

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

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No potential conflict of interest

**Confidentiality Statement**

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

**Protocol signatures continued**

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

**EudraCT Number:** 2020-001209-22

**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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(Please print name)

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**Site name or ID number**

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**Date**



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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 $\geq 50$ years with comorbidity, and aged $\geq 65$ 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"> <li>1) Duration of severe symptoms</li> <li>2) Time taken to self-report recovery</li> <li>3) Contacts with the health services</li> <li>4) Consumption of antibiotics</li> <li>5) Hospital assessment without admission</li> <li>6) Oxygen administration</li> <li>7) Intensive Care Unit admission</li> <li>8) Mechanical ventilation</li> <li>9) To determine if effects are specific to those with a positive test for COVID-19</li> <li>10) Duration of hospital admission</li> <li>11) Viral shedding</li> <li>12) Negative effects on well being</li> </ol>	<ol style="list-style-type: none"> <li>1-2. Patient reports the day they feel recovered</li> <li>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</li> <li>4. Bi-weekly reports from participants' primary care medical records</li> <li>5-8 and 10. Patient report/carer report/medical record in primary and secondary care</li> <li>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.</li> </ol>	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  $\geq 50$  years with comorbidity, and aged  $\geq 65$  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 $\geq 50$ years with comorbidity, and aged $\geq 65$ 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  $\geq 50$  years with comorbidity, and patients aged  $\geq 65$  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  $\geq 50$ -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  $\geq 65$  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.<sup>(12)</sup>

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"> <li>• results in death</li> <li>• is life-threatening</li> <li>• requires inpatient hospitalisation or prolongation of existing hospitalisation</li> <li>• results in persistent or significant disability/incapacity</li> <li>• consists of a congenital anomaly or birth defect*.</li> </ul> <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"> <li>• in the case of a product with a marketing authorisation, in the approved summary of product characteristics (SmPC) for that product</li> <li>• in the case of any other investigational medicinal product, in the approved investigator’s brochure (IB) relating to the trial in question.</li> </ul>

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  $\theta_j$  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.  $\geq 0.99$ ), 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.  $\geq 0.99$ ), 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**

<b>Amendment No.</b>	<b>Protocol Version No.</b>	<b>Date issued</b>	<b>Author(s) of changes</b>	<b>Details of Changes made</b>
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 EC<sub>90</sub> 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  $\alpha$ -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.



**Trial Title:** Platform Randomised trial of Interventions against COVID-19 In older people

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#### 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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**Protocol signatures continued**

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**EudraCT Number:** 2020-001209-22

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**Protocol signature page**

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

---

**Principal Investigator**  
(Please print name)

---

**Signature**

---

**Site name or ID number**

---

**Date**

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Mr Tim Mustill

## LAY SUMMARY

The risk of complications from suspected ~~COVID-19 coronavirus~~ COVID-19 (the disease caused by SARS-CoV-2 ~~infectionavirus~~ infection) is generally greater in people aged 50 years and older with underlying health conditions, and in those aged 65 years and older. ~~The The infection~~ COVID-19 pandemic is having a devastating effect on people's health and society. (1-4) So far, ~~there are no~~ specific treatments for COVID-19 ~~that have been proven~~ to be effective in well-conducted clinical trials ~~to be effective~~. Most cases of probable COVID-19 ~~infections~~ are being managed in the community. An ideal treatment for patients with suspected COVID-19 ~~infection~~ in the community is one that is ~~would be~~ safe, with few side-effects, can be provided by existing NHS services, ~~and~~ helps patients recover quicker, ~~and prevents and without having to go to hospital admissions~~.

Setting up a new clinical trial each time a ~~potential possible~~ treatment becomes available is time consuming and inefficient ~~(5-7)~~. (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 ~~poorer outcomes~~ 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) ~~This is particularly important as new candidate treatments are being considered on a regular basis.~~ The overall goal is to find treatments suitable for widespread use in the community that will help affected people recover sooner, and ~~prevent without needing to be admitted to hospital admissions~~.

## 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 <u>as detailed in the inclusion criteria</u> below (see section 7.1.1), <del>and</del> aged ≥65 with or without comorbidity, presenting within 14 days since onset of symptoms with a new continuous cough and/or high

	temperature during <u>a time of prevalent COVID-19 infections, or -with a positive test for SARS-Co-V-2 infection -and who have symptoms consistent with COVID-19, within 14 days since onset of symptoms-</u>		
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 <u>this date</u> 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 <u>the</u> effectiveness of trial treatments in reducing the need for hospital admission or death, for patients aged ≥50 years with <u>serious</u> comorbidity, and aged ≥65 with or without comorbidity and suspected COVID-19 <u>infection</u> during <u>a time of prevalent of where prevalent COVID-19 disease is prevalent infections</u>	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"> <li>1) Duration of severe symptoms</li> <li>2) Time taken to self-report recovery</li> <li>3) Contacts with the health services</li> <li>4) Consumption of antibiotics</li> <li>5) Hospital assessment without admission</li> <li>6) Oxygen administration</li> <li>7) Intensive Care Unit admission</li> <li>8) Mechanical ventilation</li> <li>9) To determine if effects are specific to</li> </ol>	<ol style="list-style-type: none"> <li>1-2. Patient reports <u>the</u> on day they feel <u>to have</u> recovered</li> <li>3. Contacts with health services reported by patients and/or captured by reports of patients' medical records <u>if where</u> the practice is a member of <u>the RCGP RSC network</u></li> <li>4. Bi-weekly reports from participants' primary care medical records</li> <li>5-8 and 10. <u>P</u>patient report/carer report/medical record in primary <u>care</u> and <u>hospital secondary</u> care</li> <li>9. Swab results either at baseline or day 5 for</li> </ol>	Daily online symptoms scores. Telephone call or text on days <u>2, 7, 14</u> and 28 if data <u>is not being received-obtained through the online diary</u> GP notes review <u>if where</u> available through Oxford RCGP RSC network; <u>otherwise, or</u> other sources of routinely collected data after 28 days

	<p>those with <u>a positive test the infectious syndrome but who test positive</u> for COVID-19</p> <p>10) Duration of hospital admission</p> <p>11) Viral shedding</p> <p>12) Negative effects on well being</p>	<p><del>COVID-19</del>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 <u>historic</u> COVID-19 <del>infection</del>.</p> <p>11. Follow up swabs at day 5 (if available) will indicate ongoing <u>viral</u> shedding, allowing <del>for</del> comparison between groups</p> <p>12. WHO-5 Well Being Index</p>	<p>HES/ONS/EMIS/Medical record data linkage after 28 days <u>if where</u> patients have been assessed in hospital</p> <p>Swab result <u>available</u> from medical records, <u>and from</u> the supporting laboratory and/or convalescent blood test for evidence of <u>historic</u> COVID-19 <del>infection</del></p> <p>WHO 5 Well Being Index at baseline, day 14, and day 28, either via online diary or telephone</p>
Qualitative sub-study	<p>1. To explore patients' experiences of consulting, being tested and taking (trial) medication for suspected COVID-19.</p> <p>2. To explore healthcare professionals' views of taking part in research during pandemics.</p>	<p>1. Telephone interviews with patients.</p> <p>2. <u>2</u>Telephone interviews with healthcare professionals.</p>	<p>1. After 28 days.</p> <p>2. Once practice has completed recruitment.</p>
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 <del>first</del> obtained.		
Comparator	<p>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 <u>in the first instance</u>. Additional arms may be added as the trial progresses. These will be detailed in the Appendices. If <u>an intervention arm trial arm that included a study drug</u> is shown to be superior, then <u>this</u> <del>that</del> will become the <u>new</u> standard of care. <u>However, the primary analysis of subsequent interventions will correspond to the comparison versus the original Usual Care arm (usual care) in the trial and any further interventions will be compared against that interventionthe new standard of care.</u></p>		

## 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 <del>Research and Development</del> 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

## BACKGROUND AND RATIONALE

### Introduction

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

We urgently need to know whether there are readily available treatments that might modify the course of COVID-19 ~~infections~~, particularly amongst those who are at higher risk of complications. At ~~the~~ present time, 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, but that~~ will also ~~have the~~ flexibility ~~enough~~ to allow the addition of further interventions into the trial platform, should such interventions suitable for pragmatic evaluation in ~~primary~~ ~~Care~~ become available ~~during the course of the trial~~. New interventions will not be added into the trial without first obtaining the required permissions.

The ~~r~~Research ~~t~~Team ~~has~~ already conducted the world's first publicly funded platform, open, response-adaptive randomised controlled trial in primary care. Conducted in 13 countries, the ALIC4E trial of oseltamivir for influenza-like illness in primary care has been at the forefront of such efficient trial designs.(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 ~~introduced~~ will be outlined in an appendix to this protocol. Treatments ~~which that~~ are found to be ineffective should not be commissioned, as ineffective treatments ~~simply~~ put people at unnecessary risk of side-effects and waste resources. We urgently need to know whether 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 epidemic-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 pPrimary cCare platform trial for UK COVID-19, assessing the effectiveness of trial treatments in reducing the need for hospital admission or death for patients with suspected COVID-19 infection-aged ≥50 years with serious comorbidity, and aged ≥65 with or without comorbidity, and during a time of when prevalent COVID-19 is prevalent infections in the context of current care delivery. Thus, the trial will need to be as streamlined as possible so that it fits with minimal disruption into routine care during a period of widespread infection and considerable pressure on the NHS and society. 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 according to clinical criteria.

### **Platform trial**

A platform trial, in contrast to traditional two-arm designs, allows multiple arms to be considered simultaneously, and interventions can be dropped, added and/or replaced as evidence emerges for effectiveness, or lack of it 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 <u>the</u> effectiveness of trial treatments in reducing the need for hospital admission or death, for	Hospital admission or mortality related to suspected COVID-19	Within 28 days

	patients aged ≥50 years with <del>serious</del> comorbidity, and aged ≥65 with or without comorbidity and suspected COVID-19 <del>infection</del> during a time of <del>prevalent</del> <del>of where</del> <del>prevalent</del> COVID-19 <del>disease is</del> <del>prevalent</del> <del>infections</del>		
Secondary	<p>To explore whether trial treatment reduces</p> <p>13) Duration of severe symptoms</p> <p>14) Time taken to self-report recovery</p> <p>15) Contacts with the health services</p> <p>16) Consumption of antibiotics</p> <p>17) Hospital assessment without admission</p> <p>18) Oxygen administration</p> <p>19) Intensive Care Unit admission</p> <p>20) Mechanical ventilation</p> <p>21) To determine if effects are specific to those with <u>a positive test the infectious syndrome but who test positive</u> for COVID-19</p> <p>22) Duration of hospital admission</p> <p>23) Viral shedding</p> <p>24) Negative effects on well being</p>	<p>1-2. Patient reports <u>the on</u> day they feel <del>to have</del> recovered</p> <p>3. Contacts with health services reported by patients and/or captured by reports of patients' medical records <u>if where</u> the practice is a member of <u>the RCGP RSC network</u></p> <p>4. Bi-weekly reports from participants' primary care medical records</p> <p>5-8 and 10. <u>P</u>patient report/carer report/medical record in primary <del>care</del> and <u>hospital</u> <u>secondary</u> care</p> <p>9. Swab results either at baseline or day 5 for <del>COVID-19</del> <u>SARS-CoV-2</u> will indicate an "Intention to Treat Infected" group within the overall cohort for sub analysis. Blood test on recovery (optional) for evidence of <u>historic</u> COVID-19 <del>infection</del>.</p> <p>11. Follow up swabs at day 5 (if available) will indicate ongoing <u>viral</u> shedding, allowing <del>for</del> comparison between groups</p> <p>12. WHO-5 Well Being Index</p>	<p>Daily online symptoms scores.</p> <p>Telephone call or text <u>on</u> days <u>2, 7</u>, 14 and 28 if data <u>is not being received-obtained through the online diary</u></p> <p>GP notes review <u>if where</u> available through Oxford RCGP RSC network; <u>otherwise, or</u> other sources of routinely collected data after 28 days</p> <p>HES/ONS/EMIS/Medical record data linkage after 28 days <u>if where</u> patients have been assessed in hospital</p> <p>Swab result <del>available</del> from medical records, <u>and from</u> the supporting laboratory and/or convalescent blood test for evidence of <u>historic</u> COVID-19 <del>infection</del></p> <p>WHO 5 Well Being Index at baseline, day 14, and day 28, either via online diary or telephone</p>

Qualitative sub-study	<p>1. To explore patients' experiences of consulting, being tested and taking (trial) medication for suspected COVID-19.</p> <p>2. To explore healthcare professionals' views of taking part in research during pandemics.</p>	<p>1. Telephone interviews with patients.</p> <p>2. Telephone interviews with healthcare professionals.</p>	<p>1. After 28 days.</p> <p>2. Once practice has completed recruitment.</p>
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 first 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 in the first instance. Additional arms may be added as the trial progresses. These will be detailed in the Appendices. If an intervention arm trial arm that included a study drug is shown to be superior, then this will become the new standard of care (usual care) in the trial and any further interventions will be compared against that intervention the new standard of care. However, the primary analysis of subsequent interventions will correspond to the comparison versus the original Usual Care arm.		

