

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.

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

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Protocol Date and Version No: v3.0 19 May 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.

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Signature

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Date

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1. KEY TRIAL CONTACTS

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2. LAY SUMMARY

The risk of complications from suspected COVID-19 (the disease caused by SARS-CoV-2 virus) is generally greater in people aged 50 years and older with underlying health conditions, and in those aged 65 years and older. The COVID-19 pandemic is having a devastating effect on people's health and society. (1-4) So far, no treatments for COVID-19 have been proven to be effective in well-conducted clinical trials. Most cases of probable COVID-19 are being managed in the community. An ideal treatment for patients with suspected COVID-19 in the community is one that is safe, with few side-effects, can be provided by existing NHS services, helps patients recover quicker, and prevents hospital admissions.

Setting up a new clinical trial each time a possible treatment becomes available is time consuming and inefficient. (5-7) We propose establishing a platform, randomised controlled trial in primary care that can rapidly test low-risk treatments for people at higher risk of complications from the illness. Using an efficient, open (no placebo) clinical trial design in conditions of current usual care, our trial aims to give rapid answers about the effectiveness of trial treatments. The platform trial will be flexible; it will allow further treatments to be added into the trial while the trial is already in progress, should such suitable treatments become available. (5) The overall goal is to find treatments suitable for widespread use in the community that will help affected people recover sooner, and prevent hospital admissions.

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 as detailed in the inclusion criteria below (see section 7.1.1), aged ≥65 with or without comorbidity, presenting within 14 days since onset of symptoms with a new continuous cough and/or high temperature during a time of prevalent COVID-19, or with a positive test for SARS-CoV-2 infection and symptoms consistent with COVID-19, within 14 days since onset of symptoms

Sample Size	Approximately 3000 (1500 per arm) but may be increased if additional arms are introduced and may also be modified in the light of emerging data.		
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 this date 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 the 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 i during a time of prevalent COVID-19 disease	Hospital admission or mortality related to suspected COVID-19	Within 28 days
Secondary	To explore whether trial treatment reduces <ol style="list-style-type: none"> 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 a positive test for COVID-19 10) Duration of hospital admission 11) Viral shedding 12) Negative effects on well being 	<ol style="list-style-type: none"> 1-2. Patient reports the day they feel recovered 3. Contacts with health services reported by patients and/or captured by reports of patients' medical records if the practice is a member of the RCGP RSC network 4. Bi-weekly reports from participants' primary care medical records 5-8 and 10. Patient report/carer report/medical record in primary and secondary care 9. Swab results either at baseline or day 5 for SARS-CoV-2 will indicate an "Intention to Treat Infected" group within the overall cohort for sub analysis. Blood test on recovery (optional) for evidence of historic COVID-19. 	Daily online symptom scores. Telephone call or text on days 2, 7, 14 and 28 if data is not obtained through the online diary GP notes review if available through Oxford RCGP RSC network; otherwise, other sources of routinely collected data after 28 days HES/ONS/EMIS/Medical record data linkage after 28 days if patients have been assessed in hospital Swab result from medical records, the supporting laboratory

		11. Follow up swabs at day 5 (if available) will indicate ongoing viral shedding, allowing comparison between groups 12. WHO-5 Well Being Index	and/or convalescent blood test for evidence of historic COVID-19 WHO 5 Well Being Index at baseline, day 14, and day 28, either via online diary or telephone
Qualitative sub-study	1. To explore patients' experiences of consulting, being tested and taking (trial) medication for suspected COVID-19. 2. To explore healthcare professionals' views of taking part in research during pandemics.	1. Telephone interviews with patients. 2. Telephone interviews with healthcare professionals.	1. After 28 days. 2. Once practice has completed recruitment.
Intervention(s)	All trial interventions are detailed in the Appendices. Further interventions may be added or replaced during the course of the trial, subject to suitable interventions becoming available and all necessary approvals being obtained.		
Comparator	In the first instance, this will be a two-arm trial, with the intervention arm being usual care plus a trial drug and the comparator being usual care. There will be no placebo control in this study. Additional arms may be added as the trial progresses. These will be detailed in the Appendices. If an intervention arm is shown to be superior, then this will become the new standard of care. However, the primary analysis of subsequent interventions will correspond to the comparison versus the original Usual Care arm.		

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
HCP	Healthcare professional
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 Research and Development 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
TSC	Trial Steering Committee
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 admission.

We urgently need to know whether there are readily available treatments that might modify the course of COVID-19, particularly amongst those who are at higher risk of complications. At present, those who are higher risk appear to be people aged 50 and over with comorbidity and those aged 65 and over.(1-4)

We therefore propose a platform trial that has the capability of rapidly evaluating potential drug treatments in this high-risk population group. The trial will also have the flexibility to allow the addition of further interventions into the trial platform, should such interventions suitable for pragmatic evaluation in primary care become available. New interventions will not be added into the trial without first obtaining the required permissions.

The research team have 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.(1-4)

In the first instance, PRINCIPLE will be a two-arm trial. In keeping with a pragmatic trial design, 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 (depending on swab availability) so that their COVID-19 status can be ascertained by laboratory analysis. Participants will also be offered a blood test (if available) to check for historic SARS-CoV-2 infection within 6 months of recruitment to the study. 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 potential drug treatments that are available for rapid pragmatic evaluation benefit patients. All approved intervention arms will be outlined in an appendix to this protocol. Treatments that are found to be ineffective should not be commissioned, as ineffective treatments put people at unnecessary risk of side-effects and waste resources. We urgently need to know whether potential COVID-19 treatments that are 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 pandemic caused by the highly infectious SARS-CoV-2 virus.(5, 6) 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.(6, 7)

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 three 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)

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 aged ≥ 50 years with comorbidity, and aged ≥ 65 with or without comorbidity, and

during a time when COVID-19 is prevalent. 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. In line with common practice for pragmatic trials, this trial will be an open trial with no placebo control.(8-11) The primary outcome is hospitalisation and death, with the decision to hospitalise being made by clinicians independent of the trial.

