Trial Title: Platform Randomised trial of INterventions against COVID-19 In older peoPLE

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No potential conflict of interest

Confidentiality Statement

This document contains confidential information that must not be disclosed to anyone other than the Sponsor, the Investigator Team, HRA, host organisation, and members of the Research Ethics Committee and Regulatory Authorities unless authorised to do so.

Protocol signatures continued

Trial Title: Platform Randomised trial of INterventions against COVID-19 In older peoPLE (PRINCIPLE)

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The undersigned has read and understood the trial protocol detailed above and agrees to conduct the trial in compliance with the protocol.

Principal Investigator (Please print name)	**Signature**	**Site name or ID number**	**Date**

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1. KEY TRIAL CONTACTS

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2. LAY SUMMARY

COVID-19 disproportionately affects people over 50 years old with comorbidities and those over 65 years old. The infection causes considerable morbidity and mortality in this population group in particular, and is having a devastating effect on people's health, and society in the UK and internationally.(1-4) So far, there are no specific treatments for COVID-19 that have been proven in rigorous clinical trials to be effective. Most

cases are being managed in the community. It is essential that we urgently identify interventions that may favourably modify progression of the infection. An ideal intervention would be one that is safe, with few side-effects, helps prevent disease progression, and can be administered in the community using existing NHS processes and capability.

Setting up a bespoke randomised controlled trial for each potential intervention that might become available will be inefficient.(5-7) We therefore propose establishing a platform, randomised controlled trial in primary care that can be rapidly deployed to evaluate low risk interventions for high risk people. This platform trial will, in the first instance, evaluate a drug called hydroxychloroquine. This is a drug that is already available within the NHS (although not for this indication currently), and has a generally benign side effect profile(8), but that has not been subject to randomised controlled trials for this indication in Europe or in community healthcare settings. Using an efficient open clinical trial design, with procedures embedded in existing health service structures and capabilities as afar as possible, our trial aims to give a rapid answer about the effectiveness of trial treatments in modifying the disease course. The goal is to prevent disease progression such that affected individuals will recover sooner, but critically, avoid the need for hospital admission. The platform trial will be flexible in that it will operate under a master protocol that will allow the addition of further interventions into the trial while the trial is already in progress, should such suitable interventions become available for this kind of evaluation.(5) This means that a new trial does *not* need to be started afresh each time an additional suitable intervention becomes available, and it also means that existing controls can be used efficiently to give rapid answers about the effectiveness of new interventions. This is particularly important as new candidate interventions are being considered on a regular basis.

The trial will be implemented in the first instance by the Oxford Royal College of General Practitioners (RCGP) Research and Surveillance Centre (RSC) general practices. This is one of Europe's oldest sentinel systems. RCGP RSC has produced a weekly report of influenza, respiratory and other infections in primary care for over 50 years. RCGP RSC works closely with Public Health England (PHE). More information at: www.rcgp.org.uk/rsc. The RCGP RSC Network has over 500 practices, including 100 practices currently swabbing patients with suspected COVID-19 in partnership with Public Health England (PHE).

Trial aspects will be managed by the UK Clinical Research Collaboration Registered University of Oxford Primary Care and Vaccines Clinical Trials Unit.

3. SYNOPSIS

Trial Title	Platform Randomised trial of INterventions against COVID-19 In older peoPLE		
Internal ref. no. (or short title)	PRINCIPLE		
Trial registration	ISRCTN 86534580		
Sponsor	University of Oxford		
Funder	UKRI/NIHR		
Clinical Phase	III		
Trial Design	Pragmatic, platform, randomised controlled trial of interventions for COVID-19 in PRIMARY CARE		
Trial Participants	Patients ≥50-64 years with comorbidities detailed below, and aged ≥65 with or without comorbidity presenting within 7 days since onset of symptoms with a new continuous cough and/or high temperature during time of prevalent COVID-19 infections		
Sample Size	Approximately 3000 (1500 per arm)		
Planned Trial Period	The trial will start as soon as permissions are in place and procedures and structures implemented. The platform trial will be ongoing until cases of COVID-19 wane to a low level and/or there are no new interventions that require evaluation in pragmatic randomised controlled trial in primary care. March 2022 has been decided as the formal end date at this stage, but that may need to be amended, depending on circumstances prevailing at the time.		
Planned Recruitment period	The first inclusion is planned for as soon as possible, and the duration of the trial will depend on evolving circumstances.		
	Objectives	Outcome Measures	Timepoint (s)
Primary	To assess effectiveness of trial treatments in reducing the need for hospital admission or death, for patients aged ≥50 years with serious comorbidity, and aged ≥65 with or without comorbidity and suspected COVID-19 infection during time of prevalent COVID-19 infections	Hospital admission or mortality related to suspected COVID-19	Within 28 days
Secondary	To explore whether trial treatment reduces: 1) Duration of severe symptoms 2) Time taken to self-report recovery	1-2 Patient report on day they feel to have recovered 3. Contacts with health services reported by patients and captured by reports of patients 'medical	Daily online symptoms score. Telephone call or text day 7, 14 and 28 if data not being received online

	3) Contacts with the health services 4) Consumption of antibiotics 5) Hospital assessment not leading to admission 6) Oxygen administration 7) Intensive Care Unit admission 8) Mechanical ventilation 9) To determine if effects are specific to those with the infections syndrome but who test positive for COVID-19 10) Duration of hospital admission	records where the practice is a member of RSC 4. Bi-weekly reports from participants primary care medical records 5-8 and 10 patient report/carer report/medical record in primary care and hospital care 9. Swab results for COVID-19 will indicate an "Intention to Treat Infected" group within the overall cohort for sub analysis	GP notes review where available through Oxford RCGP RSC network after 28 days HES/ONS/EMIS data linkage after 28 days where patients have been assessed in hospital Swab result available once processed from GP record and from PHE laboratory
Intervention(s)	1. Hydroxychloroquine 200 mg twice a day for 7 days Further interventions may be added during the course of the trial, subject to suitable interventions becoming available and all necessary approvals being first obtained.		
Comparator	In the first instance, this will be a two-arm trial, with the intervention am being usual care plus hydroxychloroquine and the comparator being usual care. There will be no placebo control in this study in the first instance		

4. ABBREVIATIONS

AE	Adverse event
AR	Adverse reaction
CI	Chief Investigator
CRF	Case Report Form
CT	Clinical Trials
CTA	Clinical Trials Authorisation
CTRG	Clinical Trials and Research Governance
DMSC	Data Monitoring Committee / Data Monitoring and Safety Committee
DSUR	Development Safety Update Report
GCP	Good Clinical Practice
GP	General Practitioner

HRA	Health Research Authority
IB	Investigators Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IMP	Investigational Medicinal Product
MHRA	Medicines and Healthcare products Regulatory Agency
NHS	National Health Service
NIHR	National Institute of Health Research
RES	Research Ethics Service
PHE	Public Health England
PI	Principal Investigator
PIL	Participant/ Patient Information Leaflet
R&D	NHS Trust R&D Department
RCGP RSC	Royal College of General Practitioners Research Surveillance Centre
REC	Research Ethics Committee
RSI	Reference Safety Information
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SDV	Source Data Verification
SMPC	Summary of Medicinal Product Characteristics
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reactions
TMF	Trial Master File

5. BACKGROUND AND RATIONALE

Introduction

There are no specific interventions against COVID-19 that have been proven, in rigorous trials, to alter the disease course by reducing the need for hospital assessment and admission.

A candidate intervention, a drug called hydroxychloroquine, has become available following early evaluation in some studies in China.(9, 10) This drug may work through limiting viral replication.(11, 12) Hydroxychloroquine is already available within the NHS on prescription for other indications, and has a generally benign safety profile.(8) Chloroquine is available to buy in the UK over the counter in some formulations and is used as antimalarial prophylaxis and treatment.

We urgently need to know whether this drug might modify the course of COVID-19 infections, particularly amongst those who are at higher risk of complications. At the present time, those are higher risk appear to be people aged 50 and over with comorbidity and those aged 65 and over.(1-3, 13)

It is also possible that new interventions may come on stream for evaluation in the near future. We therefore propose a platform trial that has the capability of rapidly evaluating hydroxychloroquine in the high-risk population group, but that will also be flexible enough to allow the addition of further interventions into the trial platform, should such interventions suitable for pragmatic evaluation in Primary Care become available during the course of the trial. New interventions will not be added into the trial without first obtaining the required permissions.

The Research Team has already conducted the world's first publicly funded platform, open, response-adaptive randomised controlled trial in primary care. Conducted in 13 countries, the ALIC4E trial of oseltamivir for influenza-like illness in primary care has been at the forefront of such efficient trial designs.(14)(1-4)

In the first instance, PRINCIPLE will be a two-arm trial comparing standard care to standard care plus hydroxychloroquine. There will be no placebo control. The primary outcome measure will be hospital admission or mortality related to suspected COVID-19.

Analysis will be by intention-to-treat. However, all participants recruited into the study will be asked to provide a swab so that their COVID-19 status can be ascertained by laboratory analysis. We will therefore, in addition to an "intention to treat analysis", conduct an "intention to treat infected" analysis.

The study aims to be rapidly initiated, so we can urgently determine if hydroxychloroquine (and any other suitable intervention that becomes available for rapid pragmatic evaluation) benefits patients. Treatments which are found to be ineffective should not be commissioned, as ineffective treatments simply put people at unnecessary risk of side-effects and waste resources. We urgently need to know whether hydroxychloroquine (and any other suitable intervention that becomes available for rapid pragmatic evaluation) might benefit patients and enhance the sustainability of NHS care during this crisis.

COVID 19

Europe is now the centre of the COVID-19 epidemic caused by the highly infectious SARS-COV2 virus.(4, 15) As of 22 March 2020 in the UK, 5,018 confirmed cases, and 233 deaths have been reported in the UK, and modelling studies suggest the pandemic will worsen rapidly in the UK and elsewhere.(4, 16)

The UK case definition for possible COVID-19 is dependent on care setting. COVID-19 is defined, where patients are well enough to remain in the community, as suspected for those who meet the following criteria:

- A new continuous cough - this means coughing a lot for more than an hour, or 3 or more coughing episodes in 24 hours (if you usually have a cough, it may be worse than usual)

And/or

- high temperature - this means you feel hot to touch on your chest or back (you do not need to take your temperature)

First Candidate Intervention: Hydroxychloroquine

Hydroxychloroquine is a hydroxylated version of the drug chloroquine.(10, 11) Both agents are commonly in use as anti-malarials, and are used in a variety of auto-immune diseases. They have received significant recent interest as potential modifiers of disease activity in COVID (17)19.(10, 18) Hydroxychloroquine is available in the UK by prescription, chloroquine is available to buy in the UK over the counter in some formulations for short term use.

Chloroquine is known to block virus infection by increasing endosomal pH required for virus/cell fusion, as well as interfering with the glycosylation of cellular receptors of SARS-CoV.(5) Besides its antiviral activity, chloroquine has an immune-modulating activity, which may synergistically enhance its antiviral effect *in vivo*.(11) Chloroquine is widely distributed in the whole body, including lungs, after oral administration.(10) The EC_{90} value of chloroquine against the 2019-nCoV in Vero E6 cells was 6.90 µM in one study (9) which can be clinically achievable as demonstrated in the plasma of rheumatoid arthritis patients who received 500 mg administration.(8)

Hydroxychloroquine has been found to be effective against intracellular micro-organisms including malaria and intracellular bacteria *Coxiella burnetii* and *Tropheryma Whipplei*.(11) Both chloroquine and hydroxychloroquine have been shown to have *in vitro* antiviral activity against SARS coronavirus in a number of studies.(11) Most recently activity against SARSCOV2 was shown to be greater for hydroxychloroquine than chloroquine (12).

In human COVID-19 trials in China, chloroquine has been shown to reduce length of hospital stay and severity of symptoms in a trial of 100 people (17), and there are multiple other trials registered as ongoing (https://clinicaltrials.gov/ct2/show/NCT04315896?term=hydroxychloroquine&cond=Corona+Virus+Infection&draw=2&rank=3).(10)

A pragmatic trial

The aim of PRINCIPLE is to be the national Primary Care platform trial for UK COVID-19, assessing the effectiveness of trial treatments in reducing the need for hospital admission or death for patients with suspected COVID-19 infection aged ≥50 years with serious comorbidity, and aged ≥65 with or without comorbidity, and during time of prevalent COVID-19 infections in the context of current care delivery. Thus, the trial will need to be as streamlined as possible so that it fits with minimal disruption into routine care during a period of widespread infection and considerable pressure on the NHS and society.

Platform trial

A platform trial, in contrast to traditional two-arm design, allows multiple arms to be considered simultaneously, and interventions can be dropped, added and/or replaced as evidence emerges for effectiveness, or lack of it. The intent is to establish an on-going trial infrastructure within a master protocol that uses all the data already accumulated for the assessment of current and subsequently introduced interventions.

New interventions will only be added after submission to the appropriate approval bodies.

Objectives	Outcome Measures	Timepoint(s) of evaluation of this outcome measure (if applicable)
Primary Objective To assess effectiveness of trial treatments in reducing the need for hospital admission or death, for patients aged ≥50 years with comorbidity, and aged ≥65 with or without comorbidity and suspected COVID-19 infection during time of prevalent COVID-19 infections	Hospital admission or mortality related to suspected COVID-19	Within 28 days
Secondary Objectives To explore whether trial treatment reduces 1) Duration of severe symptoms 2) Time taken to self-report recovery 3) Contacts with the health services 4) Consumption of antibiotics 5) Hospital assessment without admission 6) Oxygen administration 7) Intensive Care Unit admission 8) Mechanical ventilation 9) To determine if effects are specific to those with the infections syndrome but who test positive for COVID-19 10) Duration of hospital admission	1-2 Patient report on day they feel to have recovered 3. Contacts with health services reported by patients and captured by reports of patients 'medical records where the practice is a member of RSC 4. Bi-weekly reports from participants primary care medical records 5-8 and 10 patient report/carer report/medical record in primary care and hospital care 9. Swab results for COVID-19 will indicate an "Intention to Treat Infected" group within the overall cohort for sub analysis	Daily online symptoms score. Telephone call or text day 7, 14 and 28 if data not being received online GP notes review where available through Oxford RCGP RSC network after 28 days HES/ONS/EMIS data linkage after 28 days where patients have been assessed in hospital Swab result available once processed from GP record and from the supporting PHE laboratory

6. TRIAL DESIGN

This will be an open, prospective, individually randomised, platform, controlled clinical trial in community care. The trial will initially be two-arm, comparing standard care to standard care plus hydroxychloroquine.

The trial will be implemented in the first instance in practices that are already part of the RCGP RSC Network. Currently over 500 practices are part of this network, with 100 already offering a sentinel viral swabbing service which is being scaled up. Due to the pandemic, almost all practices in the UK have been asked to join the RCGP RSC Network.

7. PARTICIPANT IDENTIFICATION

7.1 Trial Participants

Patients ≥50 years with serious comorbidity, and patients aged ≥65 with or without comorbidity presenting in the community within 7 days since onset of symptoms, with a new continuous cough and/or high temperature during a time of prevalent COVID-19 infections.

A new continuous cough is taken to mean, "coughing a lot for more than an hour, or 3 or more coughing episodes in 24 hours (if you usually have a cough, it may be worse than usual)."

A high temperature is taken to mean, "you feel hot to touch on your chest or back (you do not need to take your temperature)"

7.1.1 Inclusion Criteria

- Participant is willing and able to give informed consent for participation in the study;
- Participant is willing to comply with all trial procedures;
- Onset of symptoms of possible COVID-19 in the community (continuous cough and/or high temperature) within 7 days of inclusion;
- Patients aged ≥50-64 years with any of the following listed comorbidities:
    - Known weakened immune system due to a serious illness or medication (e.g. chemotherapy);
    - Known heart disease and/ or hypertension;
    - Known asthma or lung disease;
    - Known diabetes not treated with insulin;
    - Known mild hepatic impairment;
    - Known stroke or neurological problem;

OR

- Patients aged ≥65 with or without comorbidity

7.1.2 Exclusion Criteria

- Pregnancy;
- Breastfeeding;
- Known severe hepatic impairment;
- Known severe renal impairment;
- Known porphyria;
- Type 1 diabetes or insulin dependent Type 2 Diabetes mellitus ;
- Known G6PD deficiency;
- Known myasthenia gravis;
- Known severe psoriasis;
- Known severe neurological disorders (especially those with a history of epilepsy—may lower seizure threshold);
- Previous adverse reaction to, or currently taking, hydroxychloroquine;
- Patients taking the following drugs: penicillamine, amiodarone, ciclosporin, chloroquine
- Known retinal disease;
- Judgement of the recruiting clinician deems ineligible.

8 TRIAL PROCEDURES

8.1 Recruitment

Recruitment will be possible through a variety of mechanisms due to the changing pandemic environment, and will include:

People who are concerned about COVID-19 continue to contact their general practices in large numbers. In the first instance, we will ask participating general practices to record whether a person phoning about COVID-19 is potentially eligible for the study. The practice will then ask the person if they are interested in finding out about potential trial participation or seek verbal consent if they are happy to be contacted by the trial team to discuss this further. If they are, information will be provided verbally and online either by the GP surgery or their contact details passed to the trial team who will provide such information on how they might join the study. Full information will be available to view on a web site and subsequently on the Participant Information Sheet (PIS). This information will inform potentially eligible and interested patients about how to access further trial information and consider participation, as well as the procedures involved in joining the study, and what participation would involve.

In addition to receiving calls from potentially eligible participants, participating practices will also be able to contact patients, preferably by text, who they have screened from their GP Practice list and who fall into the correct age and co-morbidity categories, to tell them about the study and to let them know that, should they develop relevant symptoms, they may wish to contact the practice or trial team directly to discuss participation in the trial.

The Study Team will be contacted directly by some potentially eligible patients due to word of mouth and media exposure. They may approach the Study Team by calls, emails and other mechanisms. The Study Team will then also be able to provide such people with information about potentially joining the trial, and the steps involved.

Any agencies from national bodies, such as NHS 111, who receive COVID-19 calls will be able to give information about possible trial participation and direct interested patients to the online information on and/or how to contact the Study Team.

An online screening, eligibility and consent procedure will be followed, with telephone calls as back-up for potential participants to be able to ask questions and clarifications about the study and their potential participation.

Participants will preferably complete the Informed Consent Form (ICF) online. They will be able to download their consent form for their records. This online process avoids risk from paper copies handled by people with infection, and is efficient during a time or rapid recruitment during a pandemic. Remote online consent or via telephone call is also required as the majority of GP practices will not conduct face-to-face appointments in the COVID-19 pandemic, and all potential COVID-19 sufferers are being informed by a national campaign to contact clinicians by telephone or online.

During this process, we will ask the potential participant to, if possible, include a phone number for a Study Partner, who may provide assistant to the study participant in completing trail procedures while the participant is ill. Identifying a Study Partner is not a requirement of study participation, merely a suggested mechanism to aid participation for consenting patients.

Once informed consent has been obtained and a medically qualified clinician has checked eligibility, participants will be randomised via a secure in line link using our in-house Sortition module. The participant, trial team and participant's GP will be notified electronically of what treatment allocation they have been randomised to. The participant and GP can review the PIS and completed ICF at any time using a secure log-in access code.

If not sampled face-to-face, all participants will be sent a sampling kit for self-sampling by their practice, study team or other facilities such as Public Health England (PHE). They will receive clear instructions on how to self-sample, as per PHE standard advice. Once the sample has been taken, they will be asked to place the sample in the provided container, sealed in a double envelope, which will be posted to PHE laboratory according to their standard practice for COVID-19. For trial purposes, we will not store the swabs after testing but PHE may keep the specimen for up to 5 years following their own approved processes. Participants will be informed of their COVID-19 swab result by their GP.

Participants will be issued with an online link where they will be asked to record the presence and severity of a few simple symptoms each day. Where online data is not being entered by participants, the research team will contact the participants and/or their study partner following days 7, 14 and 28. The study team will make no more than three attempts to contact the participant/Trial Partner at each of these follow-up points. We will also obtain consent to ascertain relevant data from hospital records about length of stay and ICU admission and ventilation.

The RCGP RSC will report to the central trial office at least twice weekly about healthcare contacts in the participating patient's clinical records, as they are able to download this information centrally for study participants. This will be used as confirmation and a back-up for information obtained directly from study participants and other data sources outlined above.

8.2 Screening and Eligibility Assessment

Participants will be screened after they read the PIS, by completing online eligibility questions in lay terms (based on section 7), and if they meet screening criteria, they will be asked to complete an online consent form (see above). A screening trial ID number will be assigned. The participant will go on to enter online baseline information, including their contact details and those of a Study Partners, if they have a Study Partner available to help them with the study. The trial team and responsible clinician or delegate will be notified electronically, the medically qualified clinician will confirm eligibility online and complete the eligibility CRF online. Once deemed eligible, the clinician will go on to randomise the participant. The

participant, clinician and trial team will be notified of the randomisation and the treatment group allocated.