## 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 which that is being scaled up. Due to the pandemic, almost all practices in the UK have been asked to join the RCGP RSC Network.

## PARTICIPANT IDENTIFICATION

### 7.1 Trial Participants

Patients ≥50 years with serious comorbidity, and patients aged ≥65 with or without comorbidity, presenting in the community within 14 days since onset of symptoms, with a new continuous cough and/or high temperature -during a time of prevalent when- COVID-19 is prevalent infections, or a positive test for SARS-CoV-2 infection which was taken fewer than 15 days ago, AND symptoms of COVID-19, with a positive test for SARS-CoV-2 infection and other symptoms consistent with 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)."

TM101-C

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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-CoV-2 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. Onset of other symptoms of possible COVID-19 in the community (including, but not limited to, shortness of breath, malaise, myalgia, diarrhoea, vomiting) within 14 days of inclusion AND with a positive test for SARS-CoV-2 infection.~~

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

OR

~~Patients with a positive test for SARS-CoV-2 infection and who have symptoms consistent with COVID-19.~~

#### 7.1.2 Exclusion Criteria

- ~~Pregnancy;~~
- ~~Breastfeeding;~~
- ~~Known severe hepatic impairment;~~

**Commented [EC1]:** Does the positive test have to be within the last 14 days? I also found PIS wording a bit unclear.

**Commented [HS2R1]:** Just the symptoms. Hopefully PIS wording is clearer now.

**Commented [JB3]:** I presume this is the case?

Otherwise this would remove the age criteria where a participant has a positive test (or is that the intention?).

**Commented [HS4R3]:** Yes, thank you

- 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, chloroquine, azithromycin or other macrolides or ketolides
- Patients taking the following drugs: penicillamine, amiodarone, sotalol, ciclosporin, digoxin, chloroquine, bromocriptine, cabergoline, ergotamine, ergometrine, methysergide or any ergot derivatives;
- Already taking antibiotics for an acute condition
- Patient currently admitted in hospital
- Known congenital or documented QT prolongation
- Known allergy to soya or peanut due to the risk of hypersensitivity reactions
- Known retinal disease;
- 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

**Commented [JD5]:** Moved to HCQ and AZM appendix

**Commented [JD6]:** Moved to HCQ appendix

**Commented [JD7]:** Moved to HCQ and AZM appendix

**Commented [JD8]:** Moved to HCQ appendix

**Commented [JD9]:** Moved to AZM appendix

**Commented [JD10]:** Moved to HCQ appendix

**Commented [JD11]:** Moved to HCQ and AZM appendix

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**Commented [JD13]:** Moved to HCQ and AZM appendix

**Commented [JD14]:** Moved to HCQ appendix

**Commented [JD15]:** Moved to AZM appendix

**Commented [JD16]:** Moved to AZM appendix

**Commented [JD17]:** Moved to HCQ and AZM appendix

**Commented [JD18]:** Moved to AZM appendix

**Commented [JD19]:** Moved to HCQ appendix

**Commented [JD20]:** We could remove this as HCQ and AZM are in the appendices as contraindications/exclusion criteria to each other

**Commented [JB21]:** For each of the criteria that includes 'severe' can this be defined in clinical terms in each instance.

**Commented [EO22R21]:** Thanks Joe. Unfortunately not, we wanted it to be severe meaning it is known to the pt and after initial discussion with you we thought we'd be tying ourselves in knots to link to specific number ranges for conditions. The clinical team are the only ones confirming eligibility and they're aware of ranges

**Commented [EC23]:** So, if a patient is only eligible for one arm, how will the randomisation be handled? Please add details to the appropriate section(s). Presumably you can do this via Sortition? Also, this change is not mentioned in the amendment form or REC letter.

**Commented [EO24R23]:** Added detail to sortition section

Additional exclusions specific to each intervention arm are listed below and in the Appendix related to that intervention. Participants will be able to be randomised into the study if they are eligible to be randomised to at least one intervention arm as well as the control arm. Participants will be able to be randomised into 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, and will include:

People who are concerned about COVID-19 continue to contact ~~their~~ general practices ~~in large numbers~~. In the first instance, we will ask participating general practices to record whether a person making contact ~~phoning~~ about COVID-19 is potentially eligible for the study. The practice will then ask the person if they are interested in finding out about potential trial participation, or seek verbal consent if they are happy to be contacted by the trial team to discuss this further. If ~~so they are~~, 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. ~~Full Detailed~~ information about the study will be available to view on ~~a~~ web-site and subsequently on the Participant Information Sheet (PIS). A ~~simplified summary, pictorial~~ Participant Information Leaflet ~~PIS may also be provided~~ is also available to supplement the full PIS. This information will inform potentially eligible and interested patients ~~about 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 ~~(up to)~~ 14 days for potentially eligible participants ~~to be approached~~ 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, to~~ tell them about the study and ~~to~~ let them know that, should they develop relevant symptoms, they may wish to contact the practice or trial team directly to discuss participation in the trial.

The ~~sStudy tTeam~~ will be ~~can be~~ contacted directly by ~~some~~ potentially eligible ~~patients~~ participants who have heard about the study through ~~due to~~ word of mouth, ~~and~~ 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. They ~~Potential participants~~ Potential participants may approach the ~~sStudy tTeam~~ by telephone calls, email, ~~or and through by the study website~~, ~~s and other mechanisms~~. The ~~sStudy tTeam~~ will then also be able to provide such people with information

about potentially joining the trial, ~~and~~ the steps involved, ~~and~~ guide them through the consent process and joining the trial including the consent process.

~~AA~~ agencies from national bodies, such as NHS 111, ~~and CC~~ COVID-19 'Hot Hubs', ~~and~~ hospital emergency departments ~~which that receive COVID-19 calls, 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 sStudy pPartners-see below) and verbally about possible trial participation. ~~They can also, and~~ direct interested patients to the online information about the study ~~and/or how to contact the sStudy tTeam. General media releases and, including social media posts, will also signpost direct potential participants to the study.~~

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

Participants will preferably complete the Informed Consent Form (ICF) online. They will be able to download their consent form for their own records. This online process avoids risks associated with from paper ~~copies documents being~~ handled by people with infection, and is efficient during a time or 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 potential COVID-19 sufferers/patients are being informed by a national campaign to contact clinicians by telephone or online.

During this process, we the study team will ask the potential participant to, if possible, include a phone number and email address for a sStudy pPartner, who may provide assistance ~~et~~ to the study participant in completing trial procedures. Identifying a sStudy pPartner is not ~~a requirement of study participation 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 rResearch nNurse who is suitably trained and experienced ~~who 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 arms 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 what 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 two2 sampling kits (depending on availability) for self-sampling by their practice, study team, Public Health England (PHE) or other central service, ~~if such sampling kits are~~

**Commented [JB25]:** This should be included in the substantial amendment form – please also comment on the security of this arrangement (either in the protocol or IRAS amendment justification).

**Commented [EO26R25]:** Study materials are couriered to pts or collected from GP practices by the pt/trial partner, detailed below

**Commented [JB27]:** Please include an OID and SoE for Trusts conducting eligibility assessments.

**Commented [HS28R27]:** Done

available. 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, will may in addition, be asked if they wish to be put in touch with a research team from Imperial College league, 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 trialStudy for on patients who also consent into to take part in the Imperial College study.

Once recruited, participants will be issued with an online link where they to a symptom diary and will be asked to record the presence and severity of a few simple-symptoms each day. IfWhere online data is not being entered by \_ participants, the research team will contact the participants and/or their Sstudy Ppartner following on days 2, 7, 14 and 28. The study team will make no more than three six attempts to contact the participant/tTrial pPartner 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 at least twice weekly about healthcare contacts in the participating patient's 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. Where if notes review is not possible using this route – for example, where a patient has been 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 trials 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), and 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 go on to then enter online baseline information, including their address and contact details and those of a SStudy PPartner, if they have one a Study Partner available to help them with the study. 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 go on to randomise the participant. The participant, GP, and trial team will be notified electronically of the study participation participant's enrolment and the treatment group allocated.

The participant, trial team and participant's GP will be notified electronically or sent a secure email informing them of what treatment allocation they have been randomised to. The participant and GP can review the PIS and completed ICF at any time using a secure log in access code.

Commented [JD29]: This is duplicated from section above



### 8.3 Informed Consent

Written and verbal versions of the ~~Participant Information Sheet (PIS)~~ and ~~the Informed Consent Form (ICF)~~ will be presented to the participants detailing no less than: the exact nature of the ~~trial~~ study; the implications and constraints of the protocol, and; the known side-effects and risks involved in taking part. The ~~trial~~ study will provide a PIS that includes all necessary information in appropriate wording and format for the participant. It will be clearly stated that the participant is free to withdraw from the study at any time for any reason without ~~prejudice to 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 ~~to them~~ and to ask any questions they may have about the trial before deciding whether they will participate ~~in the study~~. However, they must still be recruited within the stated number of days of the onset of their symptoms to participate.

### 8.4 Randomisation

Participants will be randomised using a fully validated and compliant web-based randomisation system called Sortition. At the baseline assessment, the recruiter or a member of the trial team will enter the participant's baseline data into the online system, which will then enable ~~the~~ randomisation to take place. The randomisation process will take only a few moments via the online system and will not delay trial participation. 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), ~~unless~~ if a sample can be taken face-to-face by the general practice, or another facility soon after inclusion, ~~in which case~~ 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 may~~ be issued centrally from the trial team.

### 8.7 Subsequent Visits

There is no requirement for participants to have a ~~research-specific~~ face-to-face visit as part of ~~their study 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 ~~Sstudy Ppartners~~, 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 ~~Well Being Index~~ 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 ~~process evaluation~~ ~~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 ~~covid-19~~ SARS-CoV-2 blood test (if ~~it is~~ ~~one suitable for the purposes of this study~~ becomes available) ~~will be contacted by the study team within 6 months of completing the study and will be given more information in an additional participant information sheet PIS and consent form ICF, including detailing where blood sampling will take place and that blood samples will not be stored.~~

Commented [EC30]: Does sentence still make sense?

Commented [E031R30]: No it didn't! edited

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

~~Where notes review is not possible using these routes – for example if where a patient has been 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 trials team to request a limited notes review.~~

Commented [OG32]: Already mentioned in 8.1 – can remove.

## 8.8 Sample Handling

We will request two biological samples to test for ~~COVID-19~~ SARS-CoV-2 from all consenting participants, the first at baseline and the second at day 5. ~~Unless a swab can be taken face to face in the course of usual care, 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 ~~contained~~ packaging, double bagged, and posted to the PHE laboratory that is supporting the ~~study 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 ~~won't~~

~~will not~~ be stored for the purpose of this trial. The swab material will fall under PHE's ~~remit, and~~ not the trial's; ~~remit, and~~ PHE may retain the swab for up to 5 years.

If a ~~suitable~~ blood test for ~~covid-19~~SARS-CoV-2 becomes available, participants who have consented to being contacted ~~for a blood test~~ will receive further information about this ~~test~~ 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~~~~won't~~ 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~~3 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 ~~process evaluation 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 ~~on day 0 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 ~~will~~ 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 ~~prior to interviews starting 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 participant's ~~s~~ 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/where 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 ~~will be~~ expected to last approximately 30-45 minutes and interviews with HCPs ~~will be~~ 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 ~~ImmaF~~ form process. All GP practices in England are already set up on ~~ImmaF~~ form, as they use this system to order influenza vaccines from Public Health England. —GPs will be provided with an envelope by the ~~trial study~~ team which will be labelled appropriately for trial medication, and they will add the patient's details to this label. This pack, containing instructions on using the medication 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 which 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 ~~which~~ 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.

Commented [JB33]: Please include in Amendment form.