Platform trial

A platform trial, in contrast to traditional two-arm designs, allows multiple arms to be considered simultaneously. Interventions can be dropped, added and/or replaced as evidence emerges for effectiveness, or lack thereof. All arms are detailed in the Appendices to this master protocol. 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)
Primary	To assess the 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 i during a time of prevalent COVID-19 disease	Hospital admission or mortality related to suspected COVID-19	Within 28 days
Secondary	To explore whether trial treatment reduces 13) Duration of severe symptoms 14) Time taken to self-report recovery 15) Contacts with the health services 16) Consumption of antibiotics 17) Hospital assessment without admission 18) Oxygen administration 19) Intensive Care Unit admission 20) Mechanical ventilation 21) To determine if effects are specific to	1-2. Patient reports the day they feel recovered 3. Contacts with health services reported by patients and/or captured by reports of patients' medical records if the practice is a member of the RCGP RSC network 4. Bi-weekly reports from participants' primary care medical records 5-8 and 10. Patient report/carer report/medical record in primary and secondary care 9. Swab results either at baseline or day 5 for SARS-	Daily online symptom scores. Telephone call or text on days 2, 7, 14 and 28 if data is not obtained through the online diary GP notes review if available through Oxford RCGP RSC network; otherwise, other sources of routinely collected data after 28 days HES/ONS/EMIS/Medical record data linkage

	those with a positive test for COVID-19 22) Duration of hospital admission 23) Viral shedding 24) Negative effects on well being	CoV-2 will indicate an "Intention to Treat Infected" group within the overall cohort for sub analysis. Blood test on recovery (optional) for evidence of historic COVID-19. 11. Follow up swabs at day 5 (if available) will indicate ongoing viral shedding, allowing comparison between groups 12. WHO-5 Well Being Index	after 28 days if patients have been assessed in hospital Swab result from medical records, the supporting laboratory and/or convalescent blood test for evidence of historic COVID-19 WHO 5 Well Being Index at baseline, day 14, and day 28, either via online diary or telephone
Qualitative sub-study	1. To explore patients' experiences of consulting, being tested and taking (trial) medication for suspected COVID-19. 2. To explore healthcare professionals' views of taking part in research during pandemics.	1. Telephone interviews with patients. 2. Telephone interviews with healthcare professionals.	1. After 28 days. 2. Once practice has completed recruitment.
Intervention(s)	All trial interventions are detailed in the Appendices. Further interventions may be added or replaced during the course of the trial, subject to suitable interventions becoming available and all necessary approvals being obtained.		
Comparator	In the first instance, this will be a two-arm trial, with the intervention arm being usual care plus a trial drug and the comparator being usual care. There will be no placebo control in this study. Additional arms may be added as the trial progresses. These will be detailed in the Appendices. If an intervention arm is shown to be superior, then this will become the new standard of care. However, the primary analysis of subsequent interventions will correspond to the comparison versus the original Usual Care arm.		

6. TRIAL DESIGN

This will be an open, prospective, individually randomised, platform, response adaptive, controlled clinical trial in community care. The trial will initially be two-arm, but additional arms may be added as the trial progresses.

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 that is being scaled up.

7. PARTICIPANT IDENTIFICATION

7.1 Trial Participants

Patients ≥ 50 years with comorbidity, and patients aged ≥ 65 with or without comorbidity, presenting in the community within 14 days since onset of symptoms, with a new cough and/or high temperature during a time when COVID-19 is prevalent, or a **positive test** for SARS-Co-V2 infection which was taken fewer than 15 days ago, AND symptoms of COVID-19.

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)”

The study is for people with ongoing symptoms. People who feel they are already well on the way to recovery should not take part.

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 (new continuous cough and/or high temperature) within 14 days of inclusion;

OR

- a **positive test** for SARS-Co-V2 infection which was taken fewer than 15 days ago, AND the participant is unwell with symptoms of COVID-19. These symptoms may include, but are not limited to, shortness of breath, general feeling of being unwell, muscle pain, diarrhoea, vomiting, fever and cough, and they must have had them for **fewer than 15 days**.

AND, EITHER:

- 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

- Patient currently admitted in hospital
- Almost recovered (generally much improved and symptoms now mild or almost absent)
- Judgement of the recruiting clinician deems ineligible.
- Patient already taking an intervention arm medication (hydroxychloroquine or azithromycin) or other macrolides or ketolides

Additional exclusions specific to each intervention arm are listed below and in the Appendix related to that intervention. Participants can take part in the study if they are eligible to be randomised to at least one intervention arm as well as the control arm.

Exclusion criteria related to hydroxychloroquine:

- 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 or chloroquine
- Patients currently taking the following drugs: penicillamine, amiodarone, ciclosporin, digoxin, azithromycin or other macrolides or ketolides
- Known congenital or documented QT prolongation
- Known retinal disease

Exclusion criteria related to azithromycin:

- Pregnancy
- Breastfeeding
- Known severe hepatic impairment;
- Known severe renal impairment;
- Known myasthenia gravis;
- Previous adverse reaction to, or currently taking, azithromycin or other macrolides or ketolides
- Patients taking the following drugs: hydroxychloroquine or chloroquine, sotalol, amiodarone, ciclosporin, digoxin, bromocriptine, cabergoline, ergotamine, ergometrine, methysergide or any ergot derivatives.
- Already taking antibiotics for an acute condition
- Known congenital or documented QT prolongation
- Known allergy to soya or peanut due to the risk of hypersensitivity reactions

8 TRIAL PROCEDURES

8.1 Recruitment

Recruitment will be possible through a variety of mechanisms due to the changing pandemic environment. The different routes are outlined below.

People who are concerned about COVID-19 continue to contact general practices. In the first instance, we will ask participating general practices to record whether a person making contact 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 so, information will be provided verbally, on paper and/or 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. Detailed information about the study will be available to view on a website and subsequently on the Participant Information Sheet (PIS). A summary, pictorial PIS is also available to supplement the full PIS. This information will inform potentially eligible and interested patients of how to access further trial information and consider participation, as well as the procedures involved in joining the study, and what participation would involve. Practices can also choose to screen contacts from the previous 14 days for potentially eligible participants to discuss participation in the study.

In addition to receiving calls/contacts from potentially eligible participants, participating practices will also be able to contact patients, preferably by text (or by letter), who they have screened from their GP Practice list and who fall into the correct age and co-morbidity categories. The practice can tell them about the study and 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 can be contacted directly by potentially eligible participants who have heard about the study through word of mouth, media exposure, or a range of health and social care professionals. Health and social care professionals may also provide potential participants with a letter or summary leaflet about possible study participation. Potential participants may approach the study team by telephone, email, or through the study website. The study team will then also be able to provide such people with information about potentially joining the trial, the steps involved, and guide them through the consent process and joining the trial.

Agencies from national bodies, such as NHS 111, COVID-19 'Hot Hubs', hospital emergency departments, care homes, and pharmacies will be able to give information via a trial poster (also in the form of a leaflet or letter that can be handed to potential participants and their potential study partners-see below) and verbally about possible trial participation. They can also direct interested patients to the online information about the study and/or how to contact the study team. General media releases and social media posts will also direct potential participants to the study.