8.3 Informed Consent

Written and verbal versions of the Participant Information Sheet (PIS) and the Informed Consent Form (ICF) will be presented to the participants detailing no less than: the exact nature of the study; the implications and constraints of the protocol, and, the known side-effects and risks involved in taking part. The study will provide a PIS that includes all necessary information in appropriate wording and format for the participant. It will be clearly stated that the participant is free to withdraw from the study at any time for any reason without prejudice to future care, and with no obligation to provide the reason for withdrawal.

Adequate time will be given to the participant to consider the information given to them and to ask any questions they may have about the trial before deciding whether they will participate in the study. However, they must still be recruited within the stated number of days of the onset of their symptoms to participate.

8.4 Randomisation

Participants will be randomised using a fully validated and compliant web-based randomisation system called Sortition. At the baseline assessment, the recruiter will enter the participant's baseline data into the online system, which will then enable the randomisation to take place. The randomisation process will take only a few moments via the online system and will not delay trial participation. Full details of response adaptive randomisation are described in section 11.2.4.

8.5 Blinding and code-breaking

PRINCIPLE will be an open-label trial. The participant and the recruiting clinician will know the participant's allocation. Therefore, no unblinding or code breaking is required in the event of a relevant emergency. However, those telephoning participants and managing the data will be blind to participant allocation.

The trial team and recruiting clinicians will be blinded to emerging results. During the course of the trial, only those on the Data Monitoring Committee will have access to the unblinded interim results.

8.6 Baseline Assessments

Once eligibility is confirmed, participants will be randomised using Sortition online. A sampling kit with insert containing instructions will be sent to the participant's home for self-sampling unless a sample can be taken face-to-face by the general practice. All participants, whether in the intervention or control group, will be asked to provide a swab or self-swab. Once participants take their own swab, they will put it in the secure container and double bag, and post it to the PHE laboratory supporting the study.

For those randomised to receive the first study intervention, hydroxychloroquine, the participant will be told how the drug can be obtained, either through collection at a pharmacy, GP practice, or by home delivery. GPs will be able to issue the study medication directly to participants.

8.7 Subsequent Visits

There is no requirement for participants to have a research-specific face-to-face visit as part of their study participation, as requiring additional health care contacts should be avoided if at all possible during the

COVID-19 pandemic. All subsequent measurements consist of self-completed questionnaires online or through telephone calls from the trial team and primary care and hospital record searches.

Participant follow-up will be primarily online, where they will be asked to complete questions about the presence and severity of symptoms each day for 28 days. If not completed, the trial team will contact the participant and/or their Study Partner to obtain the information.

The practice network that will be implementing the trial in the first instance, the Oxford Royal College of General Practitioners Surveillance Network, has the capacity to extract patient information from the clinical records twice a week. This more-or-less real-time ascertainment of primary care will augment information captured from patients themselves, their families or from the hospital records about intensive care admission and ventilation. Participant records will be accessed up to 3 months following enrolment to ascertain follow up data to day 28 from enrolment. Data will be collected in real time as far as possible, RCGP RCS, EMIS and NHS Digital will be utilised if required. We are engineering a new digital platform to enable daily extracts shortly.

8.8 Sample Handling

We will request a biological sample to test for COVID-19 from all consenting participants. Unless a swab can be taken face-to-face in the course of usual care, this will be a self-swab process with the practice generating the required forms. Once the swab has been taken it will be put in the regulation contained packaging, double bagged, and posted to the PHE laboratory that is supporting the study using their existing, safe, compliant processes. The trial team will utilise PHE and their existing processes and documentation. The trial team do not intend to store the swab once tested, and it won't be stored for the purpose of this trial. The swab material will fall under PHE and not the trial remit, and PHE may retain the swab for up to 5 years.

8.9 Early Discontinuation/Withdrawal of Participants

Each participant has the right to withdraw from the study at any time. In addition, the Investigator may discontinue a participant from the study at any time if the Investigator considers it necessary for any reason including:

- Ineligibility (either arising during the study or retrospectively having been overlooked at screening)
- Withdrawal of consent

The reason for withdrawal will be recorded on the CRF. Data that has already been collected about the participant will be kept and used. Swabs may be stored outside of the trial remit, for PHE purposes adhering to their retention policy.

8.10 Definition of End of Trial

Last data capture of last participant, when: no further suitable interventions are available and/or COVID 19 is no longer prevalent. March 2022 has been decided as the formal end date at this stage, but that may need to be amended, depending on circumstances prevailing at the time.

9 TRIAL INTERVENTIONS

9.1 Investigational Medicinal Product(s) (IMP) Description

First trial drug: Hydroxychloroquine sulphate 200 milligram (mg) tablets. The tablets are for oral administration.

One tablet (200mg) hydroxychloroquine to be taken twice daily for 7 days by mouth (14 tablets in total).

Special instructions:

Each dose should be taken with a meal or glass of milk.

Antacids may reduce absorption of hydroxychloroquine so it is advised that a 4-hour interval be observed between taking hydroxychloroquine and an antacid.

This is the standard therapeutic dose for its normal indication in adults which is for the treatment of rheumatoid arthritis, discoid and systemic lupus erythematosus, and dermatological conditions caused or aggravated by sunlight.

The Marketing Authorisation holder is Zentiva Pharma UK Limited Guildford Surrey GU1 4YS United Kingdom. Marketing authorisation number is PL 17780/0748.

9.2. Blinding of IMPs

There is no blinding of IMPs in the trial.

9.3. Storage of IMP

Hydroxychloroquine: Stored at room temperature in locked cupboards in restricted access rooms in the Primary Care Clinical Trials Unit (PC-CTU); in locked cupboards in restricted access rooms in GP Practices; in Pharmacies.

GP practices can order a supply of hydroxychloroquine from Public Health England using the existing Inform process. All GP practices in England are already set up on Inform, as they use this system to order influenza vaccines form Public Health England. Public Health England holds stock of Hydroxychloroquine in various forms, but for the purposes of the PRINCIPLE Trial, they will issue GPs with a supply from Zentiva, which comes in packs containing four blisters of 15 tablets each in each pack, totalling 60 tablets per pack (4 blisters of 15 tablets each). GPs will be provided with an envelope by the study team which will be labelled appropriately for trial medication, and they will add the patient's details to this label. This pack, containing instructions on using the medication, and containing 15 tablets, will be provided to the patient or their representative.

9.4. Compliance with Trial Treatment

Participants will receive a daily email asking for them to log on with a unique access code to an electronic system where they will record their symptoms. If uncompleted, the trial team will contact the participant and/or their Study Partner to obtain the data. Non-compliance can be assessed daily.

9.5. Accountability of the Trial Treatment

A risk-adapted approach will be used for drug accountability. Accountability logs will be kept by PC-CTU for when they ship drug.

9.6. Concomitant Medication

Hydroxychloroquine: Hydroxychloroquine will be used for short-term use (7 days) in this trial. The SmPC and precautions listed below focus on longer term chronic use.

Hydroxychloroquine might lower blood sugar levels in some people. If participants develop these symptoms they will be advised in the Patient Information documents to eat something sweet and seek clinical advice if the symptoms continue.

Hydroxychloroquine occasionally causes blurred vision, which typically resolves once the medication is stopped. Participants will be advised via the Participant Information documents that if they develop any

problems with vision, they should stop taking the medication immediately, seek clinical advice, and do not drive or operate any heavy machinery.

Hydroxychloroquine sulfate has been reported to increase plasma digoxin levels. Serum digoxin levels should be closely monitored in participants receiving concomitant treatment. Hydroxychloroquine sulfate may also be subject to several of the known interactions of chloroquine even though specific reports have not appeared. These include: potentiation of its direct blocking action at the neuromuscular junction by aminoglycoside antibiotics; inhibition of its metabolism by cimetidine which may increase plasma concentration of the antimalarial; antagonism of effect of neostigmine and pyridostigmine; reduction of the antibody response to primary immunisation with intradermal human diploid-cell rabies vaccine. As with chloroquine, antacids may reduce absorption of hydroxychloroquine so it is advised that a 4 hour interval be observed between hydroxychloroquine and antacid dosaging. As hydroxychloroquine may enhance the effects of a hypoglycaemic treatment, a decrease in doses of insulin or antidiabetic drugs may be required. Halofantrine prolongs the QT interval and should not be administered with other drugs that have the potential to induce cardiac arrhythmias, including hydroxychloroquine. Also, there may be an increased risk of inducing ventricular arrhythmias if hydroxychloroquine is used concomitantly with other arrhythmogenic drugs, such as amiodarone and moxifloxacin. An increased plasma ciclosporin level was reported when ciclosporin and hydroxychloroquine were co-administered. Hydroxychloroquine can lower the convulsive threshold. Co-administration of hydroxychloroquine with other antimalarials known to lower the convulsion threshold (e.g. mefloquine) may increase the risk of convulsions. Also, the activity of anti-epileptic drugs might be impaired if co-administered with hydroxychloroquine. In a single-dose interaction study, chloroquine has been reported to reduce the bioavailability of praziquantel. It is not known if there is a similar effect when hydroxychloroquine and praziquantel are co-administered. Per extrapolation, due to the similarities in structure and pharmacokinetic parameters between hydroxychloroquine and chloroquine, a similar effect may be expected for hydroxychloroquine. There is a theoretical risk of inhibition of intra-cellular α-galactosidase activity when hydroxychloroquine is co-administered with agalsidase.

10 SAFETY REPORTING

Hydroxychloroquine: Hydroxychloroquine has a well-documented safety profile and is a commonly used medication in a primary care setting (see above). We will collect symptoms and side effects from symptom diaries and participant telephone calls.

Common symptoms include abdominal pain; appetite decreased; diarrhoea; emotional lability; headache; nausea; skin reactions; vision disorders; and vomiting. Daily symptom diaries and participant telephone calls will record any symptoms and side effects from the trial medication. This information will be analysed as part of the whole trial analysis.

10.1 Adverse Event 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)	An untoward and unintended response in a participant to an investigational medicinal product which is related to any dose administered to that participant.

	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. 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.
Serious Adverse Event (SAE)	A serious adverse event is any untoward medical occurrence that: • 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 a serious adverse event when, based upon appropriate medical judgement, the event may jeopardise the participant and may require medical or surgical intervention to prevent one of the outcomes listed above. 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. *NOTE: Pregnancy is not, in itself an SAE. In the event that a participant or his/her partner becomes pregnant whilst taking part in a clinical trial or during a stage where the foetus could have been exposed to the medicinal product (in the case of the active substance or one of its metabolites having a long half-life) the pregnancy should be followed up by the investigator until delivery for congenital abnormality or birth defect, at which point it would fall within the definition of "serious".
Serious Adverse Reaction (SAR)	An adverse event that is both serious and, in the opinion of the reporting Investigator, believed with reasonable probability to be due to one of the trial treatments, based on the information provided.
Suspected Unexpected Serious Adverse Reaction (SUSAR)	A serious adverse reaction, the nature and severity of which is not consistent with the Reference Safety Information for the medicinal product in question set out: • in the case of a product with a marketing authorisation, in the approved summary of product characteristics (SmPC) for that product • in the case of any other investigational medicinal product, in the approved investigator's brochure (IB) relating to the trial in question.

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.

10.2 Assessment results outside of normal parameters as AEs and SAEs
There are no additional assessment results in this study

10.3 Assessment of Causality

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

- **Unrelated** – where an event is not considered to be related to the IMP
- **Possibly** – although a relationship to the IMP cannot be completely ruled out, the nature of the event, the underlying disease, concomitant medication or temporal relationship make other explanations possible.
- **Probably** – the temporal relationship and absence of a more likely explanation suggest the event could be related to the IMP.
- **Definitely** – the known effects of the IMP, its therapeutic class or based on challenge testing suggest that the IMP is the most likely cause.

All AEs (SAEs) labelled possibly, probably or definitely will be considered as related to the IMP.

10.4 Procedures for Reporting Adverse Events
All AEs will be collected from daily participant diaries, calls to participants/Study Partners and RCGP data downloads.

The severity of events will be assessed on the following scale: minor problem/moderate problem/major problem.

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.

10.5 Reporting Procedures for Serious Adverse Events

Hospitalisation and death due to COVID-19 are our primary outcomes so we will collect this data using a risk-adapted approach and will not report such as SAEs. SAE information will be collected from daily diaries, calls to participants and their Study Partner and RCGP data downloads and hospital records and analysed as part of the interim and whole trial analysis and will be reviewed at each Data Monitoring Committee meeting.

SAEs other than hospitalisation or death due to COVID-19 infection must be reported by the person who has discovered the SAE or nominated delegate within 24 hours of becoming aware of the event. The sponsor or delegate will perform an initial check of the report, request any additional information, and ensure it is reviewed by the CI or other delegated personnel for relatedness and expectedness as soon as possible taking into account the reporting time for a potential SUSAR according to the relevant competent authority. Additional and further requested information (follow-up or corrections to the original case) will be detailed on a new SAE Report Form and reviewed by the sponsor or delegate. If the event has not resolved, at the 28 day time point the SAE will be reviewed again to see if resolution has occurred. If the event is considered 'resolved' or 'resolving' no further follow up is required. If not, the event must be followed up until such a time point.

10.5.1. Other events exempt from immediate reporting as SAEs

Hospitalisations will be defined as at least a 1 night admission to hospital.

Hospitalisation for a pre-existing condition, including elective procedures planned prior to study entry, which has not worsened, does not constitute a serious adverse event and standard supportive care for the disease under study are not SAEs, and do not require SAE reporting.

10.5.2. Procedure for immediate reporting of Serious Adverse Events

- Study team will complete an SAE report form for all reportable SAEs.
- GP practice/study team/RCGP will provide additional, missing or follow up information in a timely fashion.

The CI or delegate will review the SAE once reported, collect as much information and report to the Sponsor within the timeframe according to the PC-CTU SOPs.

10.5.3 Expectedness

For SAEs that require reporting, expectedness of SARs will be determined according to the relevant RSI section of the Summary of Product Characteristics/IB. The RSI will be the current Sponsor and MHRA approved version at the time of the event occurrence. For assessment of expectedness in the Development Safety Update Report, see section 10.7 below.

10.6 SUSAR Reporting

All SUSARs will be reported by the sponsor delegate to the relevant Competent Authority and to the REC and other parties as applicable. For fatal and life-threatening SUSARS, this will be done no later than 7 calendar days after the Sponsor or delegate is first aware of the reaction. Any additional relevant information will be reported within 8 calendar days of the initial report. All other SUSARs will be reported within 15 calendar days.

Principal Investigators will be informed of all SUSARs for the relevant IMP for all studies with the same Sponsor, whether or not the event occurred in the current trial.

10.7 Development Safety Update Reports

The DSUR will be developed and submitted annually on the anniversary date that the trial receives Clinical Trial Authorisation +60 days. Due to the nature of this trial and the importance of sharing the science of COVID-19 and the drug, internationally, we expect to produce reports to the UK Government and regulatory agency more frequently upon request.

11 STATISTICS

11.1 Statistical Analysis Plan (SAP)

The statistical design and pre-specified analyses will be described in detail in a Statistical Analysis Plan (SAP) drafted by a Trial Statistician and signed off by the CI and Lead/senior statistician. A broad overview of the design and primary analyses is provided below.

11.2 Open Adaptive Platform Trial

PRINCIPLE is an open, adaptive, platform trial to evaluate emerging treatments of the novel COVID-19 virus. A "platform trial" is a trial in which multiple treatments for the same disease are tested simultaneously. The backbone of the trial is an adaptive clinical trial design. Pre-specified decision criteria allow for dropping a treatment for futility, declaring a treatment superior, or adding a new treatment to be tested. If at any point a treatment is deemed superior to the control arm, the superior treatment will replace the control arm as the new standard of care, and all subsequent treatments will be compared to the new standard of care. Because the process of dropping and adding treatments may be on-going for an indefinite period of time, platform trials may be better conceived of as a process rather than a singular clinical trial. In the context of the COVID-19 pandemic, the trial may continue as long as the pandemic persists.

The PRINCIPLE trial will begin as a 1:1 randomised trial of standard care versus standard care plus hydroxychloroquine but will have the capability to add additional interventions over time. The evaluation of any new interventions will be governed by the master protocol, including adaptive and decision criteria. In addition, the inclusion of any new interventions will require amendments and/or supplements to the protocol and SAP.

11.2.1 Primary Endpoint & Analysis

The primary endpoint is hospital admission or death as a result of COVID-19 infection. The primary analysis will be a Bayesian generalised linear model of the primary outcome regressed on treatment and stratification covariates (age, comorbidity). Let p_j denotes the probability of hospitalisation/death for persons in treatment group *j*, where $j = 0$ denotes the control arm and $j = 1$ denotes the intervention arm. A Bayesian posterior distribution will be derived for the estimated difference in probability of hospitalisation/death between treatment groups. The primary analysis for intervention *j* will test the following hypothesis:

$$H_0: p_j - p_0 \geq 0$$

$$H_1: p_j - p_0 < 0$$

If the Bayesian posterior probability of beneficial treatment effect is sufficiently large (e.g. ≥ 0.99), the null hypothesis will be rejected and the intervention will be deemed superior to control. The exact threshold of the superiority decision criterion (e.g. 0.99) will be determined *a priori* via simulation to control the one-sided Type I error of the study at approximately 0.025. The primary analysis for any additional interventions added later in the trial (i.e. not enrolling at the trial start) will only include control subjects who are concurrently randomised.

11.2.2 Adaptive Design

The pre-specified design will allow adaptations to the trial based on the observed data. These adaptations include the declaration of success or futility of an arm at an interim analysis, the addition or removal of treatment arms, and changes in the randomisation probabilities. Adaptations will occur at a given interim analysis if pre-specified conditions are satisfied. All will be documented in the SAP, including prespecified criteria and required precision for decisions about futility or effectiveness of interventions and/or replacing interventions in the trial.

11.2.3 Interim Analyses

The first interim analysis will occur when first 100 randomised participants have been followed up to 28 days, and subsequent weekly interim analyses. At each interim analysis, all enrolled intervention arms will

be evaluated for success or futility using the Bayesian primary analysis. If the Bayesian posterior probability of superiority of a given intervention is sufficiently large (e.g. ≥ 0.99), superiority will be declared. If there are additional intervention arms in the study (either currently or subsequently), the superior arm will replace the control arm as the new standard of care, and any subsequent interventions will be compared to the new control arm.

If the Bayesian posterior probability of a clinically meaningful treatment effect (≥ 0.05 decrease in the proportion hospitalized/dead) is sufficiently small (e.g. < 0.05) the intervention arm will be dropped from the study for futility. If there are no other intervention arms available, the trial will be suspended; otherwise accrual continues to the remaining treatment arms. The exact futility threshold will be pre-specified and determine via simulation.

11.2.4 Allocation & Response Adaptive Randomisation

Initially, randomisation will be fixed 1:1 for hydroxychloroquine versus usual care, with stratification by age (less than 65, greater than or equal to 65), and comorbidity (yes/no). If a second intervention arm is added to the study, randomisation will initially be 1:1:1 (stratified by age and comorbidity), and the additional arm will be included in the interim analyses (evaluating success and futility) if at least 50 participants have 28 days of follow-up. If there are at least 3 arms (2 intervention arms plus usual) in the study with at least 50 participants with 28-day outcomes, each interim analysis will incorporate modified randomisation probabilities via response adaptive randomisation (RAR). The general idea is to allocate more participants to the intervention arms that have the best observed outcomes.

More specifically, after RAR is activated, control allocation will be fixed at 1/Z, where Z is the total number of treatment arms. For example, for 3 arms (2 intervention arms plus control), the usual care allocation will be fixed at 1/3, and the remaining 2/3 participant allocation will be determined for the two intervention arms via response adaptive randomisation. The RAR probabilities for the intervention arms will be proportional to the Bayesian posterior probability that a given intervention is the best intervention.

11.2.5 Sample Size Justification

Given the open perpetual trial structure, the trial does not have a finite ending based on sample size. Rather, the trial will continue until either superiority or futility is claimed for an intervention, or until the pandemic expires in the population. We estimate that approximately 1500 participants per arm (3000 participants total if only a single intervention vs. usual care) will be required to provide 90% power for detecting a 5 percentage point benefit in the proportion of subjects experiencing hospitalisation/death. This calculation is based on the assumption of an underlying 20% combined hospitalisation/death rate in the study population, with an intervention lowering the hospitalisation/death rate to 15%, with some adjustments for the multiple interim analyses. On average, we expect fewer participants to be required when there is a large treatment benefit or complete lack of benefit. For example, if the true benefit is a 10 percentage point decrease in hospitalisation/mortality (20% usual care vs. 10% treatment), on average only 250 subjects per arm are required to provide sufficient power. The primary advantage of the adaptive design is the ability to adapt the sample size to the observed data, thus addressing the primary hypothesis as quickly and as efficiently as possible.