#### 9.4. Compliance with Trial Treatment

Participants will receive a daily email asking ~~for~~ them to log ~~in~~ with a unique access code to an ~~electronic system online diary~~ where they will record their symptoms. If ~~uncompleted 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 ~~for~~ 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"> <li>• results in death</li> <li>• is life-threatening</li> <li>• requires inpatient hospitalisation or prolongation of existing hospitalisation</li> <li>• results in persistent or significant disability/incapacity</li> <li>• consists of a congenital anomaly or birth defect*.</li> </ul> <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 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"> <li>• in the case of a product with a marketing authorisation, in the approved summary of product characteristics (SmPC) for that product</li> <li>• in the case of any other investigational medicinal product, in the approved investigator's brochure (IB) relating to the trial in question.</li> </ul>

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

## 10.2 Assessment results outside of normal parameters as AEs and SAEs

There are no additional assessment results in this study.

## 10.3 Assessment of Causality

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

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

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

#### 10.4 Procedures for Reporting Adverse Events

All AEs will be collected from daily participant diaries, calls to participants/Study Partners and RCGP data downloads.

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

It will be left to the Investigator's clinical judgment to decide whether or not an AE is of sufficient severity to require the participant's removal from treatment. A participant may also voluntarily withdraw from treatment due to what he or she perceives as an intolerable AE.

#### 10.5 Reporting Procedures for Serious Adverse Events

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

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

##### 10.5.1. Other events exempt from immediate reporting as SAEs

Hospitalisations will be defined as at least a ~~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, serious adverse event~~ and standard supportive care for the disease under study are not SAEs, and do not require SAE reporting.

##### 10.5.2. Procedure for immediate reporting of Serious Adverse Events

- ~~Trial~~ Study team will complete an SAE report form for all reportable SAEs.
- GP practice/~~study 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~~7 calendar days after the Sponsor or delegate is first aware of the reaction. Any additional relevant information will be reported within ~~eight~~8 calendar days of the initial report. All other SUSARs will be reported within 15 calendar days.

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

### 10.7 Development Safety Update Reports

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

## 11 STATISTICS

### 11.1 Master Statistical Analysis Plan (M-SAP)

~~The Details of the statistical design and methods and pre-specified analyses will be described in detail in a Master Statistical Analysis Plan (M-SAP), in which an appendix to the M-SAP titled -drafted by a Trial Statistician and signed off by the CI and Lead/senior statistician- "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 ~~control Usual Care~~ arm, the superior treatment will replace the ~~control Usual Care~~ arm as the new standard of care, ~~and all subsequent treatments will be compared to 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 as a result of~~ COVID-19 infection. The primary analysis will be a Bayesian generalised linear model of the primary outcome regressed on treatment and stratification covariates (age, comorbidity). Let  $\theta_j$  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.  $\geq 0.99$ ), 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 M-SAP](#) will also specify ~~appropriate details 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 ~~control 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 M-SAP](#), 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 will occur when first 2400 randomised participants have the opportunity to complete 28 days of follow-up, and there are a sufficient number of hospital admissions/deaths. S followed by subsequent weekly interim analyses will be conducted at regular intervals with frequency as , to be determined by the availability of additional outcome data 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.  $\geq 0.99$ ), 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.  $\geq 25\%$  ~~0.05 reduction in relative risk of decrease in the proportion 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 M-SAP](#) 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 (~~e.g. 1:1:1 stratified by age and comorbidity~~), and the additional intervention will be included in the interim analyses (with evaluation for success and futility) as detailed in the [Adaptive Design ReportM-SAP](#). 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 ReportM-SAP](#); 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 ReportM-SAP/appendices](#)), 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 ReportM-SAP and corresponding appendices](#).

#### 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 ~~at the~~ participant fails to complete data online and after ~~three~~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 ~~of which 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

**Commented [JB34]:** Something should be included here regarding (potential) study partners details – how these are stored and for how long (including how long should they or their participant partner not go on to be enrolled or be withdrawn).

**Commented [E035R34]:** Added below

on a secure server – data will be entered in a web browser ~~on PCs~~  
~~computers in the Clinical Trials Unit building~~ and then transferred to the OpenClinica Database by encrypted (Https) transfer. OpenClinica™ meets FDA part 11B standards. This includes safety data, laboratory data and outcome data. Safety data will also be collected through electronic diaries which are stored on a secure server.

Sentry is an online secure data entry system developed in-house at PC-CTU and hosted at Oxford. It is designed to collect sensitive data, such as participant ~~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 ~~and~~ 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~~ 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

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

### 13.2 Monitoring

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

### 13.3 Trial committees

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

- DMSC- to review the data at each interim analysis as described in the Statistical Analysis section, as the updates to the randomisation scheme occur in order to ensure that the process is working correctly and to review and monitor the accruing data to ensure the rights, safety and wellbeing of the trial participants.
- 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 C-I, the serious breach will be reviewed by the Sponsor and, if appropriate, the Sponsor will report it to the approving REC committee and the relevant NHS host organisation within seven calendar days.

## 16 ETHICAL AND REGULATORY CONSIDERATIONS

### 16.1 Declaration of Helsinki

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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 charge, should a prescription be issued as a result of trial participation. Most people with the co-morbidities outlined 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	<a href="#">Day 28-6 months</a>
	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	<a href="#">Contacted by study team if consent provided</a>
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	
<a href="#">Optional SARS-CoV-2 blood test</a>							<a href="#">X</a>

**23 APPENDIX B: AMENDMENT HISTORY**

**Commented [JB36]:** Please update to reflect this latest amendment, using tracked changes and with the correct [protocol versions identified.

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	<del>2.13-0</del>		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
<del>4</del>	<del>2.1</del>		<del>No changes to the protocol</del>	
<del>5</del>	<del>3.0</del>		<del>Hannah Swayze; Chris Butler; Emma Ogburn; Gail Hayward</del>	<del>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.</del>

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.

Date and version No: ~~1924~~.054.2020 version ~~3.02.4~~



**APPENDIX C: USUAL CARE ARM**

**Commented [JB37]:** The footnotes remain in the text but the references have been removed, unclear why this is – please explain.

**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.<sup>(1-3, 6)</sup> 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.

**3.1 Investigational Medicinal Product (IMP) description**

Not applicable

**3.2 Storage of IMP**

Not applicable

**4 Safety reporting**

Mechanisms for safety reporting are outlined in the trial protocol.

**5 References**

1. — Wu Z, McGoogan JM. Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72314 Cases From the Chinese Center for Disease Control and Prevention. JAMA. 2020.
2. — Paules CI, Marston HD, Fauci AS. Coronavirus Infections—More Than Just the Common Cold. JAMA. 2020.
3. — Livingston E, Bucher K. Coronavirus Disease 2019 (COVID-19) in Italy. JAMA. 2020.
4. — Neil M Ferguson DL, Gemma Nedjati-Gilani, Natsuko Imai, Kylie Ainslie, Marc Baguelin, Sangeeta Bhatia, Adhiratha Boonyasiri, Zulma Cucunubá, Gina Cuomo-Dannenburg, Amy Dighe, Ilaria Dorigatti, Han Fu, Katy Gaythorpe, Will Green, Arran Hamlet, Wes Hinsley, Lucy C Okell, Sabine van Elsland, Hayley Thompson, Robert Verity, Erik Volz, Haowei Wang, Yuanrong Wang, Patrick GT Walker, Caroline Walters,

Date and version No: ~~1924.054~~.2020 version ~~3.02.1~~



~~Peter Winskill, Charles Whittaker, Christl A Donnelly, Steven Riley, Azra C Ghani. Impact of non-pharmaceutical interventions (NPIs) to reduce COVID-19 mortality and healthcare demand 2020 [Available from: <https://www.imperial.ac.uk/media/imperial-college/medicine/sph/ide/gida-fellowships/Imperial-College-COVID19-NPI-modelling-16-03-2020.pdf>.~~

## APPENDIX ~~2D~~: USUAL CARE PLUS HYDROXYCHLOROQUINE ARM

### 1 Background and rationale

#### 1.1 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 EC<sub>90</sub> 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](#)

### **23 Outcome measures related to hydroxychloroquine**

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

### **34 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.

#### **3.14.1 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.

#### **3.24.2 Storage of IMP**

: Stored at room temperature in locked cupboards in restricted access rooms in the ~~Primary Care Clinical Trials Unit (PC-CTU)~~ [Nuffield Department of Primary Care Health Sciences](#); in locked cupboards in restricted access rooms in GP Practices; in Pharmacies.

#### **3.24.3 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.

##### **3.3.14.3.1 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.



### ~~3.3.24~~.3.2 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  $\alpha$ -galactosidase activity when hydroxychloroquine is co-administered with agalsidase.

### ~~3.3.34~~.3.3 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.

#### 45 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.

#### 5 References

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2. Devaux CA, Rolain JM, Colson P, Raoult D. New insights on the antiviral effects of chloroquine against coronavirus: what to expect for COVID-19? *Int J Antimicrob Agents*. 2020:105938.
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5. Colson P, Rolain JM, Raoult D. Chloroquine for the 2019 novel coronavirus SARS-CoV-2. *Int J Antimicrob Agents*. 2020;55(3):105923.
6. Mackenzie AH. Dose refinements in long term therapy of rheumatoid arthritis with antimalarials. *Am J Med*. 1983;75(1A):40-5.
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## APPENDIX E3: USUAL CARE PLUS AZITHROMYCIN ARM

### 1 Background and rationale

#### 1.1 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 administered 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)

#### 1.2 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

## 3.4 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.

### 3.4.1 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**

### **3.24.2 Storage of IMP**

Azithromycin: Stored at room temperature in locked cupboards in restricted access rooms in the ~~Primary Care Clinical Trials Unit (PC-CTU)~~ Nuffield Department of Primary Care Health Sciences; in locked cupboards in restricted access rooms in GP Practices; in Pharmacies.

### **3.24.3 SmPC precautions and concomitant medication**

#### **3.3.14.3.1 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.

#### **3.3.24.3.2 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*

TM101-C

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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.

### **3.3.34.3.3 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.

## **4.5 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.

## **5 References**

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## Platform Randomised trial of Interventions against COVID-19 In older people - PRINCIPLE

REC Number: 20/SC/058

IRAS Number: 281958

EudraCT Number:

2020-001209-22

Chief Investigator: Professor Christopher Butler

Participant ID:

### CONSENT FORM

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

Please read the [Participant Information Sheet](#) if you haven't already done so, and if you are willing to participate please select 'Yes', TYPE your FIRST and LAST names below and then click Submit  
**If you agree, please select 'Yes' to confirm that you have read and understood the following:**

		YES	NO
1	I confirm I have read and understood the information sheet version number ____ - _____ dated ____ / ____ / ____ for the above study. I have had the opportunity to ask questions and had these answered satisfactorily.		
2	I understand my participation is voluntary and that I am free to withdraw at any time, without giving any reason, and without my medical care or legal rights being affected.		
3	I understand that I will be randomised to receive either: standard care plus the trial treatment or standard care and I will not be able to choose which I will receive.		
4	I understand that relevant sections of my GP and Hospital medical notes and data collected during the study may be looked at by members of the research team and individuals from University of Oxford. It may also be reviewed by relevant people from regulatory authorities and from the NHS Trust(s). I give permission for these individuals to have access to my records.		
5	I consent to being contacted by the research team for the purposes of trial follow up and I understand that this will require me to provide my contact details to the research team.		
6	I consent to my GP and/or Care Home being informed of my participation within the study.		
7	I agree to take part in the study		
	<b>ADDITIONAL (optional, not required for study participation)</b>	YES	NO
	<i>I agree to provide the research team with the contact details of my Trial Partner. I confirm my Trial partner is aware of their role and willing to answer questions.</i>		
	<i>I am happy to be contacted by the research team to be invited to a telephone interview at the end of the study.</i>  <i>(Taking part in the interview is optional and will not affect your study participation. If you agree to be contacted, the research team will contact you with details of the interview in approximately 28 days. You can then decide whether you want to take part or not.)</i>		



	<i>I am happy to be contacted by the research team to be invited to a blood test for COVID-19 infection within six months of completing the study</i>		
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**Signature:**

**First Name:** \_\_\_\_\_ **Last Name:** \_\_\_\_\_

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

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

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

Tel: 0800 138 0880 Email [principle@phc.ox.ac.uk](mailto:principle@phc.ox.ac.uk)

**Participant:**

Name: \_\_\_\_\_ Date: \_\_ \_\_ / \_\_ \_\_ / \_\_ \_\_ \_\_ \_\_

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



## Platform Randomised trial of Interventions against COVID-19 In older peoPLE

### PARTICIPANT INFORMATION LEAFLET

We would like to invite you to take part in a study about treatments  
for COVID-19 infection called PRINCIPLE.