An online screening, eligibility and consent procedure will be used. Telephone calls will be used as a back-up, allowing potential participants to ask questions 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 own records. This online process avoids risks associated with paper documents being handled by people with infection, and is efficient during a time of rapid recruitment during a pandemic. The completed ICF may also be printed and delivered to participants along with study materials such as IMP or swabs. Remote, online consent, or via a telephone call, is also required as the majority of GP practices may not conduct face-to-face appointments in the COVID-19 pandemic, and all patients are being informed by a national campaign to contact clinicians by telephone or online.

During this process, the study team will ask the potential participant to, if possible, include a phone number and email address for a study partner, who may provide assistance to the study participant in completing trial procedures. Identifying a study partner is not obligatory, but merely a suggested mechanism to aid participation for consenting patients. A study partner letter may be used in environments such as residential and nursing homes, to provide guidelines on how study partners can support participants in the trial. The letter will be provided to residential and nursing homes, to distribute as required when potential patients self-refer to the trial.

Eligibility can be checked at study sites. In addition, eligibility can be checked centrally by a medically qualified clinician or a research nurse who is suitably trained and experienced and has been delegated this responsibility, with appropriate access to the participant's medical records. If a participant's medical notes cannot be accessed centrally, the clinician/delegate will contact the participant's GP for information to enable the study team to confirm eligibility to be randomised at least to one intervention, as well as the control arm. Participants will not be randomised to an arm if an exclusion criterion to that arm applies to them, but will need to have no exclusions relevant to at least one intervention and the usual care arm.

Once informed consent has been obtained, and eligibility confirmed, participants will be randomised via a secure online link using our in-house Sortition module. The participant, trial team and participant's GP will be notified electronically of the treatment allocation they have been randomised to. The research team may also send the GP or Care Home an email or letter via secure systems, containing personally identifiable data and treatment allocation. The participant and GP can review the PIS and completed ICF at any time using a secure log-in access code. A letter confirming enrolment and randomisation can also be posted to the participant should this be more convenient.

All participants will be provided with two sampling kits (depending on availability) for self-sampling by their practice, study team, Public Health England (PHE) or other central service.. Where possible and availability of sampling kits allows, one sample will be taken as close to study entry as possible, to assess COVID-19 status, and the second five days after enrolment to assess COVID-19 status and viral shedding. Where swabbing facilities are unavailable, for example, if there is no supply of suitable swabs, patients may still participate in the trial and be included in the intention to treat analysis only.

Participants will receive clear instructions on how to self-sample, as per 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 a laboratory according to their standard practice for COVID-19 swab testing. 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 or the trial team depending on recruitment route.

Participants included in the study from a limited locality in London may in addition, be asked if they wish to be put in touch with a research team from Imperial College, who together with the Oxford RCGP RSC, are conducting a study of immunological changes and household spread. This exploratory study would be conducted under a separate, approved protocol, and would share any data with the PRINCIPLE trial for patients who also consent to take part in the Imperial College study.

Once recruited, participants will be issued with an online link to a symptom diary and will be asked to record the presence and severity of a few symptoms each day. If online data is not being entered by participants, the research team will contact the participants and/or their Study Partners on days 2, 7, 14 and 28. The study team will make no more than six 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 hospital stay and ICU admission and ventilation, if applicable.

The RCGP RSC will report to the central trial office at regular intervals about healthcare contacts in the participant'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. If notes review is not possible using this route – for example, for patients recruited through an urgent or unscheduled care contact and therefore their registered GP practice has not been involved and does not wish to register with the RCGP RSC, the registered GP surgery will be contacted separately by the trial team to request a limited notes review.

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). If they meet the screening criteria they will be asked to complete an online consent form (see above). They may also complete these forms by telephone with the study team. A screening trial ID number will be assigned. The participant will then enter online baseline information, including their address and contact details and those of a Study Partner, if they have one. The trial team and responsible clinician or delegate will be notified electronically, a clinician/delegate who has access to the patient's medical records will provide information to the study team to enable them to confirm eligibility centrally. Once deemed eligible, the clinician or a member of the trial team will randomise the participant. The participant, GP, and trial team will be notified electronically of the participant's enrolment and the treatment group allocated.

8.3 Informed Consent

Written and verbal versions of the PIS and ICF will be presented to participants detailing no less than: the exact nature of the trial; the implications and constraints of the protocol, and the known side-effects and risks involved in taking part. The trial 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 affecting 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 and to ask any questions they may have about the trial before deciding whether they will participate. 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 or a member of the trial team will enter the participant's baseline data into the online system, which will then enable randomisation to take place. The randomisation process will take only a few moments via the online system and will not delay trial participation. Participants will be randomised to the arm/arms they are eligible for (at least two arms), automatically by Sortition. 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 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 Safety & 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 two sets of swabs and an insert containing instructions will be sent to the participant's home for self-sampling as soon after study inclusion as possible and then again 5 days later (swab supplies permitting). If a sample can be taken face-to-face by the general practice or another facility soon after inclusion, the initial self-

swab will not be necessary. While the aim is to have a swab result for all patients, if a swab cannot be done for supply or other logistical reasons, this will not exclude the patient from participating in the study. However, they will only be analysed in the intention to treat analysis. All participants, whether in the intervention or control group, will be asked to provide swab or self-swab at study enrolment and day 5, if swabbing facilities for this are available. If 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. Participants will be told how study materials and any medication they are randomised to receive 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 or it will be issued centrally from the trial team.

8.7 Subsequent Visits

There is no requirement for participants to have a face-to-face visit as part of trial 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 each day for 28 days. If not completed, the trial team will contact the participant and/or their Study Partner to obtain the information. In addition, at day 14 and 28 the World Health Organisation – Five Well-Being Index (WHO-5) will be administered, completed online or by telephone call at the preference of the participant.

Each day, participants, or their Study Partners, will be asked to rate the severity of a set number of symptoms, record contacts with the health services including hospital admission, record medication use, new infections in the household, and the five questions of WHO-5 on days 14 and 28. The latter instrument has been validated for measuring wellbeing over time. It is becoming increasingly apparent the COVID-19 infection may have a considerable negative impact on well-being; exploring the impact of interventions on this is important.⁽¹²⁾

A subset of participants will be contacted after 28 days by text/telephone to invite them to participate in a qualitative sub-study. Participants consenting to this sub-study will be interviewed by telephone interview about their experiences. One follow-up telephone call may be made if there is no response.

The participants who consented to be contacted by the study team for an optional SARS-CoV-2 blood test (if one suitable for the purposes of this study becomes available) within 6 months of completing the study will be given more information in an additional PIS and ICF, detailing where blood sampling will take place and that blood samples will not be stored.