11.2.6 Virtual Trial Simulations

Because of the adaptive platform trial structure, there exists no simple formula(s) to calculate power and Type I error (false positive rate). Hence, virtual trial simulations will be used to fully characterize and quantify the power and Type I error of the design. These simulations will be conducted prior to the first interim analysis, and will be used to optimize the adaptive decision criterion and RAR parameters. The simulations will include a comprehensive evaluation of trial performance across a wide range of

assumptions (e.g. underlying distribution of outcome in control arm, treatment effect, accrual rates, etc.). This will include summaries regarding the number of subjects required to make a success or futility conclusions for each intervention. For example, we will quantify the probability of claiming superiority at the first interim analysis with 100 participants with observed outcomes. Complete details of the simulations will be provided in the SAP with an accompanying adaptive design report.

11.2.7 Procedure for Accounting for Missing, Unused, and Spurious Data.

Full details of handling missing data will be specified in the SAP.

11.3 Primary Analysis Population

The primary analysis population was defined as all participants for whom data were available were analysed according to the groups they were randomly allocated to, regardless of deviation from protocol and irrespective of their COVID-19 status. Secondary analyses will conduct the primary analysis on the subset of participants with confirmed COVID-19.

11.4 Procedures for Reporting any Deviation(s) from the Original Statistical Plan

Analyses will be carried out in accordance with the SAP. Any additional analysis that is not specified in the SAP or any deviation(s) from the original SAP (and reasons) will be specified in the Statistical Report. Reasons for these changes will be documented and authorised by the Chief Investigator.

12 DATA MANAGEMENT

The data management aspects of the study are summarised here with details fully described in the Data Management Plan.

12.1 Source Data

Source documents are where data are first recorded, and from which participants' CRF data are obtained. These include, but are not limited to, hospital records (from which medical history and previous and concurrent medication may be summarised into the CRF), clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence.

If the participant fails to complete data online and after three attempts at contacting the participant/Trial Partner, the RCGP RSC may be utilised to obtain missing data. Data collected will include participant identifiable information and will be accessed at the University of Oxford according to PC-CTU Information Governance policies and GDPR. Data will only be held for the duration of which its required, this will be reviewed annually.

CRF entries will be considered source data if the CRF is the site of the original recording (e.g. there is no other written or electronic record of data). All documents will be stored safely in confidential conditions. On all study-specific documents, other than the signed consent, the participant will be referred to by the study participant number/code, not by name.

12.2 Access to Data

Direct access will be granted to authorised representatives from the Sponsor and host institution for monitoring and/or audit of the study to ensure compliance with regulations.

12.3 Data Recording and Record Keeping

A CTU data manager will be assigned to the study, as delegated by the CI, and will be responsible for overseeing the receiving, entering, cleaning, querying, analysing and storing all data that accrues from the study by designated persons. The data will be entered into the volunteers' CRFs in an electronic format by the participant or trial team (using OpenClinica™ database via Sentry). OpenClinica™ is stored on a secure server – data will be entered in a web browser on PCs in the Clinical Trials Unit building and then transferred to the OpenClinica Database by encrypted (Https) transfer. OpenClinica™ meets FDA part 11B standards. This includes safety data, laboratory data and outcome data. Safety data will also be collected through electronic diaries which are stored on a secure server.

Sentry is an online secure data entry system developed in-house at PC-CTU and hosted at Oxford. It is designed to collect sensitive data, such as participant contact details, and securely retain them separate form a trial's clinical data. Sentry can also act as a central participant portal to manage online eligibility, eConsent and ePRO - acting as an intermediary between the participant and the clinical databases. Sentry is accessed via a secure HTTPS connection and all stored sensitive data is encrypted at rest to AES-256 standards.

The Investigators will maintain appropriate medical and research records for this trial, in compliance with the requirements of the Medicines for Human Use (Clinical Trial) Regulations 2004, ICH E6 GCP and regulatory and institutional requirements for the protection of confidentiality of volunteers. The Chief Investigator, Principal Investigator, Co-Investigators and Clinical Research Nurses will have access to records. The Investigators will permit authorized representatives of the sponsor, and regulatory agencies to examine (and when required by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits and evaluation of the study safety and progress.

13 QUALITY ASSURANCE PROCEDURES

The study will be conducted in accordance with the current approved protocol, GCP, relevant regulations and PC-CTU Standard Operating Procedures. All PIs, coordinating centre staff and site staff will receive training in trial procedures according to GCP where required.

Regular monitoring will be performed according to GCP using a risk based approach. Data will be evaluated for compliance with the protocol and accuracy in relation to source documents where possible. Following written standard operating procedures, the monitors will verify that the clinical trial is conducted and data are generated, documented and reported in compliance with the protocol, GCP and the applicable regulatory requirements. The Study Monitor may also assess SAE's.

The PC-CTU Trial Management Committee will be responsible for the monitoring of all aspects of the trial's conduct and progress and will ensure that the protocol is adhered to and that appropriate action is taken to safeguard participants and the quality of the trial itself. The TMG will be comprised of individuals responsible for the trial's day to day management (e.g. the CI, trial manager, statistician, data manager) and will meet regularly throughout the course of the trial.

13.1 Risk assessment

A risk assessment and monitoring plan will be prepared before the study opens and will be reviewed as necessary over the course of the study to reflect significant changes to the protocol or outcomes of monitoring activities.

13.2 Monitoring

The monitoring will be performed by the PC-CTU Quality Assurance Manager or delegate; The level of monitoring required will be informed by the risk assessment.

13.3 Trial committees

A Data Monitoring and Safety Committee (DMSC) and Trial Management Group (TMG) will be appointed in line with standard CTU procedures. The responsibilities of each group are as follows:

- DMSC- to review the data at each interim analysis as described in the Statistical Analysis section, as the updates to the randomisation scheme occur in order to ensure that the process is working correctly and to review and monitor the accruing data to ensure the rights, safety and wellbeing of the trial participants. They will make recommendations about how the study is operating, any ethical or safety issues and any data being produced from other relevant studies that might impact the trial. This Committee will also take on the role of a Trial Steering Committee, and so act as a single oversight committee.

- TMG- is responsible for the day-to-day running of the trial, including monitoring all aspects of the trial and ensuring that the protocol is being adhered to. It will include Co-Investigators and will meet weekly in the first instance. A core project team (PT) from within the TMG will meet daily as required for daily operational decision making.

14 PROTOCOL DEVIATIONS

A study related deviation is a departure from the ethically approved study protocol or other study document or process (e.g. consent process or administration of study intervention) or from Good Clinical Practice (GCP) or any applicable regulatory requirements. Any deviations from the protocol will be documented in a protocol deviation form and filed in the study master file.

A PC-CTU SOP is in place describing the procedure for identifying non-compliances, escalation to the central team and assessment of whether a non-compliance /deviation may be a potential Serious Breach.

15 SERIOUS BREACHES

A “serious breach” is a breach of the protocol or of the conditions or principles of Good Clinical Practice which is likely to affect to a significant degree –

(a) the safety or physical or mental integrity of the trial subjects; or

(b) the scientific value of the research.

In the event that a serious breach is suspected the Sponsor must be contacted within 1 working day. In collaboration with the C.I., the serious breach will be reviewed by the Sponsor and, if appropriate, the Sponsor will report it to the approving REC committee and the relevant NHS host organisation within seven calendar days.

16 ETHICAL AND REGULATORY CONSIDERATIONS

16.1 Declaration of Helsinki

The Investigator will ensure that this study is conducted in accordance with the principles of the Declaration of Helsinki.

16.2 Guidelines for Good Clinical Practice

The Investigator will ensure that this trial is conducted in accordance with relevant regulations and with Good Clinical Practice.

16.3 Approvals

Following Sponsor approval, the protocol, informed consent form, participant information sheets and any proposed informing material will be submitted to an appropriate Research Ethics Committee (REC), regulatory authorities, and host institution(s) for written approval. The PI and coordinating centres for each country will ensure and confirm correct regulatory approvals are gained prior to recruitment.

The Investigator will submit and, where necessary, obtain approval from the above parties for all substantial amendments to the original approved documents.

16.4 Other Ethical Considerations

If a particular arm is deemed futile and dropped, no further participants will be randomised to this arm and anyone who is currently on this arm will be informed it has been dropped.

Once a particular intervention has been declared superior and effective, that will become the comparator arm (i.e. standard care).

The vast majority of participant's, due to their co-morbidities, will be exempt from prescription charges. All participants will receive a £20 voucher to cover any prescriptions and other expenses they may incur as a consequence of study participation.

We do not intend to recruit people who do not have capacity to provide consent for themselves to participate into this study.

16.5 Reporting

The CI shall submit once a year throughout the clinical trial, or on request, an Annual Progress Report to the REC, HRA (where required), host organisation, funder (where required) and Sponsor. In addition, an End of Trial notification and final report will be submitted to the MHRA, the REC, host organisation and Sponsor.

16.6 Transparency in Research

Prior to the recruitment of the first participant, the trial will have been registered on a publicly accessible database.

Results will be uploaded to the European Clinical Trial (EudraCT) Database within 12 months of the end of trial declaration by the CI or their delegate.

Where the trial has been registered on multiple public platforms, the trial information will be kept up to date during the trial, and the CI or their delegate will upload results to all those public registries within 12 months of the end of the trial declaration.

16.7 Participant Confidentiality

The study will comply with the General Data Protection Regulation (GDPR) and Data Protection Act 2018, which require data to be de-identified as soon as it is practical to do so. The processing of the personal data of participants will be minimised by making use of a unique participant study number only on all study documents and any electronic database(s). All documents will be stored securely and only accessible by study staff and authorised personnel. The study staff will safeguard the privacy of participants' personal data.

16.8 Expenses and Benefits

All participants will be reimbursed with a £20 voucher, to covers the payment of a prescription, should they incur tis as a result of study participation, and a token of recognition of giving their time and

contribution to the study. The vast majority of participants will not have to pay a prescription change, should a prescription be issued as a result of trial participation. Most people with the co-morbidities outlines and in the age range required for eligibility, are not required to pay for prescriptions.

17 FINANCE AND INSURANCE

17.1 Funding

The study is funded by the UKRI/NIHR via a MRC call.

17.2 Insurance

The University has a specialist insurance policy in place which would operate in the event of any participant suffering harm as a result of their involvement in the research (Newline Underwriting Management Ltd, at Lloyd's of London). NHS indemnity operates in respect of the clinical treatment that is provided.

17.3 Contractual arrangements

Appropriate contractual arrangements will be put in place with all third parties.

18 PUBLICATION POLICY

The Investigators (those listed on the protocol and others to be decided at publication) will be involved in reviewing drafts of the manuscripts, abstracts, press releases and any other publications arising from the

study. Authors will acknowledge the study funders. Authorship will be determined in accordance with the ICMJE guidelines and other contributors will be acknowledged.

19 DEVELOPMENT OF A NEW PRODUCT/ PROCESS OR THE GENERATION OF INTELLECTUAL PROPERTY

Ownership of IP generated by employees of the University vests in the University. The University will ensure appropriate arrangements are in place as regards any new IP arising from the trial.

20 ARCHIVING

Archiving will be done according to the UOXF PC-CTU SOP and study specific working instructions.

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21 APPENDIX A: SCHEDULE OF PROCEDURES

Procedures	**Visits**					
	Visit timing Day 0	**Day 0**	**Day 0**	**Day 0**	**Daily Day 1-28 incl**	**Day 29-3mths**
	Screening completed by participant online/phone	**Eligibility completed by participant online/phone**	**Baseline completed by participant online/phone**	**Eligibility completed by Clinician online/phone**	**Symptom Diaries completed by participant online/phone**	**Retrospective data collection by study team**
Informed consent	X	X	X	X	X	
Demographics	X	X	X			X
Medical history	X	X	X	X		X
Concomitant medications		X				X
Eligibility assessment	X	X				
Randomisation				X		
Dispensing of trial drugs				X	X	
Daily Questionnaire					X	
Compliance					X	
Adverse event assessments					X	X

22 APPENDIX B: AMENDMENT HISTORY

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made
1	1.1		Emma Ogburn; Chris Butler; Gail Hayward	Inclusion criteria: change 'known heart disease' to 'Known heart disease and/or hypertension'; Exclusion criteria: exclude patients taking the following drugs: penicillamine, amiodarone, ciclosporin, chloroquine. Update section 9.6 to include vision changes and lowering of blood sugar. Update change in Funder and update Investigator list to reflect UKRI funder bid.

List details of all protocol amendments here whenever a new version of the protocol is produced.

Protocol amendments must be submitted to the Sponsor for approval prior to submission to the REC committee, HRA (where required) or MHRA.

Trial Title: Platform Randomised trial of INterventions against COVID-19 In older peoPLE

Internal Reference Number / Short title: PRINCIPLE

Ethics Ref: 20/SC/0158

IRAS Project ID: 281958

EudraCT Number: 2020-001209-22

Date and Version No: 27 March 2020 version 1.0

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Statistician Signature:

No potential conflict of interest

Confidentiality Statement

This document contains confidential information that must not be disclosed to anyone other than the Sponsor, the Investigator Team, HRA, host organisation, and members of the Research Ethics Committee and Regulatory Authorities unless authorised to do so.

Protocol signatures continued

Trial Title: Platform Randomised trial of INterventions against COVID-19 In older peoPLE (PRINCIPLE)

EudraCT Number: 2020-001209-22
Protocol Date and Version No: v1.0 27 March 2020

Protocol signature page

The undersigned has read and understood the trial protocol detailed above and agrees to conduct the trial in compliance with the protocol.

Principal Investigator (Please print name)	Signature	Site name or ID number	Date

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1. KEY TRIAL CONTACTS

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2. LAY SUMMARY

COVID-19 disproportionately affects people over 50 years old with comorbidities and those over 65 years old. The infection causes considerable morbidity and mortality in this population group in particular, and is having a devastating effect on people's health, and society in the UK and internationally.(1-4) So far, there are no specific treatments for COVID-19 that have been proven in rigorous clinical trials to be effective. Most

cases are being managed in the community. It is essential that we urgently identify interventions that may favourably modify progression of the infection. An ideal intervention would be one that is safe, with few side-effects, helps prevent disease progression, and can be administered in the community using existing NHS processes and capability.

Setting up a bespoke randomised controlled trial for each potential intervention that might become available will be inefficient.(5-7) We therefore propose establishing a platform, randomised controlled trial in primary care that can be rapidly deployed to evaluate low risk interventions for high risk people. This platform trial will, in the first instance, evaluate a drug called hydroxychloroquine. This is a drug that is already available within the NHS (although not for this indication currently), and has a generally benign side effect profile(8), but that has not been subject to randomised controlled trials for this indication in Europe or in community healthcare settings. Using an efficient open clinical trial design, with procedures embedded in existing health service structures and capabilities as afar as possible, our trial aims to give a rapid answer about the effectiveness of trial treatments in modifying the disease course. The goal is to prevent disease progression such that affected individuals will recover sooner, but critically, avoid the need for hospital admission. The platform trial will be flexible in that it will operate under a master protocol that will allow the addition of further interventions into the trial while the trial is already in progress, should such suitable interventions become available for this kind of evaluation.(5) This means that a new trial does *not* need to be started afresh each time an additional suitable intervention becomes available, and it also means that existing controls can be used efficiently to give rapid answers about the effectiveness of new interventions. This is particularly important as new candidate interventions are being considered on a regular basis.

The trial will be implemented in the first instance by the Oxford Royal College of General Practitioners (RCGP) Research and Surveillance Centre (RSC) general practices. This is one of Europe's oldest sentinel systems. RCGP RSC has produced a weekly report of influenza, respiratory and other infections in primary care for over 50 years. RCGP RSC works closely with Public Health England (PHE). More information at: www.rcgp.org.uk/rsc. The RCGP RSC Network has over 500 practices, including 100 practices currently swabbing patients with suspected COVID-19 in partnership with Public Health England (PHE).

Trial aspects will be managed by the UK Clinical Research Collaboration Registered University of Oxford Primary Care and Vaccines Clinical Trials Unit.

3. SYNOPSIS

Trial Title	Platform Randomised trial of INterventions against COVID-19 In older peoPLE		
Internal ref. no. (or short title)	PRINCIPLE		
Trial registration	ISRCTN 86534580		
Sponsor	University of Oxford		
Funder	UKRI/NIHR		
Clinical Phase	III		
Trial Design	Pragmatic, platform, randomised controlled trial of interventions for COVID-19 in PRIMARY CARE		
Trial Participants	Patients ≥50-64 years with comorbidities detailed below, and aged ≥65 with or without comorbidity presenting within 7 days since onset of symptoms with a new continuous cough and/or high temperature during time of prevalent COVID-19 infections		
Sample Size	Approximately 3000 (1500 per arm)		
Planned Trial Period	The trial will start as soon as permissions are in place and procedures and structures implemented. The platform trial will be ongoing until cases of COVID-19 wane to a low level and/or there are no new interventions that require evaluation in pragmatic randomised controlled trial in primary care. March 2022 has been decided as the formal end date at this stage, but that may need to be amended, depending on circumstances prevailing at the time.		
Planned Recruitment period	The first inclusion is planned for as soon as possible, and the duration of the trial will depend on evolving circumstances.		
	Objectives	Outcome Measures	Timepoint (s)
Primary	To assess effectiveness of trial treatments in reducing the need for hospital admission or death, for patients aged ≥50 years with serious comorbidity, and aged ≥65 with or without comorbidity and suspected COVID-19 infection during time of prevalent COVID-19 infections	Hospital admission or mortality related to suspected COVID-19	Within 28 days
Secondary	To explore whether trial treatment reduces: 1) Duration of severe symptoms 2) Time taken to self-report recovery	1-2 Patient report on day they feel to have recovered 3. Contacts with health services reported by patients and captured by reports of patients 'medical	Daily online symptoms score. Telephone call or text day 7, 14 and 28 if data not being received online

	3) Contacts with the health services 4) Consumption of antibiotics 5) Hospital assessment not leading to admission 6) Oxygen administration 7) Intensive Care Unit admission 8) Mechanical ventilation 9) To determine if effects are specific to those with the infections syndrome but who test positive for COVID-19 10) Duration of hospital admission	records where the practice is a member of RSC 4. Bi-weekly reports from participants primary care medical records 5-8 and 10 patient report/carer report/medical record in primary care and hospital care 9. Swab results for COVID-19 will indicate an "Intention to Treat Infected" group within the overall cohort for sub analysis	GP notes review where available through Oxford RCGP RSC network after 28 days HES/ONS/EMIS data linkage after 28 days where patients have been assessed in hospital Swab result available once processed from GP record and from PHE laboratory
Intervention(s)	1. Hydroxychloroquine 200 mg twice a day for 7 days Further interventions may be added during the course of the trial, subject to suitable interventions becoming available and all necessary approvals being first obtained.		
Comparator	In the first instance, this will be a two-arm trial, with the intervention am being usual care plus hydroxychloroquine and the comparator being usual care. There will be no placebo control in this study in the first instance		

4. ABBREVIATIONS

AE	Adverse event
AR	Adverse reaction
CI	Chief Investigator
CRF	Case Report Form
CT	Clinical Trials
CTA	Clinical Trials Authorisation
CTRG	Clinical Trials and Research Governance
DMSC	Data Monitoring Committee / Data Monitoring and Safety Committee
DSUR	Development Safety Update Report
GCP	Good Clinical Practice
GP	General Practitioner

HRA	Health Research Authority
IB	Investigators Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IMP	Investigational Medicinal Product
MHRA	Medicines and Healthcare products Regulatory Agency
NHS	National Health Service
NIHR	National Institute of Health Research
RES	Research Ethics Service
PHE	Public Health England
PI	Principal Investigator
PIL	Participant/ Patient Information Leaflet
R&D	NHS Trust R&D Department
RCGP RSC	Royal College of General Practitioners Research Surveillance Centre
REC	Research Ethics Committee
RSI	Reference Safety Information
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SDV	Source Data Verification
SMPC	Summary of Medicinal Product Characteristics
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reactions
TMF	Trial Master File

5. BACKGROUND AND RATIONALE

Introduction

There are no specific interventions against COVID-19 that have been proven, in rigorous trials, to alter the disease course by reducing the need for hospital assessment and admission.

A candidate intervention, a drug called hydroxychloroquine, has become available following early evaluation in some studies in China.(9, 10) This drug may work through limiting viral replication.(11, 12) Hydroxychloroquine is already available within the NHS on prescription for other indications, and has a generally benign safety profile.(8) Chloroquine is available to buy in the UK over the counter in some formulations and is used as antimalarial prophylaxis and treatment.

