders, we cannot rule out that confounding by indication will remain after this – either due to variables we have not measured, or those we have measured imperfectly. To aid the interpretation of our results, for all detected associations we will quantify the strength an unmeasured confounder or group of unmeasured/imperfectly measured confounders would need to have to remove the observed association using e-values.

Our analyses are subject to risk of exposure misclassification. We have a broad exposure definition to capture patients who may have stockpiled medication prior to lockdown, and to identify patients who were long-term users of hydroxychloroquine. However, we do not know whether patients with these prescriptions were taking the medications as prescribed, or at the start of the cohort. There is also a potential change in exposure after cohort entry, particularly with widespread reporting of potential associations with HCQ. While we have attempted to capture oral corticosteroid dose, instructions given to patients but not captured in the structured clinical data may mean that this is misclassified.

DMARDs are predominantly prescribed in primary care but there is variation in the "shared care agreements" between GPs and specialists around England. Some patients obtain it from the hospital while others will get it from their GP (demonstrated here on OpenPrescribing). Nationally, we will not capture DMARDs that are being prescribed in secondary care at the start of therapy until shared-care approaches with GPs begin (typically after three months). Hydroxycloroquine has a long half-life, three weeks or more in blood and possibly four months in plasma,[29] so people who we do not classify as current users may continue to have some drug effect from previous exposure.

The DAG we have used to define the minimal adjustment set is based on the assumption that other immunosuppressives are captured accurately and comprehensively, which eliminates the need to additionally adjust for disease severity, measures of which are not captured in primary

care data. However, we will include additional adjustment in sensitivity analyses for other factors related to disease severity such as the presence of lung and kidney disease.

Finally, the degree of risk of SARS-CoV-2 infection may vary which may influence our results since patients were advised to undertake different degrees of isolation according to the DMARDs taken.[30]

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