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 and from the hospital records about intensive care admission and ventilation. Participant records will be accessed up to three 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 two biological samples to test for SARS-CoV-2 from all consenting participants, the first at baseline and the second at day 5. This will be a self-swab process, unless a swab can be taken face-to-face in the course of usual care, with the practice generating the required forms. Once the swab has been taken

it will be put in the regulation packaging, double bagged, and posted to the PHE laboratory that is supporting the trial 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 will not be stored for the purpose of this trial. The swab material will fall under PHE's remit, not the trial's; PHE may retain the swab for up to 5 years.

If a suitable blood test for SARS-CoV-2 becomes available, participants who have consented to being contacted for a blood test will receive further information about this and can give consent if they wish to take part. We anticipate participants will be informed of their blood test result and blood samples will not be stored.

8.9 Qualitative Sub-study

A qualitative sub-study will be nested within the trial. Qualitative work will capture data to understand how patients conceptualise their illness and how they respond to taking medication(s) as part of the trial. Once participants have completed the trial, we will interview their respective clinicians to explore their views of taking part in trials during a pandemic.

Recruitment:

When patient participants consent to take part in the trial, we will ask whether they would be happy to be contacted by telephone to be invited for a telephone interview. Patient participants will be contacted by telephone by a member of the research team within three months to invite them to participate after they complete their day 28 follow up. The researcher will provide study information over the telephone. The Interview Patient PIS, and Interview Patient ICF will be available on the study website and will be emailed to participants if requested.

Once a practice has completed patient recruitment for the trial and one of their patients has been interviewed as part of the qualitative sub-study, we may ask the practice research contact to identify 1-2 healthcare professionals who would be willing to share their experiences of taking part in the trial. Healthcare professionals will include clinicians and non-clinicians with the main criteria for inclusion in interviews being that HCP participants should have carried out trial activities in their practice. Potential HCP participants will be contacted in person or by email by the practice contact. They will be provided with the Interview HCP Invitation Email, Interview HCP PIS and Interview HCP ICF by email.

All participants will be given at least 24 hours to consider whether to participate and will be asked to contact the research team with expressions of interest.

Patients recruited to both the intervention and usual care arms will be purposively sampled across the recruiting period with approximately 15-20 patients in each arm (30-40 interviews in total). We will seek to obtain maximum variation in age and symptom severity (as reported in daily diary at baseline).

When the research team receives responses from HCPs, they will collect basic demographics to purposively select participants based on practice location, practice size, practice patient recruitment and job role. We aim to complete 20-25 interviews with HCPs.

All participants will only be required to take part in a single interview.

Interviews:

Interviews will be conducted by telephone and all participants will be asked to provide verbal consent in advance. The researcher will make a written record of this consent using the Qualitative ICFs, which will be emailed to the participant. Interviews will be audio-recorded with participants' permission.

Patient participant interviews will follow a semi-structured topic guide (Interview Patient Topic Guide) and ask about reasons for consulting and illness perceptions prior to the consultation, experiences of the

consultation, the COVID-19 testing process (if applicable, and result if the participant has been notified) and medication adherence. The topic guide will be informed by the Common Sense Model which describes how people perceive and cope with symptoms of illness.

HCP interviews will follow the Interview HCP Topic Guide and will ask about experiences of carrying out trial activities, recruiting patients and the work required to set up a clinical trial during a pandemic.

Interviews with patient participants are expected to last approximately 30-45 minutes and interviews with HCPs are expected to last 15-30 minutes.

8.10 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. Optional SARS-CoV-2 blood test samples will not be stored.

8.11 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 this date may need to be amended depending on circumstances prevailing at the time.

9 TRIAL INTERVENTIONS

9.1 Investigational Medicinal Product(s) (IMP) Description

Trial Drug information can be found in the relevant Appendices.

9.2. Blinding of IMPs

There is no blinding of IMPs in the trial.

9.3. Storage of IMP

GP practices can order a supply of trial medication from Public Health England using the existing ImmForm process. All GP practices in England are already set up on ImmForm, as they use this system to order Influenza vaccines from Public Health England. GPs will be provided with an envelope by the trial 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 will be provided to the patient or their representative. Medication may either be issued by the patient's registered GP surgery or by a surgery acting as a hub for a number of local surgeries.

Alternatively, study medication will be repackaged by an accredited licensed, central facility and may be delivered to primary care centres or to the Primary Care Clinical Trials Unit for further distribution to study participants as they are included. Distribution of trial packs to study participants will be tracked via courier or call/text message.

Lastly, for trial medications that can be prescribed and issued to patients in the community, GPs will be able to prescribe trial medication using existing NHS services. Pharmacies will then be able to issue

medication that could be delivered to the patient by community pharmacy services or NHS volunteers, or collected from the pharmacy by the participant or someone on their behalf, such as their study partner.

9.4. Compliance with Trial Treatment

Participants will receive a daily email asking them to log in with a unique access code to an online diary where they will record their symptoms. If incomplete, 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 when they ship drug.

9.6. Concomitant Medication

Please see Appendices for details of Trial Drugs and concomitant medication.

10 SAFETY REPORTING

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)	<p>An untoward and unintended response in a participant to an investigational medicinal product which is related to any dose administered to that participant.</p> <p>The phrase "response to an investigational medicinal product" means that a causal relationship between a trial medication and an AE is at least a reasonable possibility, i.e. the relationship cannot be ruled out.</p> <p>All cases judged by either the reporting medically qualified professional or the Sponsor as having a reasonable suspected causal relationship to the trial medication qualify as adverse reactions.</p>
Serious Adverse Event (SAE)	<p>A serious adverse event is any untoward medical occurrence that:</p> <ul style="list-style-type: none"> • results in death • is life-threatening • requires inpatient hospitalisation or prolongation of existing hospitalisation • results in persistent or significant disability/incapacity • consists of a congenital anomaly or birth defect*. <p>Other 'important medical events' may also be considered 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.</p> <p>NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the</p>

	<p>event; it does not refer to an event which hypothetically might have caused death if it were more severe.</p> <p>*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”.</p>
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)	<p>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:</p> <ul style="list-style-type: none"> • 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 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 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 Safety & Monitoring Committee meeting.

SAEs other than hospitalisation or death due to COVID-19 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 one 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 an SAE, 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

- Trial team will complete an SAE report form for all reportable SAEs.
- GP practice/trial 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 seven calendar days after the Sponsor or delegate is first aware of the reaction. Any additional relevant information will be reported within eight 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 Master Statistical Analysis Plan (M-SAP)

Details of the statistical design and methods will be described in a Master Statistical Analysis Plan (M-SAP), in which an appendix to the M-SAP titled “Adaptive Design Report” (ADR) provides complete specifications for the primary analysis and pre-specified adaptive algorithm. In addition, the M-SAP will be accompanied by arm-specific appendices to describe any planned deviations from the M-SAP. 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 Usual Care arm, the superior treatment will replace the Usual Care arm as the new standard of care. However, the primary analysis of subsequent interventions will correspond to the comparison versus the original Usual Care arm. 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 two arm, 1:1 randomised trial but will have the capability to add additional interventions over time. The evaluation of any new interventions will be governed by this master protocol and M-SAP (including adaptive algorithm and decision criteria), with any planned deviations from the master protocol and M-SAP to be specified in arm-specific appendices. The inclusion of any new interventions will require additional arm-specific appendices to the master protocol and M-SAP.