We urgently need to know whether this drug might modify the course of COVID-19 infections, particularly amongst those who are at higher risk of complications. At the present time, those are higher risk appear to be people aged 50 and over with comorbidity and those aged 65 and over.(1-3, 13)

It is also possible that new interventions may come on stream for evaluation in the near future. We therefore propose a platform trial that has the capability of rapidly evaluating hydroxychloroquine in the high-risk population group, but that will also be flexible enough to allow the addition of further interventions into the trial platform, should such interventions suitable for pragmatic evaluation in Primary Care become available during the course of the trial. New interventions will not be added into the trial without first obtaining the required permissions.

The Research Team has already conducted the world's first publicly funded platform, open, response-adaptive randomised controlled trial in primary care. Conducted in 13 countries, the ALIC4E trial of oseltamivir for influenza-like illness in primary care has been at the forefront of such efficient trial designs.(14)(1-4)

In the first instance, PRINCIPLE will be a two-arm trial comparing standard care to standard care plus hydroxychloroquine. There will be no placebo control. The primary outcome measure will be hospital admission or mortality related to suspected COVID-19.

Analysis will be by intention-to-treat. However, all participants recruited into the study will be asked to provide a swab so that their COVID-19 status can be ascertained by laboratory analysis. We will therefore, in addition to an "intention to treat analysis", conduct an "intention to treat infected" analysis.

The study aims to be rapidly initiated, so we can urgently determine if hydroxychloroquine (and any other suitable intervention that becomes available for rapid pragmatic evaluation) benefits patients. Treatments which are found to be ineffective should not be commissioned, as ineffective treatments simply put people at unnecessary risk of side-effects and waste resources. We urgently need to know whether hydroxychloroquine (and any other suitable intervention that becomes available for rapid pragmatic evaluation) might benefit patients and enhance the sustainability of NHS care during this crisis.

COVID 19

Europe is now the centre of the COVID-19 epidemic caused by the highly infectious SARS-COV2 virus.(4, 15) As of 22 March 2020 in the UK, 5,018 confirmed cases, and 233 deaths have been reported in the UK, and modelling studies suggest the pandemic will worsen rapidly in the UK and elsewhere.(4, 16)

The UK case definition for possible COVID-19 is dependent on care setting. COVID-19 is defined, where patients are well enough to remain in the community, as suspected for those who meet the following criteria:

- A new continuous cough - this means coughing a lot for more than an hour, or 3 or more coughing episodes in 24 hours (if you usually have a cough, it may be worse than usual)

And/or

- high temperature - this means you feel hot to touch on your chest or back (you do not need to take your temperature)

First Candidate Intervention: Hydroxychloroquine

Hydroxychloroquine is a hydroxylated version of the drug chloroquine.(10, 11) Both agents are commonly in use as anti-malarials, and are used in a variety of auto-immune diseases. They have received significant recent interest as potential modifiers of disease activity in COVID (17)19.(10, 18) Hydroxychloroquine is available in the UK by prescription, chloroquine is available to buy in the UK over the counter in some formulations for short term use.

Chloroquine is known to block virus infection by increasing endosomal pH required for virus/cell fusion, as well as interfering with the glycosylation of cellular receptors of SARS-CoV.(5) Besides its antiviral activity, chloroquine has an immune-modulating activity, which may synergistically enhance its antiviral effect *in vivo*.(11) Chloroquine is widely distributed in the whole body, including lungs, after oral administration.(10) The EC_{90} value of chloroquine against the 2019-nCoV in Vero E6 cells was 6.90 µM in one study (9) which can be clinically achievable as demonstrated in the plasma of rheumatoid arthritis patients who received 500 mg administration.(8)

Hydroxychloroquine has been found to be effective against intracellular micro-organisms including malaria and intracellular bacteria *Coxiella burnetii* and *Tropheryma Whipplei*.(11) Both chloroquine and hydroxychloroquine have been shown to have *in vitro* antiviral activity against SARS coronavirus in a number of studies.(11) Most recently activity against SARSCOV2 was shown to be greater for hydroxychloroquine than chloroquine (12).

In human COVID-19 trials in China, chloroquine has been shown to reduce length of hospital stay and severity of symptoms in a trial of 100 people (17), and there are multiple other trials registered as ongoing (https://clinicaltrials.gov/ct2/show/NCT04315896?term=hydroxychloroquine&cond=Corona+Virus+Infection&draw=2&rank=3).(10)

A pragmatic trial

The aim of PRINCIPLE is to be the national Primary Care platform trial for UK COVID-19, assessing the effectiveness of trial treatments in reducing the need for hospital admission or death for patients with suspected COVID-19 infection aged ≥50 years with serious comorbidity, and aged ≥65 with or without comorbidity, and during time of prevalent COVID-19 infections in the context of current care delivery. Thus, the trial will need to be as streamlined as possible so that it fits with minimal disruption into routine care during a period of widespread infection and considerable pressure on the NHS and society.

Platform trial

A platform trial, in contrast to traditional two-arm design, allows multiple arms to be considered simultaneously, and interventions can be dropped, added and/or replaced as evidence emerges for effectiveness, or lack of it. The intent is to establish an on-going trial infrastructure within a master protocol that uses all the data already accumulated for the assessment of current and subsequently introduced interventions.

New interventions will only be added after submission to the appropriate approval bodies.

Objectives	Outcome Measures	Timepoint(s) of evaluation of this outcome measure (if applicable)
Primary Objective To assess effectiveness of trial treatments in reducing the need for hospital admission or death, for patients aged ≥50 years with comorbidity, and aged ≥65 with or without comorbidity and suspected COVID-19 infection during time of prevalent COVID-19 infections	Hospital admission or mortality related to suspected COVID-19	Within 28 days
Secondary Objectives To explore whether trial treatment reduces 1) Duration of severe symptoms 2) Time taken to self-report recovery 3) Contacts with the health services 4) Consumption of antibiotics 5) Hospital assessment without admission 6) Oxygen administration 7) Intensive Care Unit admission 8) Mechanical ventilation 9) To determine if effects are specific to those with the infections syndrome but who test positive for COVID-19 10) Duration of hospital admission	1-2 Patient report on day they feel to have recovered 3. Contacts with health services reported by patients and captured by reports of patients 'medical records where the practice is a member of RSC 4. Bi-weekly reports from participants primary care medical records 5-8 and 10 patient report/carer report/medical record in primary care and hospital care 9. Swab results for COVID-19 will indicate an "Intention to Treat Infected" group within the overall cohort for sub analysis	Daily online symptoms score. Telephone call or text day 7, 14 and 28 if data not being received online GP notes review where available through Oxford RCGP RSC network after 28 days HES/ONS/EMIS data linkage after 28 days where patients have been assessed in hospital Swab result available once processed from GP record and from the supporting PHE laboratory

6. TRIAL DESIGN

This will be an open, prospective, individually randomised, platform, controlled clinical trial in community care. The trial will initially be two-arm, comparing standard care to standard care plus hydroxychloroquine.

The trial will be implemented in the first instance in practices that are already part of the RCGP RSC Network. Currently over 500 practices are part of this network, with 100 already offering a sentinel viral swabbing service which is being scaled up. Due to the pandemic, almost all practices in the UK have been asked to join the RCGP RSC Network.

7. PARTICIPANT IDENTIFICATION

7.1 Trial Participants

Patients ≥50 years with serious comorbidity, and patients aged ≥65 with or without comorbidity presenting in the community within 7 days since onset of symptoms, with a new continuous cough and/or high temperature during a time of prevalent COVID-19 infections.

A new continuous cough is taken to mean, "coughing a lot for more than an hour, or 3 or more coughing episodes in 24 hours (if you usually have a cough, it may be worse than usual)."

A high temperature is taken to mean, "you feel hot to touch on your chest or back (you do not need to take your temperature)"

7.1.1 Inclusion Criteria

- Participant is willing and able to give informed consent for participation in the study;
- Participant is willing to comply with all trial procedures;
- Onset of symptoms of possible COVID-19 in the community (continuous cough and/or high temperature) within 7 days of inclusion;
- Patients aged ≥50-64 years with any of the following listed comorbidities:
  - Known weakened immune system due to a serious illness or medication (e.g. chemotherapy);
  - Known heart disease and/ or hypertension;
  - Known asthma or lung disease;
  - Known diabetes not treated with insulin;
  - Known mild hepatic impairment;
  - Known stroke or neurological problem;

OR

- Patients aged ≥65 with or without comorbidity

7.1.2 Exclusion Criteria

- Pregnancy;
- Breastfeeding;
- Known severe hepatic impairment;
- Known severe renal impairment;
- Known porphyria;
- Type 1 diabetes or insulin dependent Type 2 Diabetes mellitus ;
- Known G6PD deficiency;
- Known myasthenia gravis;
- Known severe psoriasis;
- Known severe neurological disorders (especially those with a history of epilepsy—may lower seizure threshold);
- Previous adverse reaction to, or currently taking, hydroxychloroquine;
- Patients taking the following drugs: penicillamine, amiodarone, ciclosporin, chloroquine
- Known retinal disease;
- Judgement of the recruiting clinician deems ineligible.

8 TRIAL PROCEDURES

8.1 Recruitment

Recruitment will be possible through a variety of mechanisms due to the changing pandemic environment, and will include:

People who are concerned about COVID-19 continue to contact their general practices in large numbers. In the first instance, we will ask participating general practices to record whether a person phoning about COVID-19 is potentially eligible for the study. The practice will then ask the person if they are interested in finding out about potential trial participation or seek verbal consent if they are happy to be contacted by the trial team to discuss this further. If they are, information will be provided verbally and online either by the GP surgery or their contact details passed to the trial team who will provide such information on how they might join the study. Full information will be available to view on a web site and subsequently on the Participant Information Sheet (PIS). This information will inform potentially eligible and interested patients about how to access further trial information and consider participation, as well as the procedures involved in joining the study, and what participation would involve.

In addition to receiving calls from potentially eligible participants, participating practices will also be able to contact patients, preferably by text, who they have screened from their GP Practice list and who fall into the correct age and co-morbidity categories, to tell them about the study and to let them know that, should they develop relevant symptoms, they may wish to contact the practice or trial team directly to discuss participation in the trial.

The Study Team will be contacted directly by some potentially eligible patients due to word of mouth and media exposure. They may approach the Study Team by calls, emails and other mechanisms. The Study Team will then also be able to provide such people with information about potentially joining the trial, and the steps involved.

Any agencies from national bodies, such as NHS 111, who receive COVID-19 calls will be able to give information about possible trial participation and direct interested patients to the online information on and/or how to contact the Study Team.

An online screening, eligibility and consent procedure will be followed, with telephone calls as back-up for potential participants to be able to ask questions and clarifications about the study and their potential participation.

Participants will preferably complete the Informed Consent Form (ICF) online. They will be able to download their consent form for their records. This online process avoids risk from paper copies handled by people with infection, and is efficient during a time or rapid recruitment during a pandemic. Remote online consent or via telephone call is also required as the majority of GP practices will not conduct face-to-face appointments in the COVID-19 pandemic, and all potential COVID-19 sufferers are being informed by a national campaign to contact clinicians by telephone or online.

During this process, we will ask the potential participant to, if possible, include a phone number for a Study Partner, who may provide assistant to the study participant in completing trail procedures while the participant is ill. Identifying a Study Partner is not a requirement of study participation, merely a suggested mechanism to aid participation for consenting patients.

Once informed consent has been obtained and a medically qualified clinician has checked eligibility, participants will be randomised via a secure in line link using our in-house Sortition module. The participant, trial team and participant's GP will be notified electronically of what treatment allocation they have been randomised to. The participant and GP can review the PIS and completed ICF at any time using a secure log-in access code.

If not sampled face-to-face, all participants will be sent a sampling kit for self-sampling by their practice, study team or other facilities such as Public Health England (PHE). They will receive clear instructions on how to self-sample, as per PHE standard advice. Once the sample has been taken, they will be asked to place the sample in the provided container, sealed in a double envelope, which will be posted to PHE laboratory according to their standard practice for COVID-19. For trial purposes, we will not store the swabs after testing but PHE may keep the specimen for up to 5 years following their own approved processes. Participants will be informed of their COVID-19 swab result by their GP.

Participants will be issued with an online link where they will be asked to record the presence and severity of a few simple symptoms each day. Where online data is not being entered by participants, the research team will contact the participants and/or their study partner following days 7, 14 and 28. The study team will make no more than three attempts to contact the participant/Trial Partner at each of these follow-up points. We will also obtain consent to ascertain relevant data from hospital records about length of stay and ICU admission and ventilation.

The RCGP RSC will report to the central trial office at least twice weekly about healthcare contacts in the participating patient's clinical records, as they are able to download this information centrally for study participants. This will be used as confirmation and a back-up for information obtained directly from study participants and other data sources outlined above.

8.2 Screening and Eligibility Assessment

Participants will be screened after they read the PIS, by completing online eligibility questions in lay terms (based on section 7), and if they meet screening criteria, they will be asked to complete an online consent form (see above). A screening trial ID number will be assigned. The participant will go on to enter online baseline information, including their contact details and those of a Study Partners, if they have a Study Partner available to help them with the study. The trial team and responsible clinician or delegate will be notified electronically, the medically qualified clinician will confirm eligibility online and complete the eligibility CRF online. Once deemed eligible, the clinician will go on to randomise the participant. The

participant, clinician and trial team will be notified of the randomisation and the treatment group allocated.

8.3 Informed Consent

Written and verbal versions of the Participant Information Sheet (PIS) and the Informed Consent Form (ICF) will be presented to the participants detailing no less than: the exact nature of the study; the implications and constraints of the protocol, and, the known side-effects and risks involved in taking part. The study will provide a PIS that includes all necessary information in appropriate wording and format for the participant. It will be clearly stated that the participant is free to withdraw from the study at any time for any reason without prejudice to future care, and with no obligation to provide the reason for withdrawal.

Adequate time will be given to the participant to consider the information given to them and to ask any questions they may have about the trial before deciding whether they will participate in the study. However, they must still be recruited within the stated number of days of the onset of their symptoms to participate.

8.4 Randomisation

Participants will be randomised using a fully validated and compliant web-based randomisation system called Sortition. At the baseline assessment, the recruiter will enter the participant's baseline data into the online system, which will then enable the randomisation to take place. The randomisation process will take only a few moments via the online system and will not delay trial participation. Full details of response adaptive randomisation are described in section 11.2.4.

8.5 Blinding and code-breaking

PRINCIPLE will be an open-label trial. The participant and the recruiting clinician will know the participant's allocation. Therefore, no unblinding or code breaking is required in the event of a relevant emergency. However, those telephoning participants and managing the data will be blind to participant allocation.

The trial team and recruiting clinicians will be blinded to emerging results. During the course of the trial, only those on the Data Monitoring Committee will have access to the unblinded interim results.

8.6 Baseline Assessments

Once eligibility is confirmed, participants will be randomised using Sortition online. A sampling kit with insert containing instructions will be sent to the participant's home for self-sampling unless a sample can be taken face-to-face by the general practice. All participants, whether in the intervention or control group, will be asked to provide a swab or self-swab. Once participants take their own swab, they will put it in the secure container and double bag, and post it to the PHE laboratory supporting the study.

For those randomised to receive the first study intervention, hydroxychloroquine, the participant will be told how the drug can be obtained, either through collection at a pharmacy, GP practice, or by home delivery. GPs will be able to issue the study medication directly to participants.

8.7 Subsequent Visits

There is no requirement for participants to have a research-specific face-to-face visit as part of their study participation, as requiring additional health care contacts should be avoided if at all possible during the

COVID-19 pandemic. All subsequent measurements consist of self-completed questionnaires online or through telephone calls from the trial team and primary care and hospital record searches.

Participant follow-up will be primarily online, where they will be asked to complete questions about the presence and severity of symptoms each day for 28 days. If not completed, the trial team will contact the participant and/or their Study Partner to obtain the information.

The practice network that will be implementing the trial in the first instance, the Oxford Royal College of General Practitioners Surveillance Network, has the capacity to extract patient information from the clinical records twice a week. This more-or-less real-time ascertainment of primary care will augment information captured from patients themselves, their families or from the hospital records about intensive care admission and ventilation. Participant records will be accessed up to 3 months following enrolment to ascertain follow up data to day 28 from enrolment. Data will be collected in real time as far as possible, RCGP RCS, EMIS and NHS Digital will be utilised if required. We are engineering a new digital platform to enable daily extracts shortly.

8.8 Sample Handling

We will request a biological sample to test for COVID-19 from all consenting participants. Unless a swab can be taken face-to-face in the course of usual care, this will be a self-swab process with the practice generating the required forms. Once the swab has been taken it will be put in the regulation contained packaging, double bagged, and posted to the PHE laboratory that is supporting the study using their existing, safe, compliant processes. The trial team will utilise PHE and their existing processes and documentation. The trial team do not intend to store the swab once tested, and it won't be stored for the purpose of this trial. The swab material will fall under PHE and not the trial remit, and PHE may retain the swab for up to 5 years.

8.9 Early Discontinuation/Withdrawal of Participants

Each participant has the right to withdraw from the study at any time. In addition, the Investigator may discontinue a participant from the study at any time if the Investigator considers it necessary for any reason including:

- Ineligibility (either arising during the study or retrospectively having been overlooked at screening)
- Withdrawal of consent

The reason for withdrawal will be recorded on the CRF. Data that has already been collected about the participant will be kept and used. Swabs may be stored outside of the trial remit, for PHE purposes adhering to their retention policy.

8.10 Definition of End of Trial

Last data capture of last participant, when: no further suitable interventions are available and/or COVID 19 is no longer prevalent. March 2022 has been decided as the formal end date at this stage, but that may need to be amended, depending on circumstances prevailing at the time.

9 TRIAL INTERVENTIONS

9.1 Investigational Medicinal Product(s) (IMP) Description

First trial drug: Hydroxychloroquine sulphate 200 milligram (mg) tablets. The tablets are for oral administration.

One tablet (200mg) hydroxychloroquine to be taken twice daily for 7 days by mouth (14 tablets in total).

Special instructions:

Each dose should be taken with a meal or glass of milk.

Antacids may reduce absorption of hydroxychloroquine so it is advised that a 4-hour interval be observed between taking hydroxychloroquine and an antacid.

This is the standard therapeutic dose for its normal indication in adults which is for the treatment of rheumatoid arthritis, discoid and systemic lupus erythematosus, and dermatological conditions caused or aggravated by sunlight.

The Marketing Authorisation holder is Zentiva Pharma UK Limited Guildford Surrey GU1 4YS United Kingdom. Marketing authorisation number is PL 17780/0748.

9.2. Blinding of IMPs

There is no blinding of IMPs in the trial.

9.3. Storage of IMP

Hydroxychloroquine: Stored at room temperature in locked cupboards in restricted access rooms in the Primary Care Clinical Trials Unit (PC-CTU); in locked cupboards in restricted access rooms in GP Practices; in Pharmacies.

GP practices can order a supply of hydroxychloroquine from Public Health England using the existing Inform process. All GP practices in England are already set up on Inform, as they use this system to order influenza vaccines form Public Health England. Public Health England holds stock of Hydroxychloroquine in various forms, but for the purposes of the PRINCIPLE Trial, they will issue GPs with a supply from Zentiva, which comes in packs containing four blisters of 15 tablets each in each pack, totalling 60 tablets per pack (4 blisters of 15 tablets each). GPs will be provided with an envelope by the study team which will be labelled appropriately for trial medication, and they will add the patient's details to this label. This pack, containing instructions on using the medication, and containing 15 tablets, will be provided to the patient or their representative.

9.4. Compliance with Trial Treatment

Participants will receive a daily email asking for them to log on with a unique access code to an electronic system where they will record their symptoms. If uncompleted, the trial team will contact the participant and/or their Study Partner to obtain the data. Non-compliance can be assessed daily.

9.5. Accountability of the Trial Treatment

A risk-adapted approach will be used for drug accountability. Accountability logs will be kept by PC-CTU for when they ship drug.

9.6. Concomitant Medication

Hydroxychloroquine: Hydroxychloroquine will be used for short-term use (7 days) in this trial. The SmPC and precautions listed below focus on longer term chronic use.

Hydroxychloroquine might lower blood sugar levels in some people. If participants develop these symptoms they will be advised in the Patient Information documents to eat something sweet and seek clinical advice if the symptoms continue.

Hydroxychloroquine occasionally causes blurred vision, which typically resolves once the medication is stopped. Participants will be advised via the Participant Information documents that if they develop any

problems with vision, they should stop taking the medication immediately, seek clinical advice, and do not drive or operate any heavy machinery.