Before you decide if you would like to take part it is important that  
you understand why we are doing this research and what it would  
involve for you.

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

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



NUFFIELD DEPARTMENT OF  
**PRIMARY CARE**  
HEALTH SCIENCES

Primary Care | ●●●  
Clinical Trials Unit



Royal College of  
General Practitioners  
Research & Surveillance Centre



Medical  
Research  
Council

EudraCT number: 2020-001209-22



## ***What is the purpose of the trial?***

### **COVID-19**

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

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

### **The Trial**

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

We will evaluate drugs that are well known and have been used for many years around the world. Please see Appendices for drug specific information and the known side-effects.

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

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

### Aim

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

We aim to test as many people as possible included in the study for COVID-19, some will receive the trial treatment we are testing and some will be allocated to current usual care without the medication we are testing.

### *Can I take part?*

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

To take part, you need to be experiencing symptoms that are likely to be caused by a COVID-19 infection, for **fewer than 15 days**:

- A new continuous cough - this means coughing a lot for more than an hour, or 3 or more coughing episodes in 24 hours (if you usually have a cough, it may be worse than usual)
- and/or a high temperature - this means you feel hot to touch on your chest or back (you do not need to take your temperature).

**OR**

- You have had a **positive test** for SARS-Co-V2 infection which was taken fewer than 15 days ago, AND are 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 you must have had them for **fewer than 15 days**.

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

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

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



- heart disease or high blood pressure
- asthma or lung disease
- Diabetes not treated with insulin
- liver disease
- stroke or neurological problem

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

You should continue to take your usual prescribed medicines if you join the study.

### ***Do I have to take part?***

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



## ***What will happen to me if I take part?***

You will visit our website if you experience symptoms of COVID-19. The information on the website is the same as the information in this leaflet. Once you have read it, if you are interested in taking part, we will ask you to complete a short online form to see if you are eligible. If you do not have internet access or would like to call us instead, then you can contact us using the contact details on the last page.

### **Informed Consent**

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

### **Initial Questionnaire**

Then, you will be asked to complete a short questionnaire giving some details about you and the symptoms you have been experiencing. We will also collect some contact details such as your name, email address and telephone number. We will also ask you to provide details of a Trial Partner. This could be a relative, spouse, friend or carer, if such a person is available, who we will contact for information about you if we are unable to get hold of you for whatever reason. So a Trial Partner is someone who you know who might be able to help you with the study. A Trial Partner does not have to live with you, but you just need to be in regular contact with them.

### Letting Your GP Know

Once you have completed the informed consent and additional questions, the website will notify the trial team and your GP with this information. A secure email containing personally identifiable data with your recruitment allocation may also be sent to your GP. A qualified medical practitioner will then check that there are no other medical reasons why you cannot participate.

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

### Randomisation

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

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



## Swab

We hope to be able to offer swab tests for the COVID-19 coronavirus to everyone who takes part in the trial. This will be a nose and/or a throat swab. If we have swabs available, we will ask you to provide a swab at the start of the trial, and then again 5 days later.

However, there is a worldwide shortage of swabs so we may not be able to offer swab tests to all who take part in the trial. If you are offered a swab, you will be given instructions on how to take your own sample at home using a swab kit. We will also tell you how to post the sample to the labs using the envelopes we provide. If you are not able to get the swab to a post box, then store it in a fridge and post it when you are able to do so.

You will be asked to send the swab to Public Health England or another central laboratory service using the packaging we provide. The swab aims to give an idea of whether you have COVID-19, and the result will be sent to your GP. The swab test for COVID-19 has a high *false negative* rate and so although the swab result may be negative, you may still have COVID-19 and we advise that you continue with the medication regardless of the result. Public Health England (PHE) may keep the specimen for up to 5 years, following their own approved processes.



### Blood test

We are also asking everyone in the study for their consent to be contacted once their symptoms have passed, to have a blood test for COVID-19 coronavirus. You do not have to agree to be contacted about a blood test to take part in the trial. Even if you agree that we can ask you to have a blood test, you will be able to say no at the time if you don't want one.

### Trial Treatment

If you are randomised to the standard care plus trial treatment group, arrangements will be made for the drug to be delivered to you or you may collect/nominate an individual to collect the drug from a local pharmacy, or local GP. You will also receive instructions on how to take it and for how long and asked to confirm receipt via text or telephone call. Should your condition worsen at any time during the trial, you should not contact the study team but contact your GP or other usual services that are open to you.

### Follow-Up

You will receive a text message from us to ask you to complete questions relating to your symptoms and how well you feel every day for up to 28 days after you start the trial. This will be an online daily diary. If the trial team don't receive your daily diary answers online, they will text or telephone you on day 2, 7, day 14 and day 28 of the follow up period and ask you a brief set of questions over the phone.



### ***Flowchart—What Will I Need to Do?***

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

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

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

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

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

#### **Follow-up**

You should receive a swab kit if available and instructions of how to take your own sample at the start of the trial and possibly on day 5. We will also tell you how to post the sample to the labs. If randomised to the trial treatment group, you will be provided with the drug which you will be asked to take for the required number of days.

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

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

### **Optional Follow-up**

We are planning to interview a group of participants after the main trial. This is optional and you will be able to confirm on the consent form whether you are happy to be contacted by the research team. If you agree to be contacted, the research team will contact you with details of the interview in approximately 28 days. You can then decide whether you want to take part or not.

We are planning to test all participants for COVID-19 coronavirus infection from a blood sample if a suitable test becomes available. This is optional, and you will be able to confirm on the consent form whether you are happy to be contacted by the research team. If you agree to be contacted, the research team will contact you with details of the blood test within six months of completing the study. You can then decide whether you want to take part or not in the blood test. You can still take part in the trial even if you don't want to give a blood sample.

### ***What happens if I am admitted to Hospital?***

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

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

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

With any medicine, including ones that are already used within the NHS, there is a risk of side effects.

Please see Appendices for details of the side-effects common to each drug. You will be able to tell us if you are experiencing any of these symptoms in your daily diary.





### ***What are the possible benefits of taking part?***

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

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

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



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

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

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

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

### ***Expenses and Payments***

You will be reimbursed for your participation through gift vouchers worth a total of £20. You will receive the voucher at the end of your follow up period, once we have received your completed symptom diary.

### ***What if there are any problems?***

If you have any questions about this trial, please contact the Trial Team (See last page for contact details).

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

If you wish to complain about any aspect of the way in which you have been approached or treated, or how your information is handled during the course of this trial, you should contact the trial team on [principle@phc.ox.ac.uk](mailto:principle@phc.ox.ac.uk) or **0800 138 0880** or you may contact the University of Oxford Clinical Trials and Research Governance (CTRG) office on 01865 616480, or the head of CTRG, email [ctrig@admin.ox.ac.uk](mailto:ctrig@admin.ox.ac.uk)

### ***What will happen to my data?***

Data protection regulation requires that we state the legal basis for processing information about you. In the case of research, this is 'a task in the public interest.' The University of Oxford is the data controller and is responsible for looking after your information and using it properly.

Responsible members of the University of Oxford, Host Organisations, Sponsor auditors, and the Medicines and Health Care Products Regulatory Authority, may be given access to the trial data for monitoring and/or audit of the trial to ensure that the research is complying with applicable regulations.

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

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

The Royal College of General Practitioners Research Surveillance Centre may be used in order to gather data you haven't completed in your daily diaries. Data collected will include participant identifiable information and will be accessed at the University of Oxford according to PC-CTU Information Governance policies and GDPR. Data will only be held for the duration of which its required, this will be reviewed annually.

If we use a courier or home delivery service to provide you with trial materials, we will provide them with your name and address. These companies will use and store your data in accordance with GDPR. Data protection regulation provides you with control over your personal data and how it is used. When you agree to your information being used in research, however, some of those rights may be limited in order for the research to be reliable and accurate.

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

You can find out more about how we use your information by contacting [principle@phc.ox.ac.uk](mailto:principle@phc.ox.ac.uk).

### ***What if relevant new information becomes available during the trial?***

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

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

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

### ***What will happen to the results of the trial?***

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

### ***Who is organising and funding the research?***

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

### ***Who has reviewed the trial?***

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

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

***Thank you for taking the time to read  
this information leaflet and considering  
taking part in this trial.  
If you would like any further information  
about this trial, you can contact the trial  
team here:***

**Trial Address:**

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

**Trial Team:**

**Tel. 0800 138 0880**



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

### **PARTICIPANT INFORMATION LEAFLET**

We would like to invite you to take part in a study about treatments for COVID-19 infection called PRINCIPLE.

Before you decide if you would like to take part it is important that you understand why we are doing this research and what it would involve for you.

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

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

## *What is the purpose of the trial?*

### COVID-19

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

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

### The Trial

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

We will evaluate drugs that are well known and have been used for many years around the world.

Please see Appendices for drug specific information and the known side-effects.

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

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

### Aim

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



We aim to test as many people as possible included in the study for COVID-19, some will receive the trial treatment we are testing and some will be allocated to current usual care without the medication we are testing.

### Can I take part?

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

To take part, you need to be experiencing symptoms that are likely to be caused by a COVID-19 infection, **for fewer than 15 days:**

- **A new continuous cough** - this means coughing a lot for more than an hour, or 3 or more coughing episodes in 24 hours (if you usually have a cough, it may be worse than usual)
- **and/or a high temperature** - this means you feel hot to touch on your chest or back (you do not need to take your temperature)

**OR**

- **You need to have had these symptoms for fewer than 15 days. You have had a positive test for SARS-Co-V2 infection which was taken fewer than 15 days ago, AND are 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 you must have had them for fewer than 15 days.**

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

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

- weakened immune system due to a serious illness or medication (e.g. chemotherapy)
- heart disease or high blood pressure
- asthma or lung disease
- Diabetes not treated with insulin
- liver disease
- stroke or neurological problem

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

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You should continue to take your usual prescribed medicines if you join the study.

### ***Do I have to take part?***

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

### ***What will happen to me if I take part?***

You will visit our website if you experience symptoms of COVID-19. The information on the website is the same as the information in this leaflet. Once you have read it, if you are interested in taking part, we will ask you to complete a short online form to see if you are eligible. If you do not have internet access or would like to call us instead, then you can contact us using the contact details on page 12

### **Informed Consent**

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

### **Initial Questionnaire**

Then, you will be asked to complete a short questionnaire giving some details about you and the symptoms you have been experiencing. We will also collect some contact details such as your name, email address and telephone number. We will also ask you to provide details of a Trial Partner. This could be a relative, spouse, friend or carer, if such a person is available, who we will contact for information about you if we are unable to get hold of you for whatever reason. So a Trial Partner is someone who you know who might be able to help you with the study. A Trial Partner does not have to live with you, but you just need to be in regular contact with them.

### Letting Your GP Know

Once you have completed the informed consent and additional questions the website will notify the trial team and your GP with this information. A secure email containing personally identifiable data with your recruitment allocation may also be sent to your GP. A qualified medical practitioner will then check that there are no other medical reasons why you cannot participate.

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

### Randomisation

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

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

### Swab

We hope to be able to offer swab tests for the COVID-19 coronavirus to everyone who takes part in the trial. This will be a nose and/or a throat swab. If we have swabs available, we will ask you to provide a swab at the start of the trial, and then again 5 days later.

However, there is a worldwide shortage of swabs so we may not be able to offer swab tests to all who take part in the trial. If you are offered a swab, you will be given instructions on how to take your own sample at home using a swab kit. We will also tell you how to post the sample to the labs using the envelopes we provide. If you are not able to get the swab to a post box, then store it in a fridge and post it when you are able to do so.

You will be asked to send the swab to Public Health England or another central laboratory service using the packaging we provide. The swab aims to give an idea of whether you have COVID-19, and the result will be sent to your GP. The swab test for COVID-19 has a high *false negative* rate and so although the swab result may be negative, you may still have COVID-19 and we advise that you continue with the medication regardless of the result. Public Health England (PHE) may keep the specimen for up to 5 years, following their own approved processes.