11.2.1 Primary Endpoint & Analysis

The primary endpoint is hospital admission or death related to suspected 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 θ_j denote the log odds ratio comparing the odds of hospitalisation/death for persons in treatment group j versus persons in the Usual Care arm. A corresponding Bayesian posterior distribution will be derived for the estimated log odds ratio. The primary analysis for intervention j will test the following hypothesis:

$$H_0: \theta_j \geq 0$$

$$H_1: \theta_j < 0$$

If the Bayesian posterior probability of superiority for a treatment versus Usual Care is sufficiently large (e.g. ≥ 0.99), the null hypothesis will be rejected and the intervention will be deemed superior to Usual Care. 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, and will be specified in the Adaptive Design Report (Appendix to the M-SAP). The Adaptive Design Report will also specify appropriate methodology for the primary analysis when the Usual Care arm is replaced by a superior treatment, and for when the comparison of a treatment versus Usual Care includes non-concurrent randomisations.

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 intervention 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. The adaptive algorithm will be documented in the Adaptive Design Report, including prespecified criteria for decisions regarding futility or effectiveness of interventions and/or replacing interventions in the trial.

11.2.3 Interim Analyses

Per the pre-specified design, the trial will be eligible for the first interim analysis when 200 randomised participants have the opportunity to complete 28 days of follow-up and there are a sufficient number of hospital admissions/deaths. Subsequent interim analyses will be conducted with frequency as specified in the Adaptive Design Report. 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 Usual Care arm as the new standard of care.

If the Bayesian posterior probability of a clinically meaningful treatment effect (e.g. $\geq 25\%$ reduction in relative risk of hospitalization/death) is sufficiently small (e.g. < 0.01) 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 in the Adaptive Design Report and determined via simulation.

11.2.4 Allocation & Response Adaptive Randomisation

Initially, randomisation will be fixed 1:1 for a comparison between two trial arms, 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 allocation will be modified and the additional intervention will be included in the interim analyses (with evaluation for success and futility) as detailed in the Adaptive Design Report. If there are at least 3 arms (2 intervention arms plus Usual Care) in the study, each interim analysis may incorporate modified randomisation probabilities via response adaptive randomisation (RAR). Full details for implementing RAR will be provided in the Adaptive Design Report; the general idea is to allocate more participants to the intervention arms that have the best observed outcomes.

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 (with results described in the Adaptive Design Report), 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 and each of the subsequent interim analyses. Complete details of the simulations will be provided in the 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 M-SAP.

11.3 Primary Analysis Population

The primary analysis population is defined as all randomized participants 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 Unplanned Deviation(s) from the Master Statistical Analysis Plan

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

11.5 Qualitative sub-study analysis

Audio-recordings of interviews will be transcribed verbatim and transcripts analysed using thematic analysis. Patient and HCP interviews transcripts will be analysed separately but findings will be compared and triangulated if deemed appropriate. Thematic analysis allows the research team to take a pragmatic approach to data collection, remaining grounded in the data but ensuring that the analysis answers the research objectives. NVivo software will be used to assist with the organisation and coding of data. Codes will be compared with one another to create categories, grouping similar codes together. A thematic framework will be developed to code all data and represent key themes for both sets of interviews.

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 a participant fails to complete data online and after six 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 it is 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, Trial Partner or trial team (using OpenClinica™ database via Sentry). OpenClinica™ is stored on a secure server – data will be entered in a web browser 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 and Trial Partner contact details, and securely retain them separate from 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. Participant and Trial Partner data will be kept and stored securely for as long as its required by the study and reviewed on annual basis.

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, clinical team, including Clinical Research Nurses, and other authorised members of the trial team 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.

For the qualitative sub-study:

Each interview will be audio-recorded with the participant's permission. Recordings will allow verbatim transcription of interviews in Microsoft Word. Transcription will be completed by an independent transcription company who holds a contract with the University of Oxford. Once transcribed and transcripts are checked, audio-recordings will be deleted. Transcripts will be labelled with a unique participant number and will omit any identifiable data either identifying the participant or their general practice.

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 Group 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

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.
- TSC – the Trial Steering Committee 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.

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 one working day. In collaboration with the CI, 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 cover the payment of a prescription, should they incur this 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.

Participants who complete a telephone interview as part of the qualitative sub-study will be reimbursed with a (second) £20 voucher for their time to participate.

17 FINANCE AND INSURANCE

17.1 Funding

The study is funded by the UKRI/NIHR via an 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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22 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	Day 28-6 months
	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	Contacted by study team if consent provided
Informed consent	X	X	X	X	X		
Demographics	X	X	X			X	
Medical history	X	X	X	X		X	
Swab	When available, preferably by self-swabbing at study entry and 5 days after inclusion				When available, preferably by self-swabbing at study entry and 5 days after inclusion		
Concomitant medications		X				X	
Eligibility assessment	X	X					
Randomisation				X			
Dispensing of trial drugs				X	X		
Daily Questionnaire					X		
WHO 5 Well Being Index	X				Day 14 and day 28		
Telephone interview (for subset of patient participants)					X		
Compliance					X		
Adverse event assessments					X	X	
Optional SARS-CoV-2 blood test							X

23 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.
2	2.0		Emma Ogburn; Chris Butler; Gail Hayward, Hannah Swayze	Inclusion of TSC; central facility to distribute patient packs; addition of third arm; update of secondary outcomes to include WHO wellbeing questions; qualitative sub study; sign posting to other RCGP RSC study; eligibility confirmation by research nurse.
3	2.1		Hannah Swayze; Chris Butler; Emma Ogburn; Gail Hayward	Trial rationale; secondary outcomes to include blood test; 14 days of covid-19 symptoms; call to participant at day 2; poster
4	2.1		<i>No changes to the protocol</i>	
5	3.0		Hannah Swayze; Chris Butler; Emma Ogburn; Gail Hayward	Updated Azithromycin information; broadening of inclusion criteria; first interim analysis; primary analysis details; care home materials; administrative and typographical updates; study partner letter; recruitment via social media, care homes and pharmacies; GPs prescribe trial medication; eligibility to at least one intervention arm as well as the control arm; ICF may be sent to participants.

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.