Hydroxychloroquine sulfate has been reported to increase plasma digoxin levels. Serum digoxin levels should be closely monitored in participants receiving concomitant treatment. Hydroxychloroquine sulfate may also be subject to several of the known interactions of chloroquine even though specific reports have not appeared. These include: potentiation of its direct blocking action at the neuromuscular junction by aminoglycoside antibiotics; inhibition of its metabolism by cimetidine which may increase plasma concentration of the antimalarial; antagonism of effect of neostigmine and pyridostigmine; reduction of the antibody response to primary immunisation with intradermal human diploid-cell rabies vaccine. As with chloroquine, antacids may reduce absorption of hydroxychloroquine so it is advised that a 4 hour interval be observed between hydroxychloroquine and antacid dosaging. As hydroxychloroquine may enhance the effects of a hypoglycaemic treatment, a decrease in doses of insulin or antidiabetic drugs may be required. Halofantrine prolongs the QT interval and should not be administered with other drugs that have the potential to induce cardiac arrhythmias, including hydroxychloroquine. Also, there may be an increased risk of inducing ventricular arrhythmias if hydroxychloroquine is used concomitantly with other arrhythmogenic drugs, such as amiodarone and moxifloxacin. An increased plasma ciclosporin level was reported when ciclosporin and hydroxychloroquine were co-administered. Hydroxychloroquine can lower the convulsive threshold. Co-administration of hydroxychloroquine with other antimalarials known to lower the convulsion threshold (e.g. mefloquine) may increase the risk of convulsions. Also, the activity of anti-epileptic drugs might be impaired if co-administered with hydroxychloroquine. In a single-dose interaction study, chloroquine has been reported to reduce the bioavailability of praziquantel. It is not known if there is a similar effect when hydroxychloroquine and praziquantel are co-administered. Per extrapolation, due to the similarities in structure and pharmacokinetic parameters between hydroxychloroquine and chloroquine, a similar effect may be expected for hydroxychloroquine. There is a theoretical risk of inhibition of intra-cellular α-galactosidase activity when hydroxychloroquine is co-administered with agalsidase.

10 SAFETY REPORTING

Hydroxychloroquine: Hydroxychloroquine has a well-documented safety profile and is a commonly used medication in a primary care setting (see above). We will collect symptoms and side effects from symptom diaries and participant telephone calls.

Common symptoms include abdominal pain; appetite decreased; diarrhoea; emotional lability; headache; nausea; skin reactions; vision disorders; and vomiting. Daily symptom diaries and participant telephone calls will record any symptoms and side effects from the trial medication. This information will be analysed as part of the whole trial analysis.

10.1 Adverse Event 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)	An untoward and unintended response in a participant to an investigational medicinal product which is related to any dose administered to that participant.

	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. 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.
Serious Adverse Event (SAE)	A serious adverse event is any untoward medical occurrence that: • 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 a serious adverse event when, based upon appropriate medical judgement, the event may jeopardise the participant and may require medical or surgical intervention to prevent one of the outcomes listed above. 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. *NOTE: Pregnancy is not, in itself an SAE. In the event that a participant or his/her partner becomes pregnant whilst taking part in a clinical trial or during a stage where the foetus could have been exposed to the medicinal product (in the case of the active substance or one of its metabolites having a long half-life) the pregnancy should be followed up by the investigator until delivery for congenital abnormality or birth defect, at which point it would fall within the definition of "serious".
Serious Adverse Reaction (SAR)	An adverse event that is both serious and, in the opinion of the reporting Investigator, believed with reasonable probability to be due to one of the trial treatments, based on the information provided.
Suspected Unexpected Serious Adverse Reaction (SUSAR)	A serious adverse reaction, the nature and severity of which is not consistent with the Reference Safety Information for the medicinal product in question set out: • in the case of a product with a marketing authorisation, in the approved summary of product characteristics (SmPC) for that product • in the case of any other investigational medicinal product, in the approved investigator's brochure (IB) relating to the trial in question.

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.

10.2 Assessment results outside of normal parameters as AEs and SAEs
There are no additional assessment results in this study

10.3 Assessment of Causality

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

- **Unrelated** – where an event is not considered to be related to the IMP
- **Possibly** – although a relationship to the IMP cannot be completely ruled out, the nature of the event, the underlying disease, concomitant medication or temporal relationship make other explanations possible.
- **Probably** – the temporal relationship and absence of a more likely explanation suggest the event could be related to the IMP.
- **Definitely** – the known effects of the IMP, its therapeutic class or based on challenge testing suggest that the IMP is the most likely cause.

All AEs (SAEs) labelled possibly, probably or definitely will be considered as related to the IMP.

10.4 Procedures for Reporting Adverse Events
All AEs will be collected from daily participant diaries, calls to participants/Study Partners and RCGP data downloads.

The severity of events will be assessed on the following scale: minor problem/moderate problem/major problem.

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.

10.5 Reporting Procedures for Serious Adverse Events

Hospitalisation and death due to COVID-19 are our primary outcomes so we will collect this data using a risk-adapted approach and will not report such as SAEs. SAE information will be collected from daily diaries, calls to participants and their Study Partner and RCGP data downloads and hospital records and analysed as part of the interim and whole trial analysis and will be reviewed at each Data Monitoring Committee meeting.

SAEs other than hospitalisation or death due to COVID-19 infection must be reported by the person who has discovered the SAE or nominated delegate within 24 hours of becoming aware of the event. The sponsor or delegate will perform an initial check of the report, request any additional information, and ensure it is reviewed by the CI or other delegated personnel for relatedness and expectedness as soon as possible taking into account the reporting time for a potential SUSAR according to the relevant competent authority. Additional and further requested information (follow-up or corrections to the original case) will be detailed on a new SAE Report Form and reviewed by the sponsor or delegate. If the event has not resolved, at the 28 day time point the SAE will be reviewed again to see if resolution has occurred. If the event is considered 'resolved' or 'resolving' no further follow up is required. If not, the event must be followed up until such a time point.

10.5.1. Other events exempt from immediate reporting as SAEs

Hospitalisations will be defined as at least a 1 night admission to hospital.

Hospitalisation for a pre-existing condition, including elective procedures planned prior to study entry, which has not worsened, does not constitute a serious adverse event and standard supportive care for the disease under study are not SAEs, and do not require SAE reporting.

10.5.2. Procedure for immediate reporting of Serious Adverse Events

- Study team will complete an SAE report form for all reportable SAEs.
- GP practice/study team/RCGP will provide additional, missing or follow up information in a timely fashion.

The CI or delegate will review the SAE once reported, collect as much information and report to the Sponsor within the timeframe according to the PC-CTU SOPs.

10.5.3 Expectedness

For SAEs that require reporting, expectedness of SARs will be determined according to the relevant RSI section of the Summary of Product Characteristics/IB. The RSI will be the current Sponsor and MHRA approved version at the time of the event occurrence. For assessment of expectedness in the Development Safety Update Report, see section 10.7 below.

10.6 SUSAR Reporting

All SUSARs will be reported by the sponsor delegate to the relevant Competent Authority and to the REC and other parties as applicable. For fatal and life-threatening SUSARS, this will be done no later than 7 calendar days after the Sponsor or delegate is first aware of the reaction. Any additional relevant information will be reported within 8 calendar days of the initial report. All other SUSARs will be reported within 15 calendar days.

Principal Investigators will be informed of all SUSARs for the relevant IMP for all studies with the same Sponsor, whether or not the event occurred in the current trial.

10.7 Development Safety Update Reports

The DSUR will be developed and submitted annually on the anniversary date that the trial receives Clinical Trial Authorisation +60 days. Due to the nature of this trial and the importance of sharing the science of COVID-19 and the drug, internationally, we expect to produce reports to the UK Government and regulatory agency more frequently upon request.

11 STATISTICS

11.1 Statistical Analysis Plan (SAP)

The statistical design and pre-specified analyses will be described in detail in a Statistical Analysis Plan (SAP) drafted by a Trial Statistician and signed off by the CI and Lead/senior statistician. A broad overview of the design and primary analyses is provided below.

11.2 Open Adaptive Platform Trial

PRINCIPLE is an open, adaptive, platform trial to evaluate emerging treatments of the novel COVID-19 virus. A "platform trial" is a trial in which multiple treatments for the same disease are tested simultaneously. The backbone of the trial is an adaptive clinical trial design. Pre-specified decision criteria allow for dropping a treatment for futility, declaring a treatment superior, or adding a new treatment to be tested. If at any point a treatment is deemed superior to the control arm, the superior treatment will replace the control arm as the new standard of care, and all subsequent treatments will be compared to the new standard of care. Because the process of dropping and adding treatments may be on-going for an indefinite period of time, platform trials may be better conceived of as a process rather than a singular clinical trial. In the context of the COVID-19 pandemic, the trial may continue as long as the pandemic persists.

The PRINCIPLE trial will begin as a 1:1 randomised trial of standard care versus standard care plus hydroxychloroquine but will have the capability to add additional interventions over time. The evaluation of any new interventions will be governed by the master protocol, including adaptive and decision criteria. In addition, the inclusion of any new interventions will require amendments and/or supplements to the protocol and SAP.

11.2.1 Primary Endpoint & Analysis

The primary endpoint is hospital admission or death as a result of COVID-19 infection. The primary analysis will be a Bayesian generalised linear model of the primary outcome regressed on treatment and stratification covariates (age, comorbidity). Let p_j denotes the probability of hospitalisation/death for persons in treatment group *j*, where $j = 0$ denotes the control arm and $j = 1$ denotes the intervention arm. A Bayesian posterior distribution will be derived for the estimated difference in probability of hospitalisation/death between treatment groups. The primary analysis for intervention *j* will test the following hypothesis:

$$H_0: p_j - p_0 \geq 0$$

$$H_1: p_j - p_0 < 0$$

If the Bayesian posterior probability of beneficial treatment effect is sufficiently large (e.g. ≥ 0.99), the null hypothesis will be rejected and the intervention will be deemed superior to control. The exact threshold of the superiority decision criterion (e.g. 0.99) will be determined *a priori* via simulation to control the one-sided Type I error of the study at approximately 0.025. The primary analysis for any additional interventions added later in the trial (i.e. not enrolling at the trial start) will only include control subjects who are concurrently randomised.

11.2.2 Adaptive Design

The pre-specified design will allow adaptations to the trial based on the observed data. These adaptations include the declaration of success or futility of an arm at an interim analysis, the addition or removal of treatment arms, and changes in the randomisation probabilities. Adaptations will occur at a given interim analysis if pre-specified conditions are satisfied. All will be documented in the SAP, including prespecified criteria and required precision for decisions about futility or effectiveness of interventions and/or replacing interventions in the trial.

11.2.3 Interim Analyses

The first interim analysis will occur when first 100 randomised participants have been followed up to 28 days, and subsequent weekly interim analyses. At each interim analysis, all enrolled intervention arms will

be evaluated for success or futility using the Bayesian primary analysis. If the Bayesian posterior probability of superiority of a given intervention is sufficiently large (e.g. ≥ 0.99), superiority will be declared. If there are additional intervention arms in the study (either currently or subsequently), the superior arm will replace the control arm as the new standard of care, and any subsequent interventions will be compared to the new control arm.

If the Bayesian posterior probability of a clinically meaningful treatment effect (≥ 0.05 decrease in the proportion hospitalized/dead) is sufficiently small (e.g. < 0.05) the intervention arm will be dropped from the study for futility. If there are no other intervention arms available, the trial will be suspended; otherwise accrual continues to the remaining treatment arms. The exact futility threshold will be pre-specified and determine via simulation.

11.2.4 Allocation & Response Adaptive Randomisation

Initially, randomisation will be fixed 1:1 for hydroxychloroquine versus usual care, with stratification by age (less than 65, greater than or equal to 65), and comorbidity (yes/no). If a second intervention arm is added to the study, randomisation will initially be 1:1:1 (stratified by age and comorbidity), and the additional arm will be included in the interim analyses (evaluating success and futility) if at least 50 participants have 28 days of follow-up. If there are at least 3 arms (2 intervention arms plus usual) in the study with at least 50 participants with 28-day outcomes, each interim analysis will incorporate modified randomisation probabilities via response adaptive randomisation (RAR). The general idea is to allocate more participants to the intervention arms that have the best observed outcomes.

More specifically, after RAR is activated, control allocation will be fixed at 1/Z, where Z is the total number of treatment arms. For example, for 3 arms (2 intervention arms plus control), the usual care allocation will be fixed at 1/3, and the remaining 2/3 participant allocation will be determined for the two intervention arms via response adaptive randomisation. The RAR probabilities for the intervention arms will be proportional to the Bayesian posterior probability that a given intervention is the best intervention.

11.2.5 Sample Size Justification

Given the open perpetual trial structure, the trial does not have a finite ending based on sample size. Rather, the trial will continue until either superiority or futility is claimed for an intervention, or until the pandemic expires in the population. We estimate that approximately 1500 participants per arm (3000 participants total if only a single intervention vs. usual care) will be required to provide 90% power for detecting a 5 percentage point benefit in the proportion of subjects experiencing hospitalisation/death. This calculation is based on the assumption of an underlying 20% combined hospitalisation/death rate in the study population, with an intervention lowering the hospitalisation/death rate to 15%, with some adjustments for the multiple interim analyses. On average, we expect fewer participants to be required when there is a large treatment benefit or complete lack of benefit. For example, if the true benefit is a 10 percentage point decrease in hospitalisation/mortality (20% usual care vs. 10% treatment), on average only 250 subjects per arm are required to provide sufficient power. The primary advantage of the adaptive design is the ability to adapt the sample size to the observed data, thus addressing the primary hypothesis as quickly and as efficiently as possible.

11.2.6 Virtual Trial Simulations

Because of the adaptive platform trial structure, there exists no simple formula(s) to calculate power and Type I error (false positive rate). Hence, virtual trial simulations will be used to fully characterize and quantify the power and Type I error of the design. These simulations will be conducted prior to the first interim analysis, and will be used to optimize the adaptive decision criterion and RAR parameters. The simulations will include a comprehensive evaluation of trial performance across a wide range of

assumptions (e.g. underlying distribution of outcome in control arm, treatment effect, accrual rates, etc.). This will include summaries regarding the number of subjects required to make a success or futility conclusions for each intervention. For example, we will quantify the probability of claiming superiority at the first interim analysis with 100 participants with observed outcomes. Complete details of the simulations will be provided in the SAP with an accompanying adaptive design report.

11.2.7 Procedure for Accounting for Missing, Unused, and Spurious Data.

Full details of handling missing data will be specified in the SAP.

11.3 Primary Analysis Population

The primary analysis population was defined as all participants for whom data were available were analysed according to the groups they were randomly allocated to, regardless of deviation from protocol and irrespective of their COVID-19 status. Secondary analyses will conduct the primary analysis on the subset of participants with confirmed COVID-19.

11.4 Procedures for Reporting any Deviation(s) from the Original Statistical Plan

Analyses will be carried out in accordance with the SAP. Any additional analysis that is not specified in the SAP or any deviation(s) from the original SAP (and reasons) will be specified in the Statistical Report. Reasons for these changes will be documented and authorised by the Chief Investigator.

12 DATA MANAGEMENT

The data management aspects of the study are summarised here with details fully described in the Data Management Plan.

12.1 Source Data

Source documents are where data are first recorded, and from which participants' CRF data are obtained. These include, but are not limited to, hospital records (from which medical history and previous and concurrent medication may be summarised into the CRF), clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence.

If the participant fails to complete data online and after three attempts at contacting the participant/Trial Partner, the RCGP RSC may be utilised to obtain missing data. Data collected will include participant identifiable information and will be accessed at the University of Oxford according to PC-CTU Information Governance policies and GDPR. Data will only be held for the duration of which its required, this will be reviewed annually.

CRF entries will be considered source data if the CRF is the site of the original recording (e.g. there is no other written or electronic record of data). All documents will be stored safely in confidential conditions. On all study-specific documents, other than the signed consent, the participant will be referred to by the study participant number/code, not by name.

12.2 Access to Data

Direct access will be granted to authorised representatives from the Sponsor and host institution for monitoring and/or audit of the study to ensure compliance with regulations.

12.3 Data Recording and Record Keeping

A CTU data manager will be assigned to the study, as delegated by the CI, and will be responsible for overseeing the receiving, entering, cleaning, querying, analysing and storing all data that accrues from the study by designated persons. The data will be entered into the volunteers' CRFs in an electronic format by the participant or trial team (using OpenClinica™ database via Sentry). OpenClinica™ is stored on a secure server – data will be entered in a web browser on PCs in the Clinical Trials Unit building and then transferred to the OpenClinica Database by encrypted (Https) transfer. OpenClinica™ meets FDA part 11B standards. This includes safety data, laboratory data and outcome data. Safety data will also be collected through electronic diaries which are stored on a secure server.

Sentry is an online secure data entry system developed in-house at PC-CTU and hosted at Oxford. It is designed to collect sensitive data, such as participant contact details, and securely retain them separate form a trial's clinical data. Sentry can also act as a central participant portal to manage online eligibility, eConsent and ePRO - acting as an intermediary between the participant and the clinical databases. Sentry is accessed via a secure HTTPS connection and all stored sensitive data is encrypted at rest to AES-256 standards.

The Investigators will maintain appropriate medical and research records for this trial, in compliance with the requirements of the Medicines for Human Use (Clinical Trial) Regulations 2004, ICH E6 GCP and regulatory and institutional requirements for the protection of confidentiality of volunteers. The Chief Investigator, Principal Investigator, Co-Investigators and Clinical Research Nurses will have access to records. The Investigators will permit authorized representatives of the sponsor, and regulatory agencies to examine (and when required by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits and evaluation of the study safety and progress.

13 QUALITY ASSURANCE PROCEDURES

The study will be conducted in accordance with the current approved protocol, GCP, relevant regulations and PC-CTU Standard Operating Procedures. All PIs, coordinating centre staff and site staff will receive training in trial procedures according to GCP where required.

Regular monitoring will be performed according to GCP using a risk based approach. Data will be evaluated for compliance with the protocol and accuracy in relation to source documents where possible. Following written standard operating procedures, the monitors will verify that the clinical trial is conducted and data are generated, documented and reported in compliance with the protocol, GCP and the applicable regulatory requirements. The Study Monitor may also assess SAE's.

The PC-CTU Trial Management Committee will be responsible for the monitoring of all aspects of the trial's conduct and progress and will ensure that the protocol is adhered to and that appropriate action is taken to safeguard participants and the quality of the trial itself. The TMG will be comprised of individuals responsible for the trial's day to day management (e.g. the CI, trial manager, statistician, data manager) and will meet regularly throughout the course of the trial.

13.1 Risk assessment

A risk assessment and monitoring plan will be prepared before the study opens and will be reviewed as necessary over the course of the study to reflect significant changes to the protocol or outcomes of monitoring activities.

13.2 Monitoring

The monitoring will be performed by the PC-CTU Quality Assurance Manager or delegate; The level of monitoring required will be informed by the risk assessment.

13.3 Trial committees

A Data Monitoring and Safety Committee (DMSC) and Trial Management Group (TMG) will be appointed in line with standard CTU procedures. The responsibilities of each group are as follows:

- DMSC- to review the data at each interim analysis as described in the Statistical Analysis section, as the updates to the randomisation scheme occur in order to ensure that the process is working correctly and to review and monitor the accruing data to ensure the rights, safety and wellbeing of the trial participants. They will make recommendations about how the study is operating, any ethical or safety issues and any data being produced from other relevant studies that might impact the trial. This Committee will also take on the role of a Trial Steering Committee, and so act as a single oversight committee.

- TMG- is responsible for the day-to-day running of the trial, including monitoring all aspects of the trial and ensuring that the protocol is being adhered to. It will include Co-Investigators and will meet weekly in the first instance. A core project team (PT) from within the TMG will meet daily as required for daily operational decision making.

14 PROTOCOL DEVIATIONS

A study related deviation is a departure from the ethically approved study protocol or other study document or process (e.g. consent process or administration of study intervention) or from Good Clinical Practice (GCP) or any applicable regulatory requirements. Any deviations from the protocol will be documented in a protocol deviation form and filed in the study master file.

A PC-CTU SOP is in place describing the procedure for identifying non-compliances, escalation to the central team and assessment of whether a non-compliance /deviation may be a potential Serious Breach.

15 SERIOUS BREACHES

A “serious breach” is a breach of the protocol or of the conditions or principles of Good Clinical Practice which is likely to affect to a significant degree –

(a) the safety or physical or mental integrity of the trial subjects; or

(b) the scientific value of the research.

In the event that a serious breach is suspected the Sponsor must be contacted within 1 working day. In collaboration with the C.I., the serious breach will be reviewed by the Sponsor and, if appropriate, the Sponsor will report it to the approving REC committee and the relevant NHS host organisation within seven calendar days.

16 ETHICAL AND REGULATORY CONSIDERATIONS

16.1 Declaration of Helsinki

The Investigator will ensure that this study is conducted in accordance with the principles of the Declaration of Helsinki.

16.2 Guidelines for Good Clinical Practice

The Investigator will ensure that this trial is conducted in accordance with relevant regulations and with Good Clinical Practice.