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## Blood test

We are also asking everyone in the study for their consent to be contacted once their symptoms have passed, to have a blood test for COVID-19 coronavirus. You do not have to agree to be contacted about a blood test to take part in the trial. Even if you agree that we can ask you to have a blood test, you will be able to say no at the time if you don't want one.

## Trial Treatment

If you are randomised to the standard care plus trial treatment group, arrangements will be made for the drug to be delivered to you or you may collect/nominate an individual to collect the drug from a local pharmacy, or local GP. You will also receive instructions on how to take it and for how long and asked to confirm receipt via text or telephone call. Should your condition worsen at any time during the trial, you should not contact the study team but contact your GP or other usual services that are open to you.

## Follow-Up

You will receive a text message from us to ask you to complete questions relating to your symptoms and how well you feel every day for up to 28 days after you start the trial. This will be an online daily diary. If the trial team don't receive your daily diary answers online, they will text or telephone you on day 2, 7, day 14 and day 28 of the follow up period and ask you a brief set of questions over the phone.

## What happens if I am admitted to Hospital?

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

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

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

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

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

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

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

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

#### **Follow-up**

You should receive a swab kit if available and instructions of how to take your own sample at the start of the trial and possibly on day 5. We will also tell you how to post the sample to the labs. If randomised to the trial treatment group, you will be provided with the drug which you will be asked to take for the required number of days.

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

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

#### **Optional Follow-up**

We are planning to interview a group of participants after the main trial. This is optional and you will be able to confirm on the consent form whether you are happy to be contacted by the research team. If you agree to be contacted, the research team will contact you with details of the interview in approximately 28 days. You can then decide whether you want to take part or not.

We are planning to test all participants for COVID-19 coronavirus infection from a blood sample if a suitable test becomes available.

This is optional, and you will be able to confirm on the consent form whether you are happy to be contacted by the research team. If you agree to be contacted, the research team will contact you with details of the blood test within six months of completing the study. You can then decide whether you want to take part or not in the blood test. You can still take part in the trial even if you don't want to give a blood sample.

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

With any medicine, including ones that are already used within the NHS, there is a risk of side effects.

Please see Appendices for details of the side-effects common to each drug.

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

#### ***What are the possible benefits of taking part?***

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

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

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

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

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

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

If you wish to withdraw from the trial, please contact the trial team using the contact details on page 12. The decision to withdraw will not affect the standard of care you receive from the NHS in any way, now or in the future.

### ***Expenses and Payments***

You will be reimbursed for your participation through gift vouchers worth a total of £20. You will receive the voucher at the end of your follow up period, once we have received your completed symptom diary.

### ***What if there are any problems?***

If you have any questions about this trial, please contact the Trial Team (See Page 12 for contact details).

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

If you wish to complain about any aspect of the way in which you have been approached or treated, or how your information is handled during the course of this trial, you should contact the trial team on [principle@phc.ox.ac.uk](mailto:principle@phc.ox.ac.uk) or **0800 138 0880** or you may contact the University of Oxford Clinical Trials and Research Governance (CTRG) office on 01865 616480, or the head of CTRG, email [ctrig@admin.ox.ac.uk](mailto:ctrig@admin.ox.ac.uk)

### *What will happen to my data?*

Data protection regulation requires that we state the legal basis for processing information about you. In the case of research, this is 'a task in the public interest.' The University of Oxford is the data controller and is responsible for looking after your information and using it properly.

Responsible members of the University of Oxford, Host Organisations, Sponsor auditors, and the Medicines and Health Care Products Regulatory Authority, may be given access to the trial data for monitoring and/or audit of the trial to ensure that the research is complying with applicable regulations.

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

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

The Royal College of General Practitioners Research Surveillance Centre may be used in order to gather data you haven't completed in your daily diaries. Data collected will include participant identifiable information and will be accessed at the University of Oxford according to PC-CTU Information Governance policies and GDPR. Data will only be held for the duration of which its required, this will be reviewed annually.

If we use a courier or home delivery service to provide you with trial materials, we will provide them with your name and address. These companies will use and store your data in accordance

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with GDPR.

Data protection regulation provides you with control over your personal data and how it is used. When you agree to your information being used in research, however, some of those rights may be limited in order for the research to be reliable and accurate.

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

You can find out more about how we use your information by contacting [principle@phc.ox.ac.uk](mailto:principle@phc.ox.ac.uk)

### ***What if relevant new information becomes available during the trial?***

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

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

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

### ***What will happen to the results of the trial?***

Results will be published in scientific journals, presented at scientific conferences, and published on the Oxford University departmental website. It will not be possible to identify you in any report, publication or presentation. If you would like to receive copies of any publications arising from this trial, please contact the trial team (details are on page 12).

### ***Who is organising and funding the research?***

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

### ***Who has reviewed the trial?***

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

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

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

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

**Trial Address:**

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

**Trial Team:**

Tel. 0800 xxxxxx

**Trial Email Address:**

[principle@phc.ox.ac.uk](mailto:principle@phc.ox.ac.uk)

# Participant Pictorial Information Sheet

## Platform Randomised trial of Interventions against Covid-19 In older people

### PRINCIPLE Trial

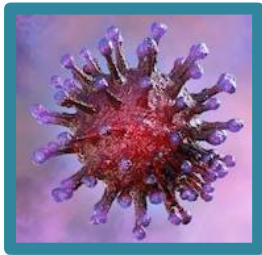
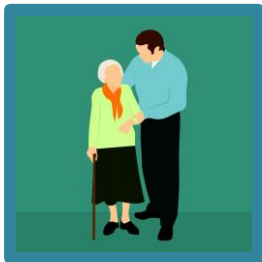
Platform Randomised trial of Interventions against COVID-19 In older people

Pictorial Participant Information Booklet v2.0, 19<sup>th</sup> May 2020,

**EudraCT number:2020-001209-22**

Professor Christopher Butler IRAS Project no. 281958 REC Reference no.:20/SC/058

# What is the trial about?



	1.	COVID-19 is caused by a new virus that is spreading quickly in many countries.
	2.	Being infected with the virus is more likely to cause more serious problems if you are older, or you have medical problems such as high blood pressure or heart disease.

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	<p>3. At the moment, we do not have treatments for COVID-19 that we know definitely work.</p>
	<p>4. The aim of this trial is to test possible treatments for COVID-19 in older adults. We hope to find treatments that stop people from getting more unwell.</p>

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# Who can take part?



5.

Anybody aged 65 years or over.

## AND

Anybody aged 50 to 64 years with:

- Weakened immune system (e.g. taking chemotherapy)
- Heart disease
- Lung disease
- Diabetes not treated with insulin
- Liver disease
- Stroke or neurological problem

## WITH

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		<p>A new or worsening continuous cough and/or fever</p> <p>OR</p> <p>You have had a <b>positive test</b> for SARS-Co-V2 infection which was taken fewer than 15 days ago, AND are unwell with symptoms of COVID-19.</p> <p><i>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 you must have had them for <b>fewer than 15 days</b>.</i> If you are starting to feel better, this study isn't for you.</p>
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## What will happen if I take part?

	<p>6. If you develop a fever or a new worsening continuous cough, OR if you have a positive test for SARS-Co-V2 infection with symptoms in the past 14 days, please visit our trial website (see end of this leaflet).</p>
	<p>7. We will ask you to fill in a short form online, to check that you can take part</p>




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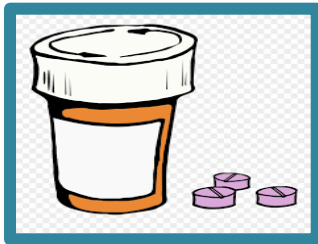
	8.	Your care will not be affected, whether or not you do take part in the trial.
	9.	If you are suitable to take part in the trial, you will be asked to fill in a consent form online, and to answer a few questions about yourself and your symptoms.
	10.	We will ask you to add details of a 'trial partner'. This is somebody that might be able help you with the study, and who we can also contact for information about

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		how you are getting on.
	11.	The information that you give us will be shared with your GP and the study team, so that we can double check that everything is in order for you to take part.
	12.	If you can take part, you will be randomly (like tossing a coin) entered into a group:-
	Or	

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<p>a) Usual care for your symptoms</p>		<p>b) You will receive one of the treatments that we are testing, in addition to usual care for your symptoms.</p> <p>We will provide you with the trial medication and instructions on how to take it.</p>
	<p>13.</p>	<p>If swabs are available, we may also ask you to take swabs from your nose and throat, to test for the virus that causes COVID-19.</p> <p>We will provide instructions on how to take the swabs and to post</p>

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		them off for testing.
	14.	Whichever group you are in, we will ask you to answer a few questions each daily in an online diary for up to 28 days, so that we know how you are feeling.
	15.	If you are unable to answer questions online, or forget to complete the questions, we might give you a phone call or send you a text message reminder.

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	16.	<p>If you are admitted to hospital, we would ask you, or someone close to you, to let us know.</p>
	17.	<p>If you agree to join the study, we will contact you at 28 days to see whether you are happy for us to arrange to speak with you in more detail about your experience of taking part in the trial. We will also ask if you are prepared to have a blood test once you are feeling better.</p>



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## What will happen to my information?

	18.	We will use the information you give us to find out which treatments work. We may also look at your general practice and hospital medical records for further information about you and your illness.
	19.	Any information that we collect about you will be kept safe. Your name will not go on any reports, presentations or publications.

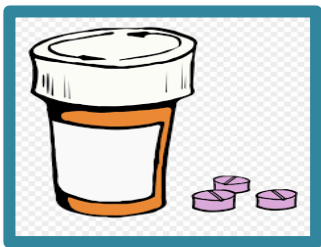
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## What are the disadvantages of taking part?

	20.	<p>There is a risk of side effects when taking any medicine. If you are taking a trial medication and have any symptoms, you can record them in the daily online diary.</p>
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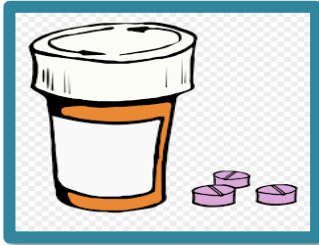
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## What are the benefits of taking part?

	21.	You will be contributing to important research to find effective treatments for COVID-19.
	22.	We have designed the trial so that whilst the trial is ongoing, if we find that one treatment is more effective, more people might receive this treatment. This means that more people in the trial have a chance of receiving the most effective trial treatment.

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# Will I be reimbursed for taking part?

	23.	You will receive a gift voucher for £20 once we receive your completed online symptom diary, as a thank you for taking part.
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# What if I do not want to carry on being part of the trial?

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	<p>24.</p>	<p>You can decide to stop taking part at any time without needing to give a reason. This will not affect the care you receive now or in the future.</p>
	<p>25.</p>	<p>If you decide to withdraw from the trial, we will use the information collected up to that point, unless you tell us not to.</p>

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

Pictorial Participant Information Booklet v2.0, 19<sup>th</sup> May 2020,

**EudraCT number:2020-001209-22**

Professor Christopher Butler IRAS Project no. 281958 REC Reference no.:20/SC/058

# What if there is a problem?

	26.	<p>If you have a concern about any aspect of this trial at any time, you can contact the trial team or the University of Oxford Clinical Trials and Research Governance (CTRG) office (Contact details below).</p>
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Platform Randomised trial of Interventions against COVID-19 In older people

Pictorial Participant Information Booklet v2.0, 19<sup>th</sup> May 2020,

**EudraCT number:2020-001209-22**

Professor Christopher Butler IRAS Project no. 281958 REC Reference no.:20/SC/058

## Trial contact details

	27.	<p>Trial team: <a href="mailto:principle@phc.ox.ac.uk">principle@phc.ox.ac.uk</a></p> <p>0800 138 0880</p> <p>Trial Website: <b><a href="http://www.principletrial.org">www.principletrial.org</a></b></p> <p>CTRG: <a href="mailto:ctrig@admin.ox.ac.uk">ctrig@admin.ox.ac.uk</a> 01865 616480</p>
	28.	<p>Thank you for taking the time to think about taking part in this trial.</p>

## Thank you!

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

Pictorial Participant Information Booklet v2.0, 19<sup>th</sup> May 2020,

**EudraCT number:2020-001209-22**

Professor Christopher Butler IRAS Project no. 281958 REC Reference no.:20/SC/058



## Participant Pictorial Information Sheet

### Platform Randomised trial of Interventions against COVID-19 In older people

#### PRINCIPLE Trial

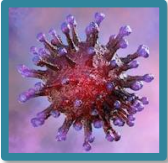

Platform Randomised trial of Interventions against COVID-19 In older people



Pictorial Participant Information Booklet v1.2.09, 19<sup>th</sup> May 2020, April 2020,

EudraCT number: 2020-001209-22

Professor Christopher Butler IRAS Project no. 281958 REC Reference no.: 20/SC/058

# What is the trial about?

	1. COVID-19 is caused by a new virus that is spreading quickly in many countries.
	2. Being infected with the virus is more likely to cause more serious problems if you are older, or you have medical problems such as high blood pressure or heart disease.