24 APPENDIX C: USUAL CARE ARM

1. Background and rationale

COVID-19 disproportionately affects people over 50 years old with comorbidities and those over 65 years old. The disease 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.(1-3, 6) So far, there are no specific treatments for COVID-19 that have been proven in rigorous clinical trials to be effective. Clinicians managing suspected COVID-19 in the community will make clinical judgements about best treatment based on the clinical situation, but care is usually supportive to begin with, unless patients deteriorate and require hospital admission (<https://www.nice.org.uk/guidance/ng163>). The National Institute for Health and Care Excellence does not recommend the immediate use of antibiotics unless there are signs of pneumonia (<https://www.nice.org.uk/guidance/ng163>).

This usual care arm will follow current NHS care provision, and provides a control against which the effect of new interventions that are added to usual care can be assessed. If a new trial intervention plus usual care is found to be superior to usual care alone, then the usual care alone arm will be dropped, and the intervention that is found to be most effective will become the standard of care within the trial.

2. Changes to outcome measures

None

3. Detail of intervention

Participants randomised to the usual care arm will receive usual clinical care as per NHS care delivery practice.

a. Investigational Medicinal Product (IMP) description

Not applicable

b. Storage of IMP

Not applicable

4. Safety reporting

Mechanisms for safety reporting are outlined in the trial protocol.

25 APPENDIX D: USUAL CARE PLUS HYDROXYCHLOROQUINE ARM

1. Background and rationale

a. Evidence for potential Hydroxychloroquine benefits in COVID-19

A candidate intervention for COVID-19, a drug called hydroxychloroquine, has become available following early evaluation in some studies in China.(13, 14) Hydroxychloroquine is a hydroxylated version of the drug chloroquine.(14, 15) Both agents are commonly in use as anti-malarials, and are used in a variety of autoimmune diseases. They have received significant recent interest as potential modifiers of disease activity in COVID-19. (14, 16, 17) Hydroxychloroquine is already available within the NHS on prescription for other indications, and has a generally benign safety profile.(18) Chloroquine is available to buy in the UK over the counter in some formulations and is used as antimalarial prophylaxis and treatment.

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*.(15) Chloroquine is widely distributed in the whole body, including lungs, after oral administration.(14) The EC₉₀ value of chloroquine against the 2019-nCoV in Vero E6 cells was 6.90 µM in one study (13) which can be clinically achievable as demonstrated in the plasma of rheumatoid arthritis patients who received 500 mg administration.(18)

Hydroxychloroquine has been found to be effective against intracellular micro-organisms including malaria and intracellular bacteria *Coxiella burnetii* and *Tropheryma Whipplei*.(15) Both chloroquine and hydroxychloroquine have been shown to have *in vitro* antiviral activity against SARS coronavirus in a number of studies.(15) Most recently activity against SARSCOV2 was shown to be greater for hydroxychloroquine than chloroquine (19).

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 (16), 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>).(14)

2. Eligibility criteria specifically related to hydroxychloroquine

Inclusion criteria: None

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 or chloroquine

- Patients currently taking the following drugs: penicillamine, amiodarone, ciclosporin, digoxin, or currently taking, azithromycin or other macrolides or ketolides
- Known congenital or documented QT prolongation
- Known retinal disease

3. Outcome measures related to hydroxychloroquine

There are no outcome measures related specifically to this usual care plus hydroxychloroquine arm

4. Detail of intervention

Participants randomised to the usual care plus hydroxychloroquine arm will receive usual clinical care as per NHS guidelines, plus a course of oral hydroxychloroquine 200mg twice daily for seven days.

a. Investigational Medicinal Product (IMP) description

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.

b. Storage of IMP

: Stored at room temperature in locked cupboards in restricted access rooms in the Nuffield Department of Primary Care Health Sciences; in locked cupboards in restricted access rooms in GP Practices; in Pharmacies.

c. SmPC precautions and 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.

i. Precautions

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 not drive or operate any heavy machinery.

ii. Concomitant medication

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 four 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.

iii. Pregnancy and Breastfeeding

A moderate amount of data on pregnant women (between 300 – 1000 pregnancy outcomes), including prospective studies in long-term use with large exposure, have not observed a significant increased risk of congenital malformations or poor pregnancy outcomes. Hydroxychloroquine crosses the placenta. Only limited non-clinical data are available for hydroxychloroquine, data on chloroquine have shown developmental toxicity at high supratherapeutic doses and a potential risk of genotoxicity in some test systems. Therefore, hydroxychloroquine sulfate should be avoided in pregnancy except when, in the judgement of the physician, the individual potential benefits outweigh the potential hazards. Careful consideration should be given to using hydroxychloroquine during lactation, since it has been shown to be excreted in small amounts in human breast milk, and it is known that infants are extremely sensitive to the toxic effects of 4-aminoquinolines.

Pregnancy and breastfeeding are exclusion criteria for the hydroxychloroquine arm of the PRINCIPLE trial.

5. Safety reporting

Hydroxychloroquine: has a well-documented safety profile and is a commonly used medication in a primary care setting (see above).

Common symptoms of hydroxychloroquine include abdominal pain; appetite decreased; diarrhoea; emotional lability; headache; nausea; skin reactions; vision disorders; and vomiting.

Mechanisms for safety reporting are outlined in the trial protocol.

26 APPENDIX E: USUAL CARE PLUS AZITHROMYCIN ARM

1. Background and rationale

a. Evidence for potential Azithromycin benefits in COVID-19

Atypical macrolides, especially Azithromycin, have activities that may be beneficial in the treatment of COVID-19 patients, and especially those in the at-risk or age range of the PRINCIPLE trial.

Firstly, Azithromycin appears to have some anti-viral mechanisms. In COVID-19, Azithromycin appears to inhibit viral replication and therefore reduces shedding. In the small open observational trial of Gautret *et al* the addition of azithromycin to hydroxychloroquine (HCQ) (at 200 tds for 10 days) in 6 of the 14 HCQ subjects of the total 36 COVID-19 patients in the study significantly reduced viral shedding at 3 days to 15% (one subject) versus 70% in the HCQ arm and 95% in the indirect control arm, with no shedding at 6 days in the combination arm versus 50% and 90% respectively.(20) Azithromycin was also used in some Chinese observational and interventional studies.