16.3 Approvals

Following Sponsor approval, the protocol, informed consent form, participant information sheets and any proposed informing material will be submitted to an appropriate Research Ethics Committee (REC), regulatory authorities, and host institution(s) for written approval. The PI and coordinating centres for each country will ensure and confirm correct regulatory approvals are gained prior to recruitment.

The Investigator will submit and, where necessary, obtain approval from the above parties for all substantial amendments to the original approved documents.

16.4 Other Ethical Considerations

If a particular arm is deemed futile and dropped, no further participants will be randomised to this arm and anyone who is currently on this arm will be informed it has been dropped.

Once a particular intervention has been declared superior and effective, that will become the comparator arm (i.e. standard care).

The vast majority of participant's, due to their co-morbidities, will be exempt from prescription charges. All participants will receive a £20 voucher to cover any prescriptions and other expenses they may incur as a consequence of study participation.

We do not intend to recruit people who do not have capacity to provide consent for themselves to participate into this study.

16.5 Reporting

The CI shall submit once a year throughout the clinical trial, or on request, an Annual Progress Report to the REC, HRA (where required), host organisation, funder (where required) and Sponsor. In addition, an End of Trial notification and final report will be submitted to the MHRA, the REC, host organisation and Sponsor.

16.6 Transparency in Research

Prior to the recruitment of the first participant, the trial will have been registered on a publicly accessible database.

Results will be uploaded to the European Clinical Trial (EudraCT) Database within 12 months of the end of trial declaration by the CI or their delegate.

Where the trial has been registered on multiple public platforms, the trial information will be kept up to date during the trial, and the CI or their delegate will upload results to all those public registries within 12 months of the end of the trial declaration.

16.7 Participant Confidentiality

The study will comply with the General Data Protection Regulation (GDPR) and Data Protection Act 2018, which require data to be de-identified as soon as it is practical to do so. The processing of the personal data of participants will be minimised by making use of a unique participant study number only on all study documents and any electronic database(s). All documents will be stored securely and only accessible by study staff and authorised personnel. The study staff will safeguard the privacy of participants' personal data.

16.8 Expenses and Benefits

All participants will be reimbursed with a £20 voucher, to covers the payment of a prescription, should they incur tis as a result of study participation, and a token of recognition of giving their time and

contribution to the study. The vast majority of participants will not have to pay a prescription change, should a prescription be issued as a result of trial participation. Most people with the co-morbidities outlines and in the age range required for eligibility, are not required to pay for prescriptions.

17 FINANCE AND INSURANCE

17.1 Funding

The study is funded by the UKRI/NIHR via a MRC call.

17.2 Insurance

The University has a specialist insurance policy in place which would operate in the event of any participant suffering harm as a result of their involvement in the research (Newline Underwriting Management Ltd, at Lloyd's of London). NHS indemnity operates in respect of the clinical treatment that is provided.

17.3 Contractual arrangements

Appropriate contractual arrangements will be put in place with all third parties.

18 PUBLICATION POLICY

The Investigators (those listed on the protocol and others to be decided at publication) will be involved in reviewing drafts of the manuscripts, abstracts, press releases and any other publications arising from the

study. Authors will acknowledge the study funders. Authorship will be determined in accordance with the ICMJE guidelines and other contributors will be acknowledged.

19 DEVELOPMENT OF A NEW PRODUCT/ PROCESS OR THE GENERATION OF INTELLECTUAL PROPERTY

Ownership of IP generated by employees of the University vests in the University. The University will ensure appropriate arrangements are in place as regards any new IP arising from the trial.

20 ARCHIVING

Archiving will be done according to the UOXF PC-CTU SOP and study specific working instructions.

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21 APPENDIX A: SCHEDULE OF PROCEDURES

Procedures	**Visits**					
	Visit timing Day 0	**Day 0**	**Day 0**	**Day 0**	**Daily Day 1-28 incl**	**Day 29-3mths**
	Screening completed by participant online/phone	**Eligibility completed by participant online/phone**	**Baseline completed by participant online/phone**	**Eligibility completed by Clinician online/phone**	**Symptom Diaries completed by participant online/phone**	**Retrospective data collection by study team**
Informed consent	X	X	X	X	X	
Demographics	X	X	X			X
Medical history	X	X	X	X		X
Concomitant medications		X				X
Eligibility assessment	X	X				
Randomisation				X		
Dispensing of trial drugs				X	X	
Daily Questionnaire					X	
Compliance					X	
Adverse event assessments					X	X

22 APPENDIX B: AMENDMENT HISTORY

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made
1	1.1		Emma Ogburn; Chris Butler; Gail Hayward	Inclusion criteria: change 'known heart disease' to 'Known heart disease and/or hypertension'; Exclusion criteria: exclude patients taking the following drugs: penicillamine, amiodarone, ciclosporin, chloroquine. Update section 9.6 to include vision changes and lowering of blood sugar. Update change in Funder and update Investigator list to reflect UKRI funder bid.

List details of all protocol amendments here whenever a new version of the protocol is produced.

Protocol amendments must be submitted to the Sponsor for approval prior to submission to the REC committee, HRA (where required) or MHRA.

Platform Randomised trial of INterventions against COVID-19 In older peoPLE - PRINCIPLE

REC Number: 20/SC/058 **IRAS Number: 281958** **EudraCT Number: 2020-001209-22**

Chief Investigator: Professor Christopher Butler **Participant ID:**

CONSENT FORM

Thank you for completing the screening questionnaire, you have passed the screening stage for the trial.

Please read the Participant Information Sheet if you haven't already done so, and if you are willing to participate please select 'Yes', TYPE your FIRST and LAST names below and then click Submit

If you agree, please select 'Yes' to confirm that you have read and understood the following:

		YES	NO
1	I confirm I have read and understood the information sheet version number ____-_____dated __ __ / __ __ __ / __ __ __ __ for the above study. I have had the opportunity to ask questions and had these answered satisfactorily.		
2	I understand my participation is voluntary and that I am free to withdraw at any time, without giving any reason, and without my medical care or legal rights being affected.		
3	I understand that I will be randomised to receive either: standard care plus the trial treatment or standard care and I will not be able to choose which I will receive.		
4	I understand that relevant sections of my GP and Hospital medical notes and data collected during the study may be looked at by individuals from University of Oxford. It may also be reviewed by relevant people from regulatory authorities and from the NHS Trust(s). I give permission for these individuals to have access to my records.		
5	I consent to being contacted by the research team for the purposes of trial follow up and I understand that this will require me to provide my contact details to the research team.		
6	I consent to my GP being informed of my participation within the study.		
7	I agree to take part in the study		
	ADDITIONAL (optional, not required for study participation)	**YES**	**NO**
	I agree to provide the research team with the contact details of my Trial Partner. I confirm my Trial partner is aware of their role and willing to answer questions.		

Signature:
First Name:_____ Last Name:_____

You will have the opportunity to print a copy of the consent form after submission. Please contact the study team if you would like a copy sent to you

By submitting, I confirm that I am the person whose name is stated above.

If you have any questions about this or any other part of the study please contact the study team:

Tel: 0800 138 0880 Email principle@phc.ox.ac.uk

Participant:

Name: _____ Date: __ __ / __ __ / __ __ __ __

You will have the opportunity to print a copy of the consent form after submission. Please contact the study team if you would like a copy sent to you

Platform Randomised trial of INterventions against COVID-19 In older peoPLE - PRINCIPLE

REC Number: 20/SC/058 ~~xxxxxx~~ **IRAS Number: 281958** **EudraCT Number:** **2020-001209-22**

Chief Investigator: **Professor Christopher Butler** **Participant ID:**

CONSENT FORM

Thank you for completing the screening questionnaire, you have passed the screening stage for the trial.

Please read the Participant Information Sheet if you haven't already done so, and if you are willing to participate please select 'Yes', TYPE your FIRST and LAST names below and then click Submit

If you agree, please select 'Yes' to confirm that you have read and understood the following:

		YES	NO
1	I confirm I have read and understood the information sheet version number ____-_____ dated __ __ / __ __ __ / __ __ __ __ for the above study. I have had the opportunity to ask questions and had these answered satisfactorily.		
2	I understand my participation is voluntary and that I am free to withdraw at any time, without giving any reason, and without my medical care or legal rights being affected.		
3	I understand that I will be randomised to receive either: standard care plus the trial treatment or standard care and I will not be able to choose which I will receive.		
4	I understand that relevant sections of my GP and Hospital medical notes and data collected during the study may be looked at by individuals from University of Oxford. It may also be reviewed by relevant people from regulatory authorities and from the NHS Trust(s). I give permission for these individuals to have access to my records.		
5	I consent to being contacted by the research team for the purposes of trial follow up and I understand that this will require me to provide my contact details to the research team.		
7	I consent to my GP being informed of my participation within the study.		
8	I agree to take part in the study		
	ADDITIONAL (optional, not required for study participation)	**YES**	**NO**
	I agree to provide the research team with the contact details of my Trial Partner. I confirm my Trial partner is aware of their role and willing to answer questions.		

Signature:

First Name:_____ Last Name:_____

You will have the opportunity to print a copy of the consent form after submission. Please contact the study team if you would like a copy sent to you

By submitting, I confirm that I am the person whose name is stated above.

If you have any questions about this or any other part of the study please contact the study team:

Tel: XXXXXXXXX Email principle@phc.ox.ac.uk

Participant:

Name: _____ Date: __ __ / __ __ / __ __ __ __

You will have the opportunity to print a copy of the consent form after submission. Please contact the study team if you would like a copy sent to you

PRINCIPLE
Platform Randomised trial of INterventions against COVID-19 In older peoPLE

Platform Randomised trial of INterventions against COVID-19 In older people

PARTICIPANT INFORMATION LEAFLET

We would like to invite you to take part in a study about treatments for COVID-19 infection called PRINCIPLE.
Before you decide if you would like to take part it is important that you understand why we are doing this research and what it would involve for you.

Please take time to read the following information carefully and decide if you wish to take part.

You may like to talk to others, friends or family members about the trial. Please ask if there is anything that is not clear or if you would like more information.

University of Oxford
NUFFIELD DEPARTMENT OF PRIMARY CARE HEALTH SCIENCES
Primary Care Clinical Trials Unit
RCGP Royal College of General Practitioners Research & Surveillance Centre
UKRI Medical Research Council
EudraCT number:2020-001209-22
NHS

What is the purpose of the trial?

COVID-19

The risk of complications from COVID-19 is generally greater in people aged 50 years and older with underlying health conditions and in those aged 65 years and older. This new viral infection can lead to significant medical problems, hospitalisation, and sometimes death.

So far, there are no treatments that have been proven in clinical trials to be effective in treating COVID-19 infection. Most of the infections are being managed in the community and it is essential that we identify treatments that help to reduce the progression of the disease and therefore the need for hospital admission. An ideal treatment would be one that is safe, with few side-effects, helps prevent disease progression, and can be administered in the community.

The Trial

As yet, there are currently no known treatments for COVID-19 that have been proven to be effective. Our trial aims to evaluate potential treatments as they are identified. To be able to do this, we aim to test one or more suitable, potential treatments for COVID-19, as soon as they become available.

In the first instance, we will evaluate a drug called hydroxychloroquine. This is a drug that is well known and has been used for many years around the world for conditions such as Malaria and Rheumatoid Arthritis, but is not currently used to treat this kind of infection.

We want to make treatments that are proven to be effective as widely and as rapidly available as possible. However, we do not want to give people medication that does not work, and may simply put them at unnecessary risk of side effects.

At the moment we really do not have enough information about whether any benefits from taking this drug outweigh any possible harms from the drug. So we do not know yet if this drug does work for COVID-19, and that is why we urgently need to do a proper trial so we have the information we need to guide the provision of best care for all.

Aim

We aim to find out whether selected treatments given to those at higher risk of becoming more ill when they are infected with COVID-19 helps reduce the need for hospitalisation and the length of stay required, helps people recover quicker and get fewer complications.

All people included in the study will be provided with a test for COVID-19, some will receive the medication we are testing and some will be allocated to current usual care without the medication we are testing.

Can I take part?

We intend to recruit at least 3000 people to the trial.

To take part, you need to be experiencing symptoms that are likely to be caused by a COVID-19 infection - a continuous cough and/or a high temperature. A high temperature means you feel hot to touch on your chest or back (you do not need to measure your temperature). A new, continuous cough means coughing a lot for more than an hour, or 3 or more coughing episodes in 24 hours (if you usually have a cough, it may be worse than usual) You need to have had these symptoms for **fewer than eight days.**

You also need to be **aged 50 to 64, with at least one of the following conditions:**

∗ • weakened immune system due to a serious illness or medication (e.g. chemotherapy)

• heart disease

• asthma or lung disease

• Diabetes not treated with insulin

• liver disease

• stroke or neurological problem

Or you can take part if you have symptoms of COVID-19 and are **aged 65 and over.**

Participants should not be taking any other medications other than their usual prescribed medication and medications prescribed in the study.

Do I have to take part?

Participation is entirely voluntary. It is up to you to decide whether to take part in the trial or not. A decision not to take part will not affect the standard of care you receive from the NHS in any way, now or in the future.

What will happen to me if I take part?

You will visit our website if you experience symptoms of COVID-19. The information on the website is the same as the information in this leaflet. Once you have read it, if you are interested in taking part, we will ask you to complete a short online form to see if you are eligible. If you would like to call us to discuss the trial before agreeing to take part, then you can contact us using the contact details on page 15.

Informed Consent

If we think you are eligible to participate in the study, you will be asked to complete an online consent form. Instructions on how to fill out the form will be provided, so you will know what to do. You will be able to download and keep a copy of your informed consent form.

Initial Questionnaire

Then, you will be asked to complete a short questionnaire giving some details about you and the symptoms you have been experiencing. We will also collect some contact details such as your name, email address and telephone number. We will also ask you to provide details of a Trial Partner. This could be a relative, spouse, friend or carer, if such a person is available, who we will contact for information about you if we are unable to get hold of you for whatever reason

Letting Your GP Know

Once you have completed the informed consent and additional questions the website will notify the trial team and your GP with this information. A qualified medical practitioner will then check that there are no other medical reasons why you cannot participate.

If we find that you cannot participate, you will be sent an email to let you know. If you are able to take part in the trial, our computer system will randomise you to let us know which group you will be in. There is more information on this in the next section.

What will happen to me if I take part? Flowchart.

You may receive a text from your practice with a link to this participant information sheet, be told about the study by another health care provider, by the trial team or you may be made aware via national media coverage. You then let us know you are interested in taking part by completing the online form you are directed to. The form will ask you some questions about your health and your symptoms. You will also complete a consent form to say that you want to take part.

We will then ask a qualified medical practitioner to confirm that there are no medical issues to stop you from taking part.

After this, our computer system will allocate you at random (like rolling a dice) to receive either:

- Standard Care as advised by the NHS plus Trial Treatment or
- Standard Care as advised by the NHS

Neither you, your GP or the trial team can choose which group you will be allocated.

Follow-up

You will receive a swab kit and instructions of how to take your own sample. We will also tell you how to post the sample to the labs. If randomised to the trial treatment group, you will be provided with the drug which you will be asked to take for the required number of days.

You will also be asked to answer some questions each day online for up to 28 days telling us about any symptoms you might be experiencing and how well you are feeling. We will ask you to complete this diary online, if we don't receive the information from you, we will call you to remind you to answer the questions.

During the follow up period we will also ask that you, or someone close to you notifies us if you are admitted to hospital.

Randomisation

The final part of the process will tell you whether you will receive standard care (which includes a swab) or standard care plus the trial treatment (includes a swab). You will be randomly allocated (like rolling a dice) by our computer system to one of these groups and neither you, your GP or the trial team can decide which group you will be in.

You will receive an email to let you know which group you have been allocated to; your GP and the trial team will also receive this email.

Swab

Everyone who takes part in the trial will be asked to take two swabs, one from their nose and one from their throat. You will instructions on how to take your own sample at home using the swab kit. We will also tell you how to post the sample to the labs using the envelopes we provide.

You will be asked to send the swab to Public Health England using the packaging we provide. The swab will confirm whether or not you have COVID-19 and the result will be sent to your GP.

Public Health England (PHE) may keep the specimen for up to 5 years, following their own approved processes.

Trial Treatment

If you are randomised to the standard care plus trial treatment group, arrangements will be made for the drug to be delivered to you or you may collect/nominate an individual to collect the drug from a local pharmacy, or local GP. You will be told exactly how you will receive the medication. You will also receive instructions on how to take it and for how long.

Should your condition worsen at any time during the trial, you should not contact the study team but contact your GP or other usual services that are open to you.

Follow-Up

You will receive a text message from us to ask you to complete questions relating to your symptoms and how well you feel every day for up to 28 days after you start the trial. This will be an online daily diary. If the trial team don't receive your daily diary answers online, they will text or telephone you on day 7, day 14 and day 28 of the follow up period and ask you a brief set of questions over the phone.

What happens if I am admitted to Hospital?

It is important that we know if you are admitted to hospital at any point during the 28 day follow up period. We need to know this whether or not you are taking the trial medication. We will give you a card that you can carry to let other healthcare professionals know that you are taking part in this trial, it is also really important that someone close to you knows that you are taking part in the trial, then if you are admitted to hospital, they can use the details on the card to let us know.

We may also access your medical records and data held about you in central NHS registries and databases (including NHS Digital, Public Health England, other equivalent bodies, and genetic or other research databases if you have provided samples to them) to collect information on any hospital admission that you may have during the follow up period

What are the possible disadvantages or side effects of taking part?

With any medicine, including ones that are already used within the NHS, there is a risk of side effects. For the treatment we are using in this trial, the common side effects (experienced by less than 10% of people who take the medication) are:

Hydroxychloroquine

* abdominal pain;
* decreased appetite;
* diarrhoea;
* headache;
* nausea;
* skin reactions;
* vomiting.

You will be able to tell us if you are experiencing any of these symptoms in your daily diary.

This medication occasionally causes blurred vision, which typically resolves once the medication is stopped. If you develop **any** problems with your vision, please stop taking the medication immediately, seek clinical advice, and do not drive or operate any heavy machinery.

This medication might lower blood sugar levels in some people. If this happens, you might feel hungry, sweaty, dizzy, have a faster or pounding heartbeat. If you develop these symptoms, please eat something sweet and seek clinical advice if the symptoms persist.

What are the possible benefits of taking part?

By taking part in this trial, you will be contributing towards the understanding of how we can treat COVID-19 and how the symptoms progress. This may or may not help to reduce the duration and severity of symptoms when people fall ill. All participants will also receive a swab, and be told if the swab is positive or not for COVID-19. We also hope to reduce the burden on the NHS.

At the moment, we really do not know if hydroxychloroquine is effective against COVID-19. The trial has been designed so that the results will be analysed not just at the end of the trial, but as the trial goes along. So as soon as we have an answer about the effectiveness of the first drug we are testing, hydroxychloroquine, we can make recommendations about best care.

Because we have designed the trial in such a way that the results will be analysed as it goes along, as soon as we get evidence that one arm is more effective, we will be able to allocate more people to the most effective arm of the study. In this way more people in the trial will have a greater chance of getting the most effective trial treatment. If it turns out that the first drug we are evaluating, hydroxychloroquine, is more effective than usual care, then this will become the standard of care in the trial, and any new drug added into the trial will be compared against it.

What will happen if I do not want to continue with the trial?

If you decide to take part, you can still withdraw at any time without giving a reason. Information collected up to that point will still be used.

The swab sample that you provide and send to Public Health England will still be processed and stored for up to five years, according to their standard processes.

If you wish to withdraw from the trial, please contact the trial team using the contact details on page 15. The decision to withdraw will not affect the standard of care you receive from the NHS in any way, now or in the future.

Expenses and Payments

You will be reimbursed for your participation through gift vouchers worth a total of £20. You will receive the voucher at the end of your follow up period, once we have received your completed symptom diary. If you would normally pay for your prescriptions, we will increase the calue of the voucher to £30, in order to offset the cost of the prescription charge.

What if there are any problems?

If you have any questions about this trial, please contact the Trial Manager (See Page 15 for contact details).

The University of Oxford, as Sponsor, has appropriate insurance in place in the unlikely event that you suffer any harm as a direct consequence of your participation in this trial.

If you wish to complain about any aspect of the way in which you have been approached or treated, or how your information is handled during the course of this trial, you should contact the trial team on principle@phc.ox.ac.uk or 01865 xxxxxx or you may contact the University of Oxford Clinical Trials and Research Governance (CTRG) office on 01865 616480, or the head of CTRG, email ctrg@admin.ox.ac.uk

What will happen to my data?

Data protection regulation requires that we state the legal basis for processing information about you. In the case of research, this is 'a task in the public interest.' The University of Oxford is the data controller and is responsible for looking after your information and using it properly. Responsible members of the University of Oxford may be given access to the trial data for monitoring and/or audit of the trial to ensure that the research is complying with applicable regulations.