	<p>3. At the moment, we do not have treatments for COVID-19 that we know definitely work.</p>
	<p>4. The aim of this trial is to test possible treatments for COVID-19 in older adults. We hope to find treatments that stop people from getting more unwell.</p>


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

Pictorial Participant Information Booklet v1.2.09, 1926<sup>th</sup> May April 2020,

**EudraCT number:2020-001209-22**

Professor Christopher Butler IRAS Project no. 281958 REC Reference no.:20/SC/058

# Who can take part?

	<p>Anybody aged 65 years or over.</p> <p><b>AND</b></p> <p>Anybody aged 50 to 64 years with:</p> <ul style="list-style-type: none"><li>• Weakened immune system (e.g. taking chemotherapy)</li><li>• Heart disease</li><li>• Lung disease</li><li>• Diabetes not treated with insulin</li><li>• Liver disease</li><li>• <u>Stroke</u> or neurological problem</li></ul> <p><b>WITH</b></p>
--	--



	<p>A new or worsening continuous cough and/or fever</p> <p><u>OR</u></p> <p><u>You have had a <b>positive test</b> for SARS-Co-V2 infection which was taken fewer than 15 days ago, AND are unwell with symptoms of COVID-19.</u></p> <p><u><i>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 you must have had them for <b>fewer than 15 days.</b></i></u></p> <p>If you are starting to feel better, this study isn't for you.</p>
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Platform Randomised trial of Interventions against COVID-19 In older people




Pictorial Participant Information Booklet v1.2.09, 1920<sup>th</sup> May April 2020,




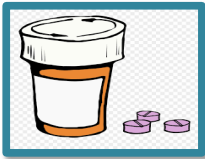
EudraCT number:2020-001209-22

Professor Christopher Butler IRAS Project no. 281958 REC Reference no.:20/SC/058

# What will happen if I take part?

	<p>6. If you develop a fever or a new worsening continuous cough, <u>OR if you have a positive test for SARS-Co-V2 infection with symptoms in the past 14 days,</u> please visit our trial website (see end of this leaflet).</p>
	<p>7. We will ask you to fill in a short form online, to check that you can take part</p>

	<p>8. Your care will not be affected, whether or not you do take part in the trial.</p>
	<p>9. If you are suitable to take part in the trial, you will be asked to fill in a consent form online, and to answer a few questions about yourself and your symptoms.</p>
	<p>10. We will ask you to add details of a 'trial partner'. This is somebody that might be able help you with the study, and who we can also contact for information about</p>


		how you are getting on.
	11.	The information that you give us will be shared with your GP and the study team, so that we can double check that everything is in order for you to take part.
	12.	If you can take part, you will be randomly (like tossing a coin) entered into a group:-
	Or	



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

Pictorial Participant Information Booklet v1-2.09, 1920<sup>th</sup> May April 2020,

EudraCT number:2020-001209-22

Professor Christopher Butler IRAS Project no. 281958 REC Reference no.:20/SC/058

<p>a) Usual care for your symptoms</p>	<p>b) You will receive one of the treatments that we are testing, in addition to usual care for your symptoms.</p> <p>We will provide you with the trial medication and instructions on how to take it.</p>
	<p>13.</p> <p>If swabs are available, we may also ask you to take swabs from your nose and throat, to test for the virus that causes COVID-19.</p> <p>We will provide instructions on how to take the swabs and to post</p>

		them off for testing.
	14.	Whichever group you are in, we will ask you to answer a few questions each daily in an online diary for up to 28 days, so that we know how you are feeling.
	15.	If you are unable to answer questions online, or forget to complete the questions, we might give you a phone call or send you a text message reminder.

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

Pictorial Participant Information Booklet v1.2.09, 1920<sup>th</sup> May April 2020,

EudraCT number:2020-001209-22

Professor Christopher Butler IRAS Project no. 281958 REC Reference no.:20/SC/058

	<p>16. If you are admitted to hospital, we would ask you, or someone close to you, to let us know.</p>
	<p>17. If you agree to join the study, we will contact you at 28 days to see whether you are happy for us to arrange to speak with you in more detail about your experience of taking part in the trial. We will also ask if you are prepared to have a blood test once you are feeling better.</p>



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

Pictorial Participant Information Booklet v1.2.09, 1920<sup>th</sup> May April 2020,

**EudraCT number:2020-001209-22**

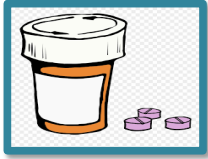
Professor Christopher Butler IRAS Project no. 281958 REC Reference no.:20/SC/058

# What will happen to my information?


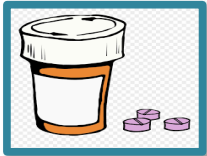
	<p>18. We will use the information you give us to find out which treatments work. We may also look at your general practice and hospital medical records for further information about you and your illness.</p>
	<p>19. Any information that we collect about you will be kept safe. Your name will not go on any reports, presentations or publications.</p>



What are the disadvantages of taking part?

	20.	There is a risk of side effects when taking any medicine. If you are taking a trial medication and have any symptoms, you can record them in the daily online diary.
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## What are the benefits of taking part?

	21.	You will be contributing to important research to find effective treatments for COVID-19.
	22.	We have designed the trial so that whilst the trial is ongoing, if we find that one treatment is more effective, more people might receive this treatment. This means that more people in the trial have a chance of receiving the most effective trial treatment.


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

Pictorial Participant Information Booklet v1.2.09, 1920<sup>th</sup> May April 2020,



EudraCT number:2020-001209-22

Professor Christopher Butler IRAS Project no. 281958 REC Reference no.:20/SC/058


Will I be reimbursed for taking part?

	23.	You will receive a gift voucher for £20 once we receive your completed online symptom diary, as a thank you for taking part.
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What if I do not want to carry on being part of the trial?

	<p>24. You can decide to stop taking part at any time without needing to give a reason. This will not affect the care you receive now or in the future.</p>
	<p>25. If you decide to withdraw from the trial, we will use the information collected up to that point, unless you tell us not to.</p>


# What if there is a problem?

	26.	If you have a concern about any aspect of this trial at any time, you can contact the trial team or the University of Oxford Clinical Trials and Research Governance (CTRG) office (Contact details below).
--	-----	---

# Trial contact details

	<div>Trial team: <a href="mailto:principle@phc.ox.ac.uk">principle@phc.ox.ac.uk</a> 0800 138 0880</div> <div>27. CTRG: <a href="mailto:ctrq@admin.ox.ac.uk">ctrq@admin.ox.ac.uk</a> 01865 616480</div> <div>Trial Website: <a href="http://www.principletrial.org">www.principletrial.org</a></div>
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Thank you!

	28.	Thank you for taking the time to think about taking part in this trial.
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## Platform Randomised trial of Interventions against COVID-19 In older people - PRINCIPLE

REC Number: 20/SC/058

IRAS Number: 281958

EudraCT Number:

2020-001209-22

Chief Investigator: Professor Christopher Butler

Participant ID:

### CONSENT FORM

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

Please read the [Participant Information Sheet](#) if you haven't already done so, and if you are willing to participate please select 'Yes', TYPE your FIRST and LAST names below and then click Submit  
**If you agree, please select 'Yes' to confirm that you have read and understood the following:**

		YES	NO
1	I confirm I have read and understood the information sheet version number ____ - _____ dated ____ / ____ / ____ for the above study. I have had the opportunity to ask questions and had these answered satisfactorily.		
2	I understand my participation is voluntary and that I am free to withdraw at any time, without giving any reason, and without my medical care or legal rights being affected.		
3	I understand that I will be randomised to receive either: standard care plus the trial treatment or standard care and I will not be able to choose which I will receive.		
4	I understand that relevant sections of my GP and Hospital medical notes and data collected during the study may be looked at by members of the research team and individuals from University of Oxford. It may also be reviewed by relevant people from regulatory authorities and from the NHS Trust(s). I give permission for these individuals to have access to my records.		
5	I consent to being contacted by the research team for the purposes of trial follow up and I understand that this will require me to provide my contact details to the research team.		
6	I consent to my GP <u>and/or Care Home</u> being informed of my participation within the study.		
7	I agree to take part in the study		
	<b>ADDITIONAL (optional, not required for study participation)</b>	YES	NO
	<i>I agree to provide the research team with the contact details of my Trial Partner. I confirm my Trial partner is aware of their role and willing to answer questions.</i>		
	<i>I am happy to be contacted by the research team to be invited to a telephone interview at the end of the study.</i>  <i>(Taking part in the interview is optional and will not affect your study participation. If you agree to be contacted, the research team will contact you with details of the interview in approximately 28 days. You can then decide whether you want to take part or not.)</i>		





	<i>I am happy to be contacted by the research team to be invited to a blood test for COVID-19 infection within six months of completing the study</i>		
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**Signature:**

**First Name:** \_\_\_\_\_ **Last Name:** \_\_\_\_\_

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

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

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

Tel: 0800 138 0880 Email [principle@phc.ox.ac.uk](mailto:principle@phc.ox.ac.uk)

**Participant:**

Name: \_\_\_\_\_ Date: \_\_\_\_ / \_\_\_\_ / \_\_\_\_

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



NUFFIELD DEPARTMENT OF  
**PRIMARY CARE**  
HEALTH SCIENCES

Primary Care  
Clinical Trials Unit



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

The medication you have been given is called **Azithromycin**. You need to take your trial medication for **3 days**. You have been given 250mg capsules and should take TWO tablets a day for 3 days, a total of 6 capsules.

Antacids may reduce your body's absorption of **Azithromycin**, so you are advised to take Azithromycin at least 1 hour before or 2 hours after antacids. Azithromycin must be taken at least 1 hour before or 2 hours after food.

The common side effects of this medication 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. You will be able to tell us if you are experiencing any of these symptoms in your daily diary.



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HEALTH SCIENCES

Primary Care  
Clinical Trials Unit



This medication can cause rare allergic reactions. **If you develop any problems please stop taking the medication immediately and seek clinical advice.**

You cannot take **Azithromycin** if you are taking any of the following medications: **bromocriptine, cabergoline, ergotamine, ergometrine, methysergide or any ergot derivatives, or if you have an allergy to soya or peanuts.** If any of these apply, please do not take the trial medication and speak to your GP.

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

Please store the medication at room temperature.

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



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HEALTH SCIENCES

Primary Care  
Clinical Trials Unit



**PRINCIPLE**  
Platform Randomised trial of Interventions  
against COVID-19 in older people

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

The medication you have been given is called **Azithromycin**. You need to take your trial medication for **3 days**. ~~Azithromycin can come in 250mg or 500mg tablets. If you have been given 250mg capsule tablets and, you~~ should take TWO tablets a day for 3 days, a total of 6 ~~capsule tablets. If you have been given 500mg tablets, you should take ONE tablet a day for 3 days, a total of 3 tablets.~~

-Antacids may reduce your body's absorption of **Azithromycin**, so you are advised to take Azithromycin at least 1 hour before or 2 hours after antacids. Azithromycin must be taken at least 1 hour before or 2 hours after food.

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**PRINCIPLE**  
Platform Randomised trial of Interventions  
against COVID-19 in older people

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

Please store the medication at room temperature.

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

Radcliffe Observatory Quarter, Woodstock Road, Oxford. OX2 6GG  
Tel: 0800 138 0880 [principle@phc.ox.ac.uk](mailto:principle@phc.ox.ac.uk) • <http://principletrial.org>

## How you can take part in a study to find treatments for coronavirus/COVID-19

Date:

Hello,

I'm writing about how you could join a research study to help find treatments for coronavirus / COVID-19.

The study is called PRINCIPLE and it is run by the University of Oxford.

The study aims to find treatments for people with symptoms of COVID-19.

If you have symptoms of COVID-19 (such as a new cough or high temperature) and have had them for less than 15 days, you may be able to take part in this study.

You also need to be aged 65 years and over, or aged 50-64 with underlying health conditions.