Azithromycin has also been shown to be active *in vitro* against Zika and Ebola viruses,(21-23) and to prevent severe respiratory tract infections when administrated to patients suffering viral infection.(24) Inhibition of viral infections by azithromycin may be linked to its suppressive effect on the production of viral interferon.(25) Longer term administration of low dose azithromycin in COPD has been shown to suppress proinflammatory cytokine production, potentiate macrophage phagocytosis and anti-inflammatory cytokine expression.(26-28) Azithromycin use is also associated with a decrease in the expression of human HLA (human leukocyte antigen) complex molecules in the respiratory tract, including HLA-A, HLA-B, HLA-DPA1, HLA-DRA, HLA-DRB4.(29)

b. Importance of treating CAP or CAP risk in the elderly or immuno-compromised

An important secondary pathway to severe illness and death with COVID-19 may be secondary infection and sepsis in the immune-compromised state, especially secondary community or hospital acquired pneumonia. Older people are more susceptible to pneumonia because of comorbidities, a weakened immune system and are therefore more likely to die.(30) The onset of pneumonia in the elderly can often be rapid, and for severe pneumonia, the prognosis is poor: as many as one in five will die.(30) Severe pneumonia is more prevalent the older you are and in those with more serious underlying diseases.(31) The leading cause of death is respiratory insufficiency. Death has been shown to increase in those not responding to initial antimicrobials, and consequently, the initial selection of the agent is important.

Common causative organisms in the elderly admitted to the hospital with pneumonia include *Haemophilus influenza*, *Staphylococcus aureus*, *Streptococcus pneumoniae*, and *Mycoplasma pneumoniae*. In severe pneumonia, *S. aureus*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa* have been identified as common causative organisms. Older patients often have polymicrobial infections, which may be a factor in non-responders. Assessment of 12,945 US Medicare inpatients over 65 with pneumonia found that initial treatment with a second-generation cephalosporin plus macrolide ([HR, 0.71; 95% CI, 0.52-0.96), a non-pseudomonas third-generation cephalosporin plus a macrolide (HR, 0.74; 0.60-0.92), or a fluoroquinolone alone (HR, 0.64; 0.43-0.94) was associated with lower 30-day mortality.(32)

For CAP management NICE guidance currently recommends Amoxycillin 500mg tds combined with Clarithromycin 500mg bd for 5 days or, in penicillin sensitive, Clarithromycin 500mg bd for 5 days or Doxycycline 200mg stat then 100mg daily for the next 4 days. They also recommend starting therapy within 4 hours. The identification of the early stages of pneumonia in older patients can prove challenging since traditional symptoms and signs, including fever, may be lacking.

Azithromycin will have at least as broad a spectrum of action as clarithromycin in terms of bacterial infections and the additional potential anti-viral activity which has not been observed for other macrolides like Clarithromycin. It will also cover atypical organisms.

2 Changes to outcome measures

The addition of this usual care plus azithromycin arm will not require any changes to outcome measures

3 Eligibility criteria specifically related to azithromycin

Inclusion criteria: No changes

Exclusion criteria:

- Pregnancy
- Breastfeeding
- Known severe hepatic impairment;
- Known severe renal impairment;
- Known myasthenia gravis;
- Previous adverse reaction to, or currently taking, azithromycin or other macrolides or ketolides
- Patients taking the following drugs: hydroxychloroquine or chloroquine, sotalol, amiodarone, ciclosporin, digoxin, bromocriptine, cabergoline, ergotamine, ergometrine, methysergide or any ergot derivatives.
- Already taking antibiotics for an acute condition
- Known congenital or documented QT prolongation
- Known allergy to soya or peanut due to the risk of hypersensitivity reactions

4 Detail of intervention

Participants randomised to the usual care plus azithromycin arm will receive usual clinical care as per NHS guidelines, plus a course of oral azithromycin 500mg daily for three days. We will use the IMP distribution methods described in the protocol to deliver IMP to participants.

a. Investigational Medicinal Product (IMP) description

Azithromycin 250mg capsules. Participants in this arm will take 500 mg (two capsules) once daily for 3 days. The capsules are for oral administration.

Special instructions:

Azithromycin must be taken at least 1 hour before or 2 hours after antacids as this affects overall bioavailability. Azithromycin must be taken at least 1 hour before or 2 hours after food.

The marketing authorisation holder is:

Teva UK Limited, Brampton Road, Hampden Park, Eastbourne, East Sussex, BN22 9AG, UK.

Marketing authorisation number: PL 00289/1570

b. Storage of IMP

Azithromycin: Stored at room temperature in locked cupboards in restricted access rooms in the Nuffield Department of Primary Care Health Sciences; in locked cupboards in restricted access rooms in GP Practices; in Pharmacies.

c. SmPC precautions and concomitant medication

i. Precautions

Azithromycin is a commonly prescribed antibiotic with an established safety profile. The SmPC advises caution using azithromycin in the following conditions:

Elderly people with proarrhythmic conditions due to the risk of developing cardiac arrhythmia and torsades de pointes including patients with congenital or documented QT prolongation; receiving treatment with other active substances known to prolong QT interval such as anti-arrhythmics (e.g. amiodarone and sotalol), cisapride, and fluoroquinolones such as moxifloxacin and levofloxacin; known hypokalaemia and hypomagnesaemia; significant hepatic or renal impairment; patients with neurological or psychiatric disorders; myasthenia gravis. Azithromycin as other with the use of nearly all antibacterial agents, alters the normal flora of the colon leading to overgrowth of *Clostridium difficile* which can lead to *Clostridium difficile* associated diarrhoea.

ii. Concomitant medications

Effects of other medicinal products on azithromycin:

Antacids

In a pharmacokinetic study investigating the effects of simultaneous administration of antacids and azithromycin, no effect on overall bioavailability was seen, although the peak serum concentrations were reduced by approximately 25%. In patients receiving both azithromycin and antacids, the medicinal products should not be taken simultaneously. Azithromycin must be taken at least 1 hour before or 2 hours after the antacids.

Co-administration of azithromycin prolonged-release granules for oral suspension with a single 20 ml dose of co-magaldrox (aluminium hydroxide and magnesium hydroxide) did not affect the rate and extent of azithromycin absorption.

Co-administration of a 600 mg single dose of azithromycin and 400 mg efavirenz daily for 7 days did not result in any clinically significant pharmacokinetic interactions.

Fluconazole

Co-administration of a single dose of 1200 mg azithromycin did not alter the pharmacokinetics of a single dose of 800 mg fluconazole. Total exposure and half-life of azithromycin were unchanged by the coadministration of fluconazole, however, a clinically insignificant decrease in C_{max} (18%) of azithromycin was observed.

Nelfinavir

Co-administration of azithromycin (1200 mg) and nelfinavir at steady state (750 mg three times daily) resulted in increased azithromycin concentrations. No clinically significant adverse effects were observed and no dose adjustment is required.

Rifabutin

Coadministration of azithromycin and rifabutin did not affect the serum concentrations of either medicinal product.

Neutropenia was observed in subjects receiving concomitant treatment of azithromycin and rifabutin. Although neutropenia has been associated with the use of rifabutin, a causal relationship to combination with azithromycin has not been established.