We will be using information from you and your medical records and data held about you in central NHS registries and databases (including NHS Digital, Public Health England, other equivalent bodies, and genetic or other research databases if you have provided samples to them) in order to undertake this trial and will use the minimum personally-identifiable information possible. We will keep identifiable information about you for up to six months after the trial has finished. This excludes any research documents with personal information, such as consent forms, which will be held securely at the University of Oxford for 20 years after the end of the study.

Berry Consultants may assist with the statistical analysis for this trial and we will have to share the trial data with them in order for them to do this. The company is based in the USA, however no identifiable data will be given to them during this process.

The Royal College of General Practitioners Research Surveillance Centre may be used in order to gather data you haven't completed in your daily diaries. Data collected will include participant identifiable information and will be accessed at the University of Oxford according to PC-CTU Information Governance policies and GDPR. Data will only be held for the duration for which its required, this will be reviewed annually.
If we use a courier or home delivery service to provide you with trial materials, we will provide them with your name and address. These companies will use and store your data in accordance with GDPR.
Data protection regulation provides you with control over your personal data and how it is used. When you agree to your information being used in research, however, some of those rights may be limited in order for the research to be reliable and accurate.

Further information about your rights with respect to your personal data is available at: https://compliance.web.ox.ac.uk/individual-rights

You can find out more about how we use your information by contacting principle@phc.ox.ac.uk

What if relevant new information becomes available during the trial?

Sometimes during the course of a research project, new information becomes available about the treatment that is studied.

If this happens, the trial team will tell you about it and discuss with you whether you want to continue in the trial or not.

If you decide to continue you may be asked to sign an updated consent form.

What will happen to the results of the trial?

Results will be published in scientific journals, presented at scientific conferences, and published on the Oxford University departmental website. It will not be possible to identify you in any report, publication or presentation. If you would like to receive copies of any publications arising from this trial, please contact the trial team (details are on page 15).

Who is organising and funding the research?

Funding has been provided by UK Research and Innovation/Medical Research Council. PRINCIPLE has been set up by the Primary Care Clinical Trials Unit at the University of Oxford.

Who has reviewed the trial?

All research in the NHS is looked at by an independent group of people called a Research Ethics Committee (REC). The REC is there to protect your safety, rights, wellbeing and dignity. This trial has been ethically reviewed and was approved by the xxx Research Ethics Committee.

This trial has also received approval from the Medicines and Healthcare products Regulatory Agency (MHRA). The MHRA regulates the use of all medicines in the UK.

Thank you for taking the time to read this information leaflet and considering taking part in this trial.

If you would like any further information about this trial, you can contact the trial team here:

Trial Address:
PRINCIPLE Trial
Nuffield Department of Primary Care Health Sciences
Radcliffe Primary Care
Radcliffe Observatory Quarter, Woodstock Road
Oxford
OX2 6GG

Trial Team:
Tel. 0800 xxxxxx

Trial Email Address:
principle@phc.ox.ac.uk

NUFFIELD DEPARTMENT OF PRIMARY CARE HEALTH SCIENCES Primary Care Clinical Trials Unit

PRINCIPLE Platform Randomised trial of INterventions against COVID-19 In older peoPLE

Thank you for taking part in the PRINCIPLE Trial. Here is some information about the trial treatment you have been given.

You need to take your trial medication for **7 days**. You should take a total of **14 tablets**, so **1 tablet twice a day**. Your blister pack contains 15 tablets, the last tablet can be discarded once you have reached the end of your 7 days.

The medication you have been given is called **Hydroxychloroquine**. The common side effects of this medication are: **Abdominal pain; Decreased appetite; Diarrhoea; Headache; Nausea; Skin reactions and Vomiting**. You will be able to tell us if you are experiencing any of these symptoms in your daily diary.

This medication occasionally causes blurred vision, which typically resolves once the medication is stopped. If you develop **any** problems with your vision, please stop taking the medication immediately, seek clinical advice, and do not drive or operate any heavy machinery.

NUFFIELD DEPARTMENT OF PRIMARY CARE HEALTH SCIENCES Primary Care Clinical Trials Unit

PRINCIPLE Platform Randomised trial of INterventions against COVID-19 In older peoPLE

This medication might lower blood sugar levels in some people. If this happens, you might feel hungry, sweaty, dizzy, have a faster or pounding heartbeat. If you develop these symptoms, please eat something sweet and seek clinical advice if the symptoms persist.

You cannot take Hydroxychloroquine if you are taking any of the following medication: **Chloroquine; Amiodarone; Ciclosporin or Penicillamine**. If you are taking any of the above medications, please do not take the trial medication and speak to your GP.

Please remember that you should not be taking any other medications other than your usual prescribed medication and the medication you have been given for the trial.

Should your condition worsen at any time during the trial, you should not contact the study team but contact your GP or other usual services that are open to you.

If you need to contact the trial team, please do so using the details in your Patient Information Sheet

PRINCIPLE

Platform Randomised trial of INterventions against COVID-19 In older peoPLE

Instructions for participants

Thank you for taking part in the PRINCIPLE trial.

This information booklet will help guide you through what will happen during your time in the trial.

Please read on for more details about the trial medication and other key details.

Contact us

If you have any questions, please contact us on:

E-mail: principle@phc.ox.ac.uk

Telephone: 0800 138 0880

Summary

Please take your medication for the first 7 days of your participation. There is more detail in this booklet about how and when to take this.

At the start of the trial, we ask you to collect a self-swab sample, using the kit provided by either your GP or in your trial pack.
There are instructions in this booklet and the swab kit on how to do this.

During the trial period, we ask you to complete a short daily diary about your symptoms. If we do not receive your diary, we will call you and/or your trial partner to ask a few short questions.

Your participation will last for a total of 28 days.

Taking your trial medication

Your medication is called Hydroxychlorquine. The medication is in tablet form; the tablets are for oral administration only. You may have been given your medication by prescription, or we have included them within this trial pack.

- One tablet (200mg) should be taken twice daily for 7 days. This equals 14 tablets in total.
- Each dose should be taken with a meal or glass of milk.
- Antacids may reduce your body's absorption of Hydroxychloroquine, so you are advised to leave a 4-hour interval between taking your trial medication and an antacid.
- Please remember to complete the whole course of medication, even if you start to feel better during the trial.
- Please store the medication at room temperature.
- You will not receive further medication after the 7-day period.

Potential Side effects of Hydroxychlorquine

This medication might lower blood sugar levels in some people. If this happens, you might feel hungry, sweaty, dizzy, have a fast or pounding heartbeat or feel tired. If you develop these symptoms please eat something sweet and seek clinical advice if the symptoms continue.

This medication occasionally causes blurred vision, which typically resolves once the medication is stopped. If you develop **any** problems with your vision, please stop taking the medication immediately, seek clinical advice, and do not drive or operate any heavy machinery.

Completing the daily online diary

We ask you to complete a short daily symptoms diary for 28 days. This will take less than ten minutes of your time each day.

- You will be issued with a unique code and an internet link, which will take you to a secure online system to collect your diary entries confidentially.
- You will receive a text asking you to submit your answers on the same day; you may prefer to do this at a regular time for your own convenience and routine.

- You will be asked to record whether you are experiencing a few simple symptoms, and to rate the severity of these symptoms.
- Please ensure that you submit your diary to us at the end of the questions, so we receive all of your answers.
- If we do not receive your completed diary, or you are unable to access the online diary, we will contact you and/or your nominated trial partner on day 7, day 14 and day 28 of the follow up period to collect this information.
- Finally, we will also ask that you, or someone close to you notifies us if you are admitted to hospital.

Collecting your self-swab sample

- Please follow the simple instructions on how to self-sample provided with the swab kit. You only need to collect the samples provided in the kit during the trial.
- Once you have taken your self-swab, please place the samples in the vial provided.

- Seal the vial in the double envelope provided, and send freepost (pre-paid). You do not need to go to a post office, the envelope can be placed in a standard post box.
- Public Health England (PHE) may keep the specimen for up to 5 years, following their own approved processes.
- Your GP will be informed of your COVID-19 swab result once it is available.

PRINCIPLE TRIAL: TEXT MESSAGE INFORMATION FOR PARTICIPANTS (111)

This is a message from the NHS 111 service in relation to the COVID-19 outbreak. An Oxford University clinical trial exploring treatment for the COVID-19 virus is taking place. If you are experiencing **a continuous cough and/or a high temperature** and have had it for **less than 8 days**, please click here if you would like to find out more.

NUFFIELD DEPARTMENT OF PRIMARY CARE HEALTH SCIENCES
UNIVERSITY OF OXFORD

PRINCIPLE
Platform Randomised trial of INterventions against COVID-19 In older peoPLE

Radcliffe Observatory Quarter, Woodstock Road, Oxford. OX2 6GG
Tel: 01865 XXXXXX • principle@phc.ox.ac.uk • www.phc.ox.ac.uk/ctu

Address

Date

PRINCIPLE: Platform Randomised trial of INterventions against COVID-19 In older people

Dear

We are writing to thank you for your participation in the PRINCIPLE study. PRINCIPLE is a trial looking at how different treatments may help to treat COVID-19. By taking part in this study you have provided invaluable information that we hope will give us a better understanding of the virus.

Without people with your public spiritedness and willingness to contribute to medical research, we would not be able to gain a better understanding of how the virus works and possible treatments.

We are extremely grateful for your commitment and time spent responding to phone calls, taking a swab sample and completing the daily diaries. The information collected in your daily diaries is vital for the study. We will use the information you have provided about your symptoms and how well you have felt to determine how well the treatments work.

Please also find enclosed a £20 gift voucher as a small token of recognition of your tremendous contribution to the PRINCIPLE trial.

Please do contact us at any time if you have any questions.

With sincere gratitude

Chief Investigator

Participant ID:

_ _ _ _ _ _ _ _

PRINCIPLE
Platform Randomised trial of INterventions against COVID-19 In older peoPLE

Trial Team Contact Details:
principle@phc.ox.ac.uk
0800 138 0880

NUFFIELD DEPARTMENT OF PRIMARY CARE HEALTH SCIENCES

This patient is taking part in the Principle Trial

In case of emergency please contact their Study Partner:

Tel Number:

_____

PRINCIPLE – Text message for Daily Diary

Daily Diary – days 1-3
Hello from the PRINCIPLE trial team. Please click [insert link] to complete todays daily diary. Also remember to send the swab to PHE. If you have trial medication please remember to take it today. Any questions or problems (no medication/swab received by day 3) please call us on XXXXXXXX. Thank you for your time. To opt out of these messages send 'PRINCIPLE STOP' to XXXX.

Daily Diary – days 4-7 (or up to day 10 if meds not received until day 2/3)
Hello, this is the PRINCIPLE trial team. Please click [insert link] to complete todays daily diary. If you have trial medication please remember to take the full course. If you have any questions or there is a problem please call trial team on XXXXXXXX. Thank you for your time. To opt out of these messages send 'PRINCIPLE STOP' to XXXX.

Daily Diary – days 8-27
Hello, this is the PRINCIPLE trial team. Please click [insert link] to complete todays daily diary. Thank you for your time. To opt out of these messages send 'PRINCIPLE STOP' to XXXX.

Daily Diary – day 28
Hello, this is the PRINCIPLE trial team. Please click [insert link] to complete the last daily diary. We will call you within the next 1 – 3 days to collect some final trial data. Thank you for your participation in the PRINCIPLE trial, your time has helped to contribute to this important research.

PRINCIPLE – Text message for Daily Diary

Daily Diary – days 1-3
Hello from the PRINCIPLE trial team. Please click [insert link] to complete todays daily diary. Also remember to send the swab to PHE. If you have trial medication please remember to take it today. Any questions or problems (no medication/swab received by day 3) please call us on XXXXXXXX. Thank you for your time. To opt out of these messages send 'PRINCIPLE STOP' to XXXX.

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Hello, this is the PRINCIPLE trial team. Please click [insert link] to complete todays daily diary. Thank you for your time. To opt out of these messages send 'PRINCIPLE STOP' to XXXX.

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Hello, this is the PRINCIPLE trial team. Please click [insert link] to complete the last daily diary. We will call you within the next 1 – 3 days to collect some final trial data. Thank you for your participation in the PRINCIPLE trial, your time has helped to contribute to this important research.

Hannah Swayze

From: berkshire.rec@hra.nhs.uk <noreply@harp.org.uk>
Sent: 31 March 2020 13:11
To: Christopher Butler; CTRG Sponsorship Correspondence
Cc: Hannah Swayze
Subject: IRAS 281958. Amendment confirmation of REC Validation, categorisation and implementation information
Attachments: IRAS 281958 SL27 _Acknowledgement_of_a_valid_notice_of_a_substantial_amendment.pdf

Amendment Confirmation of REC Validation, Categorisation and Implementation Information

Dear Dr Butler,

IRAS Project ID:	281958
Short Study Title:	PRINCIPLE
Date complete amendment submission received:	30 March 2020
Amendment No./ Sponsor Ref:	SA1
Amendment Date:	27 March 2020
Amendment Type:	Substantial
Outcome of HRA and HCRW Assessment	**HRA and HCRW Approval for the amendment is pending.** HRA and HCRW Approval for the amendment will be separately confirmed by email.
Implementation date in NHS organisations in England and/or Wales	35 days from date amendment information together with this email, is supplied to participating organisations **(provided HRA and HCRW Approval for the amendment is in place and conditions are met)**
For NHS/HSC R&D Office information	
Amendment Category	A

Thank you for submitting an amendment to your project. We have now categorised your amendment and please find this, as well as other relevant information, in the table above.

Please also find attached a copy of the REC validation letter for the submitted amendment.

What should I do next?

Please read the information in IRAS, which provides you with information on how and when you can implement your amendment at NHS/HSC sites in each nation, and what actions you should take now.

If you have participating NHS/HSC organisations in any other UK nations that are affected by this amendment please note that **we will** forward the amendment submission to the relevant national coordinating function(s).

If not already provided, please email to us any regulatory approvals (where applicable) once available. Your amendment will be reviewed by the REC, as per the attached letter.

When can I implement this amendment?

You may implement this amendment in line with the information in IRAS. Please note that you may only implement changes described in the amendment notice.

Who should I contact if I have further questions about this amendment?

If you have any questions about the ethical review of this amendment, please do not hesitate to contact me.

If you have any other questions about this amendment please contact the relevant national coordinating centre for advice:

- England – amendments@hra.nhs.uk
- Northern Ireland – research.gateway@hscni.net
- Scotland – nhsg.NRSPCC@nhs.net
- Wales – HCRW.amendments@wales.nhs.uk

Additional information on the management of amendments can be found in the IRAS guidance.

Please do not hesitate to contact me if you require further information.

Kind regards

Alison Doherty
Approvals Administrator
Health Research Authority
Ground Floor | Skipton House | 80 London Road | London | SE1 6LH
E.amendments@hra.nhs.uk
W. www.hra.nhs.uk

Sign up to receive our newsletter HRA Latest.

Hannah Swayze

From: berkshire.rec@hra.nhs.uk <noreply@harp.org.uk>
Sent: 31 March 2020 14:22
To: Christopher Butler; CTRG Sponsorship Correspondence
Cc: Hannah Swayze
Subject: IRAS PROJECT ID 281958, REC Reference 20/SC/0158 Confirmation of favourable opinion for substantial amendment
Attachments: IRAS 281958 SL32_Favourable_opinion_of_a_substantial_amendment-1.pdf

Dear Dr Butler

IRAS project ID:	281958
REC reference:	20/SC/0158
Short Study title:	PRINCIPLE
Date complete amendment submission received:	30 March 2020
Amendment No./ Sponsor Ref:	SA1
Amendment Date:	27 March 2020
Amendment Type:	**Substantial**
Outcome of HRA Assessment	**This email also constitutes HRA and HCRW Approval for the amendment, and you should not expect anything further.**

I am pleased to confirm that this amendment has been reviewed by the Research Ethics Committee and has received a Favourable Opinion. Please find attached a copy of the Favourable Opinion letter.

HRA and HCRW Approval Status

As detailed above, **this email also constitutes HRA and HCRW Approval for the amendment**. No separate notice of HRA and HCRW Approval will be issued. You should implement this amendment at NHS organisations in England and/or Wales, in line with the conditions outlined in your categorisation email.

- If this study has HRA and HCRW Approval, this amendment may be implemented at participating NHS organisations in England and/or Wales once the conditions detailed in the categorisation section above have been met
- If this study is a pre-HRA Approval study, this amendment may be implemented at participating NHS organisations in England and/or Wales that have NHS Permission, once the conditions detailed in the categorisation section above have been met. For participating NHS organisations in England and/or Wales that do not have NHS Permission, these sites should be covered by HRA and HCRW Approval before the amendment is implemented at them, please see below;
- If this study is awaiting HRA and HCRW Approval, I have passed your amendment to my colleague and you should receive separate notification that the study has received HRA and HCRW Approval, incorporating approval for this amendment.

User Feedback

The Health Research Authority is continually striving to provide a high quality service to all applicants and sponsors. You are invited to give your view of the service you have received and the application procedure. If you wish to make your views known please use the feedback form available on the HRA website: http://www.hra.nhs.uk/about-the-hra/governance/quality-assurance/.

If you require further information, please contact amendments@hra.nhs.uk

20/SC/0158/AM01 Please quote this number on all correspondence

Kind regards

Alison Doherty
Approvals Administrator
Health Research Authority
Bristol REC Centre | Whitefriars | BS1 2NT
T. 020 7104 8049
E. berkshire.rec@hra.nhs.uk
W. www.hra.nhs.uk

Sign up to receive our newsletter HRA Latest.

Medicines & Healthcare products Regulatory Agency

MHRA

MHRA
10 South Colonnade
Canary Wharf
London
E14 4PU
United Kingdom
gov.uk/mhra

Prof C Butler
UNIVERSITY OF OXFORD
NUFFIELD DEPARTMENT OF PRIMARY CARE HEALTH SCIENCES,
RADCLIFFE OBSERVATORY QUARTER, WOODSTOCK ROAD
OXFORD
OX2 6GG
UNITED KINGDOM

30/03/2020

Dear Prof C Butler

THE MEDICINES FOR HUMAN USE (CLINICAL TRIALS) REGULATIONS 2004 S.I. 2004/1031

Our Reference:	CTA 21584/0426/001-0002
Eudract Number:	2020-001209-22
Product:	Plaquenil-Hydroxychloroquine
Protocol Number:	PRINCIPLE
Substantial Amendment Code Number:	Code Number: SA1 Version: Date: 2020/03/27

ACKNOWLEDGEMENT OF AMENDMENT

Thank you for your notice of amendment, received on 27/03/2020. The information you provided to support your request is complete and therefore your request is valid.

Your request will be assessed and you will be notified of the Licensing Authority's decision within 35 days.

Please quote the EudraCT number, CTA number and your amendment code in any further communications relating to this submission.

Yours sincerely,

Submissions
MHRA

Medicines & Healthcare products Regulatory Agency

MHRA

MHRA
10 South Colonnade
Canary Wharf
London
E14 4PU
United Kingdom

gov.uk/mhra

Prof C Butler
UNIVERSITY OF OXFORD
NUFFIELD DEPARTMENT OF PRIMARY CARE HEALTH SCIENCES,
RADCLIFFE OBSERVATORY QUARTER, WOODSTOCK ROAD
OXFORD
OX2 6GG
UNITED KINGDOM

30/03/2020

Dear Prof C Butler,

THE MEDICINES FOR HUMAN USE (CLINICAL TRIALS) REGULATIONS 2004 S.I. 2004/1031

Our Reference:	CTA 21584/0426/001-0002
Eudract Number:	2020-001209-22
Product:	Plaquenil-Hydroxychloroquine
Protocol number:	PRINCIPLE
Substantial Amendment Code Number:	Code Number: SA1 Version: Date: 2020/03/27

NOTICE OF ACCEPTANCE OF AMENDMENT

I am writing to inform you that the Licensing Authority accepts the proposed amendment to your clinical trial authorisation (CTA), received on 27/03/2020.

This amendment may therefore be made.

You are reminded that where it is appropriate, the Ethics Committee should also be notified of amendments.

Yours sincerely,

Clinical Trials Unit
MHRA

Health Research Authority

South Central - Berkshire Research Ethics Committee

Bristol REC Centre
Whitefriars
Level 3, Block B
Lewins Mead
Bristol
BS1 2NT

31 March 2020

Christopher Butler
University of Oxford
Radcliffe Observatory Quarter, Woodstock Road
Oxford
OX2 6GG

Dear Dr Butler

Study title:	**Platform Randomised trial of INterventions against COVID-19 In older peoPLE**
REC reference:	**20/SC/0158**
Protocol number:	**PRINCIPLE**
EudraCT number:	**2020-001209-22**
Amendment number:	**SA1**
Amendment date:	**27 March 2020**
IRAS project ID:	**281958**

Thank you for submitting the above amendment, which was received on 27 March 2020. I can confirm that this is a valid notice of a substantial amendment and will be reviewed by the Sub-Committee of the REC at its next meeting.