For more information about the study and signing up, you can read the attached leaflet, or visit [www.principletrial.org](http://www.principletrial.org), or telephone the PRINCIPLE study team on 0800 138 0880.

You may also like to discuss whether to join the study with your family, friends or next of kin. If you do decide to join, they can also help you with taking part in the study.

Yours Sincerely

The PRINCIPLE Study Team, University of Oxford

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

Participant Introductory Letter Version/Date: v1.0 19<sup>th</sup> May 2020, EudraCT number:2020-001209-22

Professor Christopher Butler IRAS Project number: 281958 REC Reference number: 20/SC/058



### **Instructions for participants**

Thank you for taking part in the PRINCIPLE trial.

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

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

### **Contact us**

If you have any questions, please contact us on:

E-mail: [principle@phc.ox.ac.uk](mailto:principle@phc.ox.ac.uk)

Telephone: 0800 138 0880

## Summary

At the start of the trial and possibly day 5, we ask you to collect a self-swab sample, using the kit provided by either your GP or in your trial pack. There are instructions in this booklet and the swab kit on how to do this.

Please take your medication (unless in Usual Care Group) for the *required number* of days. There is more detail in this booklet about how and when to

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

Your participation will last for a total of 28 days.

### **Collecting your self-swab sample**

- Please follow the simple instructions on how to self-sample provided with the swab kit. You only need to collect the samples provided in the kit during the trial.
- Once you have taken your self-swab, please place the samples in the vial provided.
- Seal the vial in the double envelope provided, and send freepost (pre-paid). You do not need to go to a post office, the envelope can be placed in a standard post box.
- Public Health England (PHE) may keep the specimen for up to 5 years, following their own approved processes.
- Your GP will be informed of your COVID-19 swab result once it is available.

### **Taking your trial medication**

(unless in Usual Care Group)

Please see the drug information card for guidance on how you should take your medication.

## **Completing the daily online diary**

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

- You will receive a daily email with an internet link, which will take you to a secure online system to collect your diary entries confidentially.
- You will receive a text asking you to submit your answers on the same day; you may prefer to do this at a regular time for your own convenience and routine.
- You will be asked to record whether you are experiencing a few simple symptoms, and to rate the severity of these symptoms.
- Please ensure that you submit your diary to us at the end of the questions, so we receive all of your answers.
- If we do not receive your completed diary, or you are unable to access the online diary, we will contact you and/or your nominated trial partner on day 7, day 14 and day 28 of the follow up period to collect this information.
- Finally, we will also ask that you, or someone close to you notifies us if you are admitted to hospital.





## Welcome to the PRINCIPLE Trial!

**Thank you so much for agreeing to take  
part.**

### Instructions for participants

Thank you for taking part in the PRINCIPLE trial.

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

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

### Contact us

If you have any questions, please contact us on:

E-mail: [principle@phc.ox.ac.uk](mailto:principle@phc.ox.ac.uk) Telephone: 0800 138 0880

## Summary

Please take your trial medication (unless in Usual Care Group) for the *required number* of days. More detail is provided in the study medication card about how and when to take your medication

During the trial period, we ask you to answer a few short questions each day in an online daily diary about your symptoms. If we do not receive your diary answers, we will call you and/or your trial partner to ask a few short questions.

Your participation will last for a total of 28 days. We will ask for your consent to contact you if we are able to offer a blood test for COVID-19, in the recovery phase of your illness.

## **Taking your trial medication**

(unless in Usual Care Group)

Please see the drug information card for guidance on how you should take your medication.

## **Completing the daily online diary**

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

- You will receive a daily email with an internet link, which will take you to a secure online system to collect your diary entries confidentially.
- You will receive a text asking you to submit your answers on the same day; you may prefer to do this at a regular time for your own convenience and routine.
- You will be asked to record whether you are experiencing a few simple symptoms, and to rate the severity of these symptoms.
- Please ensure that you submit your diary to us at the end of the questions, so we receive all of your answers.
- If we do not receive your completed diary, or you are unable to access the online diary, we will contact you and/or your nominated trial partner on day 7, day 14 and day 28 of the follow up period to collect this information.
- Finally, we will also ask that you, or someone close to you notifies us if you are admitted to hospital.

**Your participation in this trial will  
help us identify which treatments  
are beneficial for COVID.**

**We are very grateful for your  
contribution.**

**URGENT: We are supporting a study to find treatments for COVID-19**

Dear [insert patient name] **OR** TO PATIENTS AT THE [insert practice name] SURGERY

At the [insert practice name] we are taking part in a research study to help find treatments for COVID-19. We are writing with information on how you may be able to join this study.

The study is called PRINCIPLE. It is run by the University of Oxford, and is funded by the UK government as a national priority study. The study aims to find treatments that reduce hospital admission and speed recovery for people with symptoms of COVID-19. People included in the study must be **aged over 65, or aged 50-64 with underlying health conditions**. They will either receive usual care, or usual care plus a study drug. All study drugs are widely used to treat other conditions and have been assessed as being safe for use in this study. As many people as possible who join the study will also be tested for COVID-19. **You may be able to take part in this study if:**

- i) **You have symptoms of COVID-19 (a new or worsening continuous cough and/or a high temperature), and have had them for less than 15 days**

**OR**

- ii) You have had a **positive test** for SARS-Co-V2 infection which was taken fewer than 15 days ago, AND are 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 you must have had them for **fewer than 15 days**.

**For more information about the study and signing up, please visit the study website (XXX) If you have any questions, or do not have internet access, please call the PRINCIPLE study team on 0800 138 0880.**

We are pleased to be supporting this important research, as we urgently need to find effective, early treatments for COVID-19 that can be used in the community.

So, please make contact if you have **symptoms of COVID-19 and are aged over 65, or aged 50-64 with underlying health conditions!**

Yours Sincerely

[insert practice name]



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Clinical Trials Unit



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

**Patient Recruitment Letter Version/Date: v2.0 19th May 2020, EudraCT number:2020-001209-22**

Professor Christopher Butler   IRAS Project number: 281958   REC Reference number: 20/SC/058

**PRINCIPLE TRIAL: TEXT MESSAGE INFORMATION FOR PARTICIPANTS**

This is a message from Dr **XX** at **XX** Medical Practice. A clinical trial exploring treatment for the COVID-19 virus is taking place. If you experience **a new or worsening continuous cough and/or a high temperature** and have had it for **less than 14 days and are not starting to feel better OR** you have had a **positive test** for SARS-Co-V2 infection which was taken fewer than 15 days ago, AND are unwell with symptoms of COVID-19, please click **here** to find out more. Please call the Trial Team if you have any questions or do not have access to online systems: 0800 138 0880

**PRINCIPLE TRIAL: TEXT MESSAGE INFORMATION FOR PARTICIPANTS (SHORT VERSION)**

This is from Dr **xxxxxxx** at **XX** re COVID-19. If you currently feel unwell with a **new/worsening cough or high temp OR** you have had a **positive test** for SARS-Co-V2 infection taken less than 15 days ago, AND are unwell with COVID-19 symptoms , and would like to know about a clinical trial you could participate in click **here** or call the Trial Team 0800 138 0880.

## How you can support someone to take part in a study to find treatments for coronavirus/COVID-19

Date:

Hello,

I'm writing to let you know how you can support someone taking part in a research study to help find treatments for coronavirus / COVID-19.

The study is called PRINCIPLE and it is run by the University of Oxford. It aims to find treatments for people with symptoms of COVID-19, and who are aged 65 years and over, or aged 50-64 with underlying health conditions. PRINCIPLE is supported by the UK government's Chief Medical Officer as a national priority study to find possible treatments for COVID-19.

People can get more information and sign up by telephoning 0800 138 0880 or at [www.principletrial.org](http://www.principletrial.org). There, they can also download a detailed patient information leaflet and a shorter summary that explains the study. All participants should understand the study before agreeing to take part. They will be able to nominate a 'Study Partner' (family, friend or carer e.g. care home staff) to help them with some of the things that will happen in the study. If you have any questions, please call/email the trial team, 0800 138 0880/principle@phc.ox.ac.uk.

Someone you know, who has already joined the PRINCIPLE study, may have asked you to be their Study Partner. Or you may know someone who is interested in joining and is thinking about asking you to be their Study Partner. The person joining the study has provided your contact details. Please see the Patient Information Sheet (<https://www.phctrials.ox.ac.uk/principle-trial/how-to-join>) for details about what will happen to personal data collected in the trial. The things that you could help with by being a Study Partner are described below:

What will happen in the study	How the Study Partner can help
People interested in joining the study will need to answer some questions on the telephone or online to check whether they are suitable, and provide consent.	Help with accessing information about the study and calling the study team on 0800 138 0880, or completing the online form at <a href="http://www.principletrial.org">www.principletrial.org</a> .  Provide your email and/or telephone number for the



	PRINCIPLE team to contact you as the Study Partner
Their GP, or a study nurse or doctor, will also check their medical notes to make sure it is safe for them to be in the study.	
Once signed up, the participant will either receive usual care, or usual care and a study medication which will be delivered from their GP, or directly from the study team. All study medications are already widely used in the NHS and have been approved as safe for use in this study.	Help the participant to take the medication according to instructions in the medication pack.
They will have a swab done to test for COVID-19, if swabs are available.	Help the participant to perform the swabs according to instructions in the swab pack.
If they can access the internet, for the next 28 days we would like them to complete an online diary of their symptoms and medical care they have received. The trial team may also phone them or their study partner after 2, 7, 14 and 28 days to get this information, especially if accessing the internet is difficult.	Help the participant with completing the online diary and/or by receiving telephone calls after 2, 7, 14 and 28 days (these can be timetabled with the study team). The Study Partner can also complete the diary or take the telephone calls themselves if the participant is unable to do this (for example if they feel too unwell).

Many thanks for thinking about supporting this study to find treatments for COVID-19, your help is much appreciated.

Yours Sincerely,

The PRINCIPLE Trial Team



Radcliffe Observatory Quarter, Woodstock Road, Oxford. OX2 6GG  
Tel: 0800 138 0880 [principle@phc.ox.ac.uk](mailto:principle@phc.ox.ac.uk) • <http://principletrial.org>

DATE

To whom it may concern

I can confirm that [insert patient name] has consented to take part in the PRINCIPLE trial, a research study to find effective treatments for COVID-19.

As part of this study, [insert patient name] has been provided with the study medication and instructions on dosage and how to take the medication. All study medications are already widely used in the NHS for other conditions and have been approved as safe for use in this study. A clinician on the study team at the University of Oxford and/or the patients GP has reviewed [insert patient name]'s GP notes and confirmed that this medication is safe for them to take.

PRINCIPLE is a UK national priority study that is funded by the UK Department of Health and Social Care and run by the University of Oxford. For more information please visit [www.principletrial.org](http://www.principletrial.org) or call 0800 138 0880.

Yours Sincerely

Professor Christopher Butler,  
*Chief Investigator, PRINCIPLE Trial*  
*Director of the Primary Care Clinical Trials Unit*  
*General Practitioner*

**PRINCIPLE TRIAL: Patients registering on the NHS COVID-19 testing website will be sent a confirmation email with details of their NHS testing appointment. The following text will be included to signpost to the trial:**

### **Can you help the NHS?**

If you are over 50 and recently developed coronavirus symptoms, you may be able to take part in a clinical trial.

To find out more and check if you qualify, go to [URL].



## **PRINCIPLE Trial – Social Media Post**

[Insert practice name] is taking part in the national PRINCIPLE clinical trial, which aims to find low-risk treatments for older people with COVID-19 that can be taken at home.

To be eligible to join the trial you will need to have experienced symptoms that are likely to be caused by COVID-19 for fewer than 15 days.

The trial is open to people aged 65 or over, or aged 50–64 with an underlying health condition.

If you are registered at [Insert practice name] and would like more information, please contact us on [Insert practice telephone number]. You can also join the trial online, even if you are not currently registered with our practice. For full details, visit <http://www.principletrial.org>

## Website Trial Advert

### Join a COVID-19 clinical trial

The PRINCIPLE trial aims to find treatments that reduce hospital admission and improve symptoms for people with COVID-19. You could be eligible to join if

- You have had these symptoms for fewer than 15 days:
  - a continuous new or worsening cough
  - and/or a high temperature
  - OR have a positive test for SARS-Co-V2 infection with COVID-19 symptoms in the past 14 days
- You are aged 50 to 64 with a pre-existing illness
- You are aged 65 and above
  - **Find out more**

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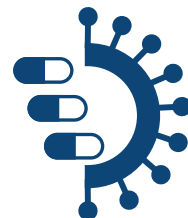
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# Help to find treatments for COVID-19



**Do you have a resident who is likely to have COVID-19, or is experiencing these symptoms?**



Continuous new or worsening cough



High temperature

And have had them for fewer than 15 days?