Terfenadine

Pharmacokinetic studies have reported no evidence of an interaction between azithromycin and terfenadine. There have been rare cases reported where the possibility of such an interaction could not be entirely excluded; however, there was no specific evidence that such an interaction had occurred.

Cimetidine

In a pharmacokinetic study investigating the effects of a single dose of cimetidine, given 2 hours before azithromycin, on the pharmacokinetics of azithromycin, no alteration of azithromycin pharmacokinetics was seen.

Effect of azithromycin on other medicinal products:

Ergotamine derivatives

Due to the theoretical possibility of ergotism, the concurrent use of azithromycin with ergot derivatives is not recommended.

Digoxin and colchicine (P-gp substrates)

Concomitant administration of macrolide antibiotics, including azithromycin, with P-glycoprotein substrates such as digoxin and colchicine, has been reported to result in increased serum levels of the P-glycoprotein substrate. Therefore, if azithromycin and P-gp substrates such as digoxin are administered concomitantly, the possibility of elevated serum concentrations of the substrate should be considered.

Coumarin-Type Oral Anticoagulants

In a pharmacokinetic interaction study, azithromycin did not alter the anticoagulant effect of a single 15-mg dose of warfarin administered to healthy volunteers. There have been reports received in the post-marketing period of potentiated anticoagulation subsequent to co-administration of azithromycin and coumarin-type oral anticoagulants. Although a causal relationship has not been established, consideration should be given to the frequency of monitoring prothrombin time when azithromycin is used in patients receiving coumarin-type oral anticoagulants.

Cyclosporin

In a pharmacokinetic study with healthy volunteers that were administered a 500 mg/day oral dose of azithromycin for 3 days and were then administered a single 10 mg/kg oral dose of cyclosporin, the resulting cyclosporin C_{max} and AUC_{0-5} were found to be significantly elevated. Consequently, caution should be exercised before considering concurrent administration of these drugs. If coadministration of these drugs is necessary, cyclosporin levels should be monitored and the dose adjusted accordingly.

Theophylline

There is no evidence of a clinically significant pharmacokinetic interaction when azithromycin and theophylline are co-administered to healthy volunteers. As interactions of other macrolides with theophylline have been reported, alertness to signs that indicate a rise in theophylline levels is advised.

Trimethoprim/sulfamethoxazole

Coadministration of trimethoprim/sulfamethoxazole DS (160 mg/800 mg) for 7 days with azithromycin 1200 mg on Day 7 had no significant effect on peak concentrations total exposure or urinary excretion of

either trimethoprim or sulfamethoxazole. Azithromycin serum concentrations were similar to those seen in other studies.

Zidovudine

Single 1000 mg doses and multiple 1200 mg or 600 mg doses of azithromycin had little effect on the plasma pharmacokinetics or urinary excretion of zidovudine or its glucuronide metabolite. However, administration of azithromycin increased the concentrations of phosphorylated zidovudine, the clinically active metabolite, in peripheral blood mononuclear cells. The clinical significance of this finding is unclear, but it may be of benefit to patients.

Azithromycin does not interact significantly with the hepatic cytochrome P450 system. It is not believed to undergo the pharmacokinetic drug interactions as seen with erythromycin and other macrolides. Hepatic cytochrome P450 induction or inactivation via cytochrome-metabolite complex does not occur with azithromycin.

Astemizole, alfentanil

There are no known data on interactions with astemizole or alfentanil. Caution is advised in the co-administration of these medicines with azithromycin because of the known enhancing effect of these medicines when used concurrently with the macrolid antibiotic erythromycin.

Atorvastatin

Coadministration of atorvastatin (10 mg daily) and azithromycin (500 mg daily) did not alter the plasma concentrations of atorvastatin (based on a HMG CoA-reductase inhibition assay).

However, post-marketing cases of rhabdomyolysis in patients receiving azithromycin with statins have been reported.

Carbamazepine

In a pharmacokinetic interaction study in healthy volunteers, no significant effect was observed on the plasma levels of carbamazepine or its active metabolite in patients receiving concomitant azithromycin.

Cisapride

Cisapride is metabolized in the liver by the enzyme CYP 3A4. Because macrolides inhibit this enzyme, concomitant administration of cisapride may cause the increase of QT interval prolongation, ventricular arrhythmias and torsades de pointes.

Cetirizine

In healthy volunteers, coadministration of a 5-day regimen of azithromycin with cetirizine 20 mg at steady-state resulted in no pharmacokinetic interaction and no significant changes in the QT interval.

Didanosins (Dideoxyinosine)

Coadministration of 1200 mg/day azithromycin with 400 mg/day didanosine in 6 HIV-positive subjects did not appear to affect the steady-state pharmacokinetics of didanosine as compared with placebo.

Efavirenz

Coadministration of a 600 mg single dose of azithromycin and 400 mg efavirenz daily for 7 days did not result in any clinically significant pharmacokinetic interactions.

Indinavir

Coadministration of a single dose of 1200 mg azithromycin had no statistically significant effect on the pharmacokinetics of indinavir administered as 800 mg three times daily for 5 days.

Methylprednisolone

In a pharmacokinetic interaction study in healthy volunteers, azithromycin had no significant effect on the pharmacokinetics of methylprednisolone.

Midazolam

In healthy volunteers, coadministration of azithromycin 500 mg/day for 3 days did not cause clinically significant changes in the pharmacokinetics and pharmacodynamics of a single 15 mg dose of midazolam.

Sildenafil

In normal healthy male volunteers, there was no evidence of an effect of azithromycin (500 mg daily for 3 days) on the AUC and C_{max} of sildenafil or its major circulating metabolite.

Triazolam

In 14 healthy volunteers, coadministration of azithromycin 500 mg on Day 1 and 250 mg on Day 2 with 0.125 mg triazolam on Day 2 had no significant effect on any of the pharmacokinetic variables for triazolam compared to triazolam and placebo.

iii. Fertility, pregnancy and lactation

Pregnancy

There are no adequate data from the use of azithromycin in pregnant women. In reproduction toxicity studies in animals azithromycin was shown to pass the placenta, but no teratogenic effects were observed. The safety of azithromycin has not been confirmed with regard to the use of the active substance during pregnancy. Therefore azithromycin should only be used during pregnancy if the benefit outweighs the risk.

5 Safety reporting

Mechanisms for safety reporting are outlined in the protocol. In brief, we will collect symptoms and side effects of azithromycin from symptom diaries and participant telephone calls.

Common symptoms of azithromycin include diarrhoea, abdominal pain, nausea and flatulence. It may also cause headache, dizziness, insomnia, altered taste, pins and needles, changes in vision or hearing, rash, itching, joint pains or fatigue.