Documents received

The documents to be reviewed are as follows:

Document	*Version*	*Date*
Annex 2: Notification of Amendment [AmendmentFormMHRAEudract_snapshot (1)]	SA1	27 March 2020
Cover Letter [REC SA1 cover letter 27.03.20_2]		27 March 2020
Non-validated questionnaire [PRINCIPLE_Baseline_v0.5_27Mar2020_ clean + changes]	0.5	27 March 2020
Other [PRINCIPLE TRIAL - text message info (111) v1.0 27.03.2020]	1.0	27 March 2020
Other [PRINCIPLE_Call CRF_v0.5_27Mar2020_clean + changes]	0.5	27 March 2020
Other [PRINCIPLE_Eligibility_v0.5_27Mar2020_clean + changes]	0.5	27 March 2020
Other [PRINCIPLE_End_of_Follow_Up_Letter_v1.0_27.03.2020 clean + TT]	1.0	27 March 2020
Other [PRINCIPLE_Screening_v0.5_27Mar2020_clean + changes]	0.5	27 March 2020
Other [Required updates 27.03.2020]		27 March 2020

Participant consent form [PRINCIPLE Consent Form V1.0_27.3.2020_clean +TT]	1.0	27 March 2020
Participant information sheet (PIS) [IMP Participant Information_V1.0_27.03.2020]	1.0	27 March 2020
Participant information sheet (PIS) [PRINCIPLE Information for participants_v1.0_27Mar2020 Clean + TT]	1.0	27 March 2020
Participant information sheet (PIS) [PRINCIPLE PIS_ v1.1_ clean + tracked changes 27.03.20]	1.1	27 March 2020
Research protocol or project proposal [PRINCIPLE_Protocol_v0.12 23.03.2020 with clean + tracked changes]	0.12	23 March 2020
Sample diary card/patient card [PRINCIPLE_Daily Diary_v0.5_27Mar2020_ clean + changes]	0.5	27 March 2020
Sample diary card/patient card [PRINCIPLE_Participant_Contact_Card_v1.0_27.03.2020 Clean + TT]	1.0	27 March 2020
Sample diary card/patient card [PRINCIPLE_text message daily diaries_ v1.0 27.03.20 clean + TT]	1.0	27 March 2020

Notification of the Committee's decision

The Committee will issue an ethical opinion on the amendment within a maximum of 35 days from the date of receipt.

R&D approval

All investigators and research collaborators in the NHS should notify the R&D office for the relevant NHS care organisation of this amendment and check whether it affects R&D approval for the research.

HRA Learning

We are pleased to welcome researchers and research staff to our HRA Learning Events and online learning opportunities– see details at: https://www.hra.nhs.uk/planning-and-improving-research/learning/

20/SC/0158:	**Please quote this number on all correspondence**

Yours sincerely

Alison Doherty
Approvals Administrator

Email: berkshire.rec@hra.nhs.uk

Copy to: *N/A N/A CTRG*

Health Research Authority

South Central - Berkshire Research Ethics Committee

Bristol REC Centre
Whitefriars
Level 3, Block B
Lewins Mead
Bristol
BS1 2NT

31 March 2020

Christopher Butler
University of Oxford
Radcliffe Observatory Quarter, Woodstock Road
Oxford
OX2 6GG

Dear Dr Butler

Study title:	**Platform Randomised trial of INterventions against COVID-19 In older peoPLE**
REC reference:	**20/SC/0158**
Protocol number:	**PRINCIPLE**
EudraCT number:	**2020-001209-22**
Amendment number:	**SA1**
Amendment date:	**27 March 2020**
IRAS project ID:	**281958**

The above amendment was reviewed by the Sub-Committee in correspondence.

Ethical opinion

The members of the Committee taking part in the review gave a favourable ethical opinion of the amendment on the basis described in the notice of amendment form and supporting documentation.

Approved documents

The documents reviewed and approved at the meeting were:

Document	*Version*	*Date*
Annex 2: Notification of Amendment [AmendmentFormMHRAEudract_snapshot (1)]	SA1	27 March 2020
Cover Letter [REC SA1 cover letter 27.03.20_2]		27 March 2020
Non-validated questionnaire [PRINCIPLE_Baseline_v0.5_27Mar2020_ clean + changes]	0.5	27 March 2020
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Participant information sheet (PIS) [PRINCIPLE Information for participants_v1.0_27Mar2020 Clean + TT]	1.0	27 March 2020
Participant information sheet (PIS) [PRINCIPLE PIS_ v1.1_ clean + tracked changes 27.03.20]	1.1	27 March 2020
Research protocol or project proposal [PRINCIPLE_Protocol_v0.12 23.03.2020 with clean + tracked changes]	0.12	23 March 2020
Sample diary card/patient card [PRINCIPLE_Daily Diary_v0.5_27Mar2020_ clean + changes]	0.5	27 March 2020
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Sample diary card/patient card [PRINCIPLE_text message daily diaries_ v1.0 27.03.20 clean + TT]	1.0	27 March 2020

Membership of the Committee

The members of the Committee who took part in the review are listed on the attached sheet.

Working with NHS Care Organisations

Sponsors should ensure that they notify the R&D office for the relevant NHS care organisation of this amendment in line with the terms detailed in the categorisation email issued by the lead nation for the study.

Statement of compliance

This Committee is recognised by the United Kingdom Ethics Committee Authority under the Medicines for Human Use (Clinical Trials) Regulations 2004, and is authorised to carry out the ethical review of clinical trials of investigational medicinal products.

The Committee is fully compliant with the Regulations as they relate to ethics committees and the conditions and principles of good clinical practice.

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

HRA Learning

We are pleased to welcome researchers and research staff to our HRA Learning Events and online learning opportunities– see details at: https://www.hra.nhs.uk/planning-and-improving-research/learning/

20/SC/0158: Please quote this number on all correspondence

Yours sincerely
PP

Mr David Carpenter
Chair

E-mail: berkshire.rec@hra.nhs.uk

Enclosures: *List of names and professions of members who took part in the review*

Copy to: *N/A N/A CTRG*

South Central - Berkshire Research Ethics Committee

Attendance at Sub-Committee of the REC meeting in correspondence

Committee Members:

Name	*Profession*	*Present*	*Notes*
Mr David Carpenter	Retired Social Scientist	Yes	Meeting Chair
Mike Proven		Yes	

Also in attendance:

Name	*Position (or reason for attending)*
Alison Doherty	Approvals Administrator

Hannah Swayze

From: Elaine Chick
Sent: 27 March 2020 17:07
To: Hannah Swayze
Cc: Emma Ogburn; 'rpm@oxfordjro.org'
Subject: PRINCIPLE Substantial Amendment 1 EudraCT: 2020-001209-22

Dear Hannah

I can confirm that the above referenced substantial amendment has been reviewed in CTRG and we are happy for it to be submitted to the relevant organisations for approval. This email can be forwarded as confirmation of sponsor approval for the amendments as required.

- Email documents to the REC that originally reviewed the study. The REC will review the amendments and categorise it. If necessary, they will transfer the amendments internally to HRA for them to review as well.
    - If the amendments does not require HRA review, the REC will state this in their categorisation letter.
    - If it is sent on to the HRA, the HRA will advise you when you can send final REC and HRA approved documents to your local sites.

- Copy in CTRG generic email address (ctrg@admin.ox.ac.uk) so the sponsor has final documents and is included in subsequent correspondence

Please make your MHRA submission, through the Common European Submission Platform (CESP).

Please send a copy of the approval letters to the CTRG generic email address (ctrg@admin.ox.ac.uk) once you have received them. Please do not implement your amendments until all approvals are in place.

Best wishes
Elaine

Elaine Chick
Deputy Head CTRG, Research Services
University of Oxford
Boundary Brook House, Headington, OX3 7LQ Tel: 01865 616481 Elaine.chick@admin.ox.ac.uk
https://researchsupport.admin.ox.ac.uk/ctrg

PID14903-A001-SP001-AC001

Participant identifier | | | | | | | | Participant initials | | | |

Baseline CRF

Introduction		
1.	Date of birth (DD/MMM/YYYY):	_ _/_ _ _/_ _ _ _
2.	Sex	Male / Female / Other
3.	Are you a current smoker?	Yes ☐ No ☐
3a)	Are you an ex-smoker?	Yes ☐ No ☐
3.	Do you have any of the following co-morbidities/conditions:	
4a)	• Asthma, COPD or other lung disease	Yes ☐ No ☐
4b)	• Diabetes	Yes ☐ No ☐
4c)	• Heart problems (e.g. angina, heart attack, heart failure, atrial fibrilation, valve problems)	Yes ☐ No ☐
4d)	• High blood pressure for which you are taking medications	Yes ☐ No ☐
4e)	• Liver disease	Yes ☐ No ☐
4f)	• Stroke or other neurological problem	Yes ☐ No ☐
5.	Are you taking ramipril, lisinopril, perindopril, captopril or enalapril?	Yes ☐ No ☐

Symptoms		
Please rate the following symptoms today:		
6.	Fever	No problem / Mild problem / Moderate problem / Major problem
7.	Cough	No problem / Mild problem / Moderate problem / Major problem
8.	Shortness of breath	No problem / Mild problem / Moderate problem / Major problem
9.	Muscle ache	No problem / Mild problem / Moderate problem / Major problem
10.	Nausea / Vomiting	No problem / Mild problem / Moderate problem / Major problem
11.	What date did you start to feel unwell with this illness (DD/MMM/YYYY)?	_ _/_ _ _/_ _ _ _
12.	Have you taken antibiotics since your illness started?	Yes ☐ No ☐

Participant identifier | | | | | | | | Participant initials | | | |

Baseline CRF

Healthcare Services		
13.	Have you had contact with the following healthcare services since your illness started? Please answer Yes or No.	
13a)	GP	Yes ☐ No ☐
13b)	Other primary Care services (e.g. walk-in services/pharmacist)	Yes ☐ No ☐
13c)	NHS 111	Yes ☐ No ☐
13d)	A&E	Yes ☐ No ☐
13e)	Other	Yes ☐ No ☐
13e. i)	If 'Other' please specify: _____	

Completed by: Print name ……Sign ……Date _ _ / _ _ _ / _ _ _ _

Participant identifier | | | | | | | | Participant initials | | | |

Day 7, 14 and 28 Call CRF

Date	
Today's date: _ _ / _ _ _ / _ _ _ _	**Day: Day 7** ☐ **Day 14** ☐ **Day 28** ☐

Hospital Admission		
1.	Have you/participant been admitted to hospital?	Yes ☐ No ☐
1a)	If yes, what date did you/participant go to hospital?	_ _/_ _ _/_ _ _ _
1b)	Were you/participant admitted overnight?	Yes ☐ No ☐
1c)	How many nights did you/participant stay in hospital?	☐☐ nights
1d)	Did you/participant stay in an Intensive Care Unit during your stay in hospital?	Yes ☐ No ☐
1e)	Did you/participant receive oxygen while in hospital?	Yes ☐ No ☐
1f)	Did you/participant receive mechanical ventilation while in hospital?	Yes ☐ No ☐

Symptoms		
2.	Do you/participant feel recovered today? (i.e. symptoms associated with illness are no longer a problem).	Yes ☐ No ☐
2a)	If yes, on what date did you/participant feel recovered?	_ _/_ _ _/_ _ _ _
3.	How well are you/participant feeling today? Please rate how you are feeling now using a scale of 1 – 10, where 1 is the worst you can imagine, and 10 is feeling the best you can imagine?	
Worst	1 2 3 4 5 6 7 8 9 10	**Best**
4.	On how many days have you/participant taken the prescribed dose of study medication?	☐
5.	Have you/participant posted your swab?	Yes ☐ No ☐

As you are feeling recovered that is all the questions for today. Thank you for your time.

Participant identifier | | | | | | | | Participant initials | | | |

Day 7, 14 and 28 Call CRF

6.	Has anybody else in your/participant's house become unwell today with a respiratory illness?	Yes ☐ No ☐

As you/participant do not feel recovered, please can you rate the following symptoms:		
7.	Fever	No problem / Mild problem / Moderate problem / Major problem
8.	Cough	No problem / Mild problem / Moderate problem / Major problem
9.	Shortness of breath	No problem / Mild problem / Moderate problem / Major problem
10.	Muscle ache	No problem / Mild problem / Moderate problem / Major problem
11.	Nausea / Vomiting	No problem / Mild problem / Moderate problem / Major problem
12.	Do you have any other symptoms with your current illness: _____ _____	

Other Healthcare Services		
13.	Please can you say whether or not you/participant have had contact with the following healthcare services since your illness started/last telephone contact? Please answer "Yes" or "No".	
13a)	GP	Yes ☐ No ☐
13b)	Other primary Care services (e.g. walk-in services/pharmacist)	Yes ☐ No ☐
13c)	NHS 111	Yes ☐ No ☐
13d)	A&E	Yes ☐ No ☐
13e)	Have you been in contact with any other healthcare service?	Yes ☐ No ☐
13e) i)	If yes, please can you specify:	

Notification of Death—TRIAL TEAM USE ONLY		
14.	Has the trial team been notified of the participant's death?	Yes ☐ No ☐

Completed by: Print name ……Sign ……Date _ _ / _ _ _ / _ _ _ _

Participant identifier | | | | | | | | Participant initials | | | |

Daily Diary

Date		
Today's date: _ _ / _ _ _ / _ _ _ _ (DD/MMM/YYYY)		
Symptoms		
1.	Do you feel recovered today? (i.e. symptoms associated with illness are no longer a problem).	Yes ☐ No ☐
2.	How well are you feeling today? Please rate how you are feeling now using a scale of 1 – 10, where 1 is the worst you can imagine, and 10 is feeling the best you can imagine?	
Worst	1 2 3 4 5 6 7 8 9 10	**Best**
3.	For those taking study medication, have you taken the prescribed dose?	Yes ☐ No ☐
3a)	If No, why not? _____	
4.	Have you posted your swab?	Yes ☐ No ☐
5.	Has anybody else in your house become unwell today with a respiratory illness?	Yes ☐ No ☐

If you feel recovered you do not need to answer any further questions today. Thank you for your time.

As you do not feel recovered, please rate the following symptoms:		
6.	Fever	No problem / Mild problem / Moderate problem / Major problem
7.	Cough	No problem / Mild problem / Moderate problem / Major problem
8.	Shortness of breath	No problem / Mild problem / Moderate problem / Major problem
9.	Muscle ache	No problem / Mild problem / Moderate problem / Major problem
10.	Nausea / Vomiting	No problem / Mild problem / Moderate problem / Major problem
11.	Please describe any other symptoms with your current illness: _____ _____ _____	

Participant identifier | | | | | | | | Participant initials | | | |

Daily Diary

Medications		
12.	Please can you say whether or not you have taken any of the following today, please confirm Yes or No.	
12a.	Paracetamol	Yes ☐ No ☐
12b.	Cough mixture	Yes ☐ No ☐
12c.	Ibuprofen	Yes ☐ No ☐
12d.	Codomol or codeine-based medication	Yes ☐ No ☐
12e.	Cold/flu tablets or sachets	Yes ☐ No ☐
12f.	Throat lozenges	Yes ☐ No ☐
12g.	Hay fever tablets (antihistamine)	Yes ☐ No ☐
12h.	Inhaler	Yes ☐ No ☐
12i.	Steroid nasal spray (e.g. Beconase)	Yes ☐ No ☐
12j.	Anti-diarrheal medication (e.g. Immodium)	Yes ☐ No ☐

Completed by: Print name ……Sign ……Date _ _ / _ _ _ / _ _ _ _

Participant identifier | | | | | | | | Participant initials | | | |

Daily Diary

Healthcare Services		
13.	Have you had contact with the following healthcare services in the last 24 hours? Please answer Yes or No.	
13a.	GP	Yes ☐ No ☐
13b.	Other primary Care services (e.g. walk-in services/pharmacist)	Yes ☐ No ☐
13c.	NHS 111	Yes ☐ No ☐
13d.	A&E	Yes ☐ No ☐
13f.	Other	Yes ☐ No ☐
13f. i)	If 'Other' please specify: _____	
14	Hospital	Yes ☐ No ☐
14a.	If yes, what date did you go to hospital (DD/MMM/YYY)?	_ _/ _ _ _/ _ _ _ _
14b.	Were you admitted overnight?	Yes ☐ No ☐
14c.	How many nights did you stay in hospital?	☐☐ nights
14d.	Did you stay in an Intensive Care Unit during your stay in hospital?	Yes ☐ No ☐
14e.	Did you receive oxygen while in hospital?	Yes ☐ No ☐
14f.	Did you receive mechanical ventilation while in hospital?	Yes ☐ No ☐

Completed by: Print name ……Sign ……Date _ _ / _ _ _ / _ _ _ _

Participant identifier | | | | | | | | Participant initials | | | |

Eligibility CRF

1.	Participant's NHS number: _____	
2.	Participant is ≥50 years old with at least one of the comorbidities listed below, or aged ≥65? • Weakened immune system due to a serious illness or infection • Heart disease or hypertension • Asthma or lung disease • Diabetes not treated with insulin • Mild hepatic impairment • Stroke or neurological problem	Yes ☐ No ☐
3.	Pregnant or planning on becoming pregnant within the next few weeks?	Yes ☐ No ☐
4.	Breastfeeding or planning on starting during the course of the trial?	Yes ☐ No ☐
5.	Has porphyria?	Yes ☐ No ☐
6.	Has type 1 diabetes or insulin dependent type 2 diabetes mellitus?	Yes ☐ No ☐
7.	Has a G6PD deficiency?	Yes ☐ No ☐
8.	Has myasthenia gravis?	Yes ☐ No ☐
9.	Has severe psoriasis?	Yes ☐ No ☐

Participant identifier | | | | | | | | Participant initials | | | |

Eligibility CRF

10.	Has a severe neurological disorder (especially those with a history of epilepsy)?	Yes ☐ No ☐
11.	Has had a previous adverse reaction to hydroxychloroquine?	Yes ☐ No ☐
12.	Is currently taking hydroxychloroquine?	Yes ☐ No ☐
13.	Is currently taking any of the following: • Amiodarone • Chloroquine • Ciclosporin • Penicillamine	Yes ☐ No ☐
14.	Has a retinal disease (e.g. macular degeneration)?	Yes ☐ No ☐
15.	Has a severe hepatic impairment.	Yes ☐ No ☐
16.	Has a severe renal impairment.	Yes ☐ No ☐
17.	Comments: _____ _____ _____	

Completed by: Print name ……Sign ……Date _ _ / _ _ _ / _ _ _ _

Participant identifier | | | | | | | | Participant initials | | | |

Screening CRF

1.	Are you are willing to give informed consent for participation in the study?	Yes ☐ No ☐
2.	Do you have symptoms of possible COVID-19 in the community which have been present for less than 8 days? **Defined:** A new continuous cough - this means coughing a lot for more than an hour, or 3 or more coughing episodes in 24 hours (if you usually have a cough, it may be worse than usual) *and/or* A high temperature - this means you feel hot to touch on your chest or back (you do not need to take your temperature)	Yes ☐ No ☐
3.	Are you are ≥50 years old with at least one of the comorbidities/conditions listed below, or aged ≥65? • Weakened immune system due to a serious illness or medication (e.g. chemotherapy) • Heart disease or hypertension • Asthma or lung disease • Diabetes not treated with insulin • Liver disease	Yes ☐ No ☐
4.	Are you pregnant or planning on becoming pregnant within the next few weeks?	Yes ☐ No ☐
5.	Are you breastfeeding or planning on starting during the course of the trial?	Yes ☐ No ☐
6.	Do you have porphyria?	Yes ☐ No ☐
7.	Do you take insulin for diabetes?	Yes ☐ No ☐
8.	Do you have a G6PD deficiency?	Yes ☐ No ☐
9.	Do you have myasthenia gravis?	Yes ☐ No ☐
10.	Do you have severe psoriasis?	Yes ☐ No ☐

Participant identifier | | | | | | | | Participant initials | | | |

Screening CRF

11.	Do you have a history of epilepsy?	Yes ☐ No ☐
12.	Have you had a previous adverse reaction to hydroxychloroquine?	Yes ☐ No ☐
13.	Are you currently taking hydroxychloroquine?	Yes ☐ No ☐
14.	Are you currently taking any of the following: • Amiodarone • Chloroquine • Ciclosporin • Penicillamine	Yes ☐ No ☐
15.	Do you have a disease which affects the retina of the eye (e.g. macular degeneration)?	Yes ☐ No ☐

Completed by: Print name ……Sign ……Date _ _ / _ _ _ / _ _ _ _