OR have they had a positive test for SARS-CoV-2 infection taken fewer than 15 days ago, AND are unwell with symptoms of COVID-19?

**Is your resident aged 65 and above?**

**Or aged 50 to 64 with any of these illnesses?**



High blood pressure and/ or heart disease



Diabetes *not* treated with insulin



Asthma or lung disease



Stroke or neurological problems



Weakened immune system due to serious illness or medication (e.g. chemotherapy).



Liver disease

**Then your resident could be eligible to join the PRINCIPLE trial to help find treatments for COVID-19.**

The PRINCIPLE trial aims to find treatments that reduce hospital admission and improve symptoms for people with COVID-19.

**To find out more and see if your resident is eligible, please visit:**

**<https://secure.phc.ox.ac.uk/carehome>**

Tel: 0800 138 0880

email: [principle@phc.ox.ac.uk](mailto:principle@phc.ox.ac.uk)



NUFFIELD DEPARTMENT OF  
**PRIMARY CARE**  
HEALTH SCIENCES

Primary Care  
Clinical Trials Unit

**NIHR** | National Institute  
for Health Research

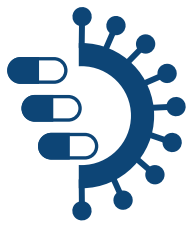


UK Research  
and Innovation



**PRINCIPLE**  
Platform Randomised trial of Interventions  
against COVID-19 in older people

# Help the fight against COVID-19



Has your doctor or nurse said you are likely to have a COVID-19 infection, or do you have any of these symptoms?



Continuous new or worsening cough



High temperature

And have had them for fewer than 15 days?

OR had you had a positive test for SARS-CoV-2 infection taken fewer than 15 days ago AND are unwell with symptoms of COVID-19?

Are you aged 65 and above?

Or aged 50 to 64 with any of these illnesses?



High blood pressure and/ or heart disease



Diabetes *not* treated with insulin



Asthma or lung disease



Stroke or neurological problems



Weakened immune system due to serious illness or medication (e.g. chemotherapy).



Liver disease

Then you could be eligible to join the PRINCIPLE trial and help the fight against COVID-19.

The PRINCIPLE trial aims to find treatments that reduce hospital admission and improve symptoms for people with COVID-19.

To find out more, please visit:

**[www.principletrial.org](http://www.principletrial.org)**

Tel: 0800 138 0880

email: [principle@phc.ox.ac.uk](mailto:principle@phc.ox.ac.uk)



NUFFIELD DEPARTMENT OF  
**PRIMARY CARE**  
HEALTH SCIENCES

Primary Care  
Clinical Trials Unit

**NIHR**

National Institute  
for Health Research



UK Research  
and Innovation



**PRINCIPLE**  
Platform Randomised trial of Interventions  
against COVID-19 in older people

## IRAS Project ID 281958. HRA Approval for the Amendment

berkshire.rec@hra.nhs.uk <noreply@harp.org.uk>

Sun 5/24/2020 21:37

To: Christopher Butler <christopher.butler@phc.ox.ac.uk>; CTRG Sponsorship Correspondence <ctrg@admin.ox.ac.uk>

Cc: Hannah Swayze <hannah.swayze@phc.ox.ac.uk>

Dear Christopher Butler,

<b>IRAS Project ID:</b>	281958
<b>Short Study Title:</b>	PRINCIPLE [COVID-19] [UPH]
<b>Amendment No./Sponsor Ref:</b>	SA5
<b>Amendment Date:</b>	20 May 2020
<b>Amendment Type:</b>	Substantial CTIMP - for review

I am pleased to confirm **HRA and HCRW Approval** for the above referenced amendment.

You should implement this amendment at NHS organisations in England and Wales, in line with the conditions outlined in your categorisation email.

### User Feedback

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

Please contact [amendments@hra.nhs.uk]amendments@hra.nhs.uk for any queries relating to the assessment of this amendment.

Kind regards

**Kevin Ahmed**

**Approvals Manager**

**Health Research Authority**

Ground Floor | Skipton House | 80 London Road | London | SE1 6LH

**E.** [amendments@hra.nhs.uk](mailto:amendments@hra.nhs.uk)

**W.** [www.hra.nhs.uk](http://www.hra.nhs.uk)

Sign up to receive our newsletter [HRA Latest](#).





## Hannah Swayze

**From:** berkshire.rec@hra.nhs.uk <noreply@harp.org.uk>  
**Sent:** 20 May 2020 12:16  
**To:** Christopher Butler; CTRG Sponsorship Correspondence  
**Cc:** nhsg.nrspcc@nhs.net; Hannah Swayze  
**Subject:** IRAS 281958. Amendment confirmation of REC Validation, categorisation and implementation information  
**Attachments:** IRAS 281958 SL27  
\_Acknowledgement\_of\_a\_valid\_notice\_of\_a\_substantial\_amendment-1.pdf  
**Follow Up Flag:** Flag for follow up  
**Flag Status:** Flagged

### Amendment Confirmation of REC Validation, Categorisation and Implementation Information

Dear Professor Butler,

<b>IRAS Project ID:</b>	281958
<b>Short Study Title:</b>	PRINCIPLE
<b>Date complete amendment submission received:</b>	20 May 2020
<b>Amendment No./ Sponsor Ref:</b>	SA5
<b>Amendment Date:</b>	20 May 2020
<b>Amendment Type:</b>	Substantial
<b>Outcome of HRA and HCRW Assessment</b>	<b>HRA and HCRW Approval for the amendment is pending.</b> HRA and HCRW Approval for the amendment will be separately confirmed by email.
<b>Implementation date in NHS organisations in England and/or Wales</b>	2 days from date amendment information together with this email, is supplied to participating organisations ( <b>provided HRA and HCRW Approval for the amendment is in place and conditions are met</b> )
<b>Implementation date in NHS/HSC organisations in Northern Ireland and/or Scotland</b>	<b>24th June 2020 (providing conditions are met)</b>
For NHS/HSC R&D Office information	
<b>Amendment Category</b>	A

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

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

#### What should I do next?

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

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

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

### When can I implement this amendment?

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

### Information relating to the addition of new sites.

This amendment also adds new participating NHS/HSC organisations to the study. The 35 day implementation date does not apply to the new sites. Please set up new sites as detailed below (as processes change from time to time, we recommend that you refer to the most up to date guidance about site set up, found within [IRAS](#)).

If your study is supported by a research network, please contact the network as early as possible to help support set up of the new site(s).

<b>For new sites in Northern Ireland and/or Scotland:</b>	Please start to set up your new sites. Sites may not open until a REC Favourable Opinion and NHS/HSC management permission is in place.
<b>For new sites in England and/or Wales:</b>	<p>For studies which already have HRA and HCRW Approval: <b>HRA and HCRW Approval for the amendment is pending</b>. You can start the process of setting up the new site but cannot open the study at the site until HRA and HCRW Approval for the amendment is in place and the site has confirmed capacity and capability (where applicable).</p> <p>For studies which do not yet have HRA and HCRW Approval: <b>HRA and HCRW Approval for the <u>initial application</u> is pending</b> and you will receive this in due course. You can start the process of setting up the new site but cannot open the study at the site until HRA and HCRW Approval is in place and the site has confirmed capacity and capability (where applicable).</p>

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

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

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

- England – [amendments@hra.nhs.uk](mailto:amendments@hra.nhs.uk)
- Northern Ireland – [research.gateway@hscni.net](mailto:research.gateway@hscni.net)
- Scotland – [nhsq.NRSPCC@nhs.net](mailto:nhsq.NRSPCC@nhs.net)
- Wales – [HCRW.amendments@wales.nhs.uk](mailto:HCRW.amendments@wales.nhs.uk)

Additional information on the management of amendments can be found in the [IRAS guidance](#).

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

Kind regards

**Alison Doherty**  
**Approvals Administrator**  
**Health Research Authority**

Ground Floor | Skipton House | 80 London Road | London | SE1 6LH

**E.** [amendments@hra.nhs.uk](mailto:amendments@hra.nhs.uk)

**W.** [www.hra.nhs.uk](http://www.hra.nhs.uk)

Sign up to receive our newsletter [HRA Latest.](#)



Medicines & Healthcare products  
Regulatory Agency



**MHRA**

10 South Colonnade  
Canary Wharf  
London  
E14 4PU  
United Kingdom

[gov.uk/mhra](https://gov.uk/mhra)

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

21/05/2020

Dear Prof C Butler,

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

Our Reference:	CTA 21584/0426/001-0006
Eudract Number:	2020-001209-22
Product:	Plaquenil-Hydroxychloroquine, Azithromycin
Protocol number:	PRINCIPLE
Substantial Amendment Code Number:	Code Number: SA5 Version: Date: 2020/05/20

**NOTICE OF ACCEPTANCE OF AMENDMENT**

I am writing to inform you that the Licensing Authority accepts the proposed amendment to your clinical trial authorisation (CTA), received on 20/05/2020.

This amendment may therefore be made.

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

Yours sincerely,

**Clinical Trials Unit  
MHRA**

**South Central - Berkshire Research Ethics Committee**

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

**Please note: This is the  
favourable opinion of the REC  
only and does not allow the  
amendment to be implemented  
at NHS sites in England until  
the outcome of the HRA  
assessment has been  
confirmed.**

22 May 2020

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

Dear Professor Butler

<b>Study title:</b>	<b>Platform Randomised trial of Interventions against COVID-19 In older peoPLE</b>
<b>REC reference:</b>	<b>20/SC/0158</b>
<b>Protocol number:</b>	<b>PRINCIPLE</b>
<b>EudraCT number:</b>	<b>2020-001209-22</b>
<b>Amendment number:</b>	<b>SA5</b>
<b>Amendment date:</b>	<b>20 May 2020</b>
<b>IRAS project ID:</b>	<b>281958</b>

The above amendment was reviewed at the meeting of the Sub-Committee held in correspondence.

**Ethical opinion**

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

**Approved documents**

The documents reviewed and approved at the meeting were:

<i>Document</i>	<i>Version</i>	<i>Date</i>
-----------------	----------------	-------------

Annex 1: Clinical Trial Application Form [MhraProductsForm_ReadyForSubmission (1)]		20 May 2020
Annex 2: Notification of Amendment [AmendmentFormMHRAEudract_snapshot (1)]	SA5	20 May 2020
Copies of advertisement materials for research participants [PRINCIPLE Social Media v1.0 19.05.20]	1.0	19 May 2020
Copies of advertisement materials for research participants [PRINCIPLE Website Advert v1.1 12.05.20_tc + clean]	1.1	12 May 2020
Copies of advertisement materials for research participants [PRINCIPLE Patient Recruitment Poster_v1.2 19.05.20 tc + clean]	1.2	19 May 2020
Copies of advertisement materials for research participants [PRINCIPLE Care Home Staff Poster, v1.0 19.05.20]	1.0	19 May 2020
Cover Letter [REC SA5 cover letter]		20 May 2020
GP/consultant information sheets or letters [Medication Letter v1.0 19.05.20]	1.0	19 May 2020
Letter from sponsor [SA5 Sponsor Approval]		20 May 2020
Letters of invitation to participant [PRINCIPLE Patient Recruitment Letter v2.0 19.05.2020_clean + tc]	2.0	19 May 2020
Letters of invitation to participant [Study Partner Letter v1.0 19.05.20]	1.0	19 May 2020
Letters of invitation to participant [Participant Introductory Letter v1.0 19.05.20]	1.0	19 May 2020
Non-validated questionnaire [PRINCIPLE_Baseline_v2.1_19May2020]	2.1	19 May 2020
Non-validated questionnaire [PRINCIPLE_Eligibility Information CRF_v3.1_19May2020]	3.1	19 May 2020
Non-validated questionnaire [PRINCIPLE_Screening_v4.1_19May2020]	4.1	19 May 2020
Organisation Information Document [OID_Trusts_Eligibility_PRINCIPLE]		
Other [PRINCIPLE NHS Testing Site Wording v1.0 19.05.2020]	1.0	19 May 2020
Other [PRINCIPLE TRIAL - Text Message Info v3.0 19.05.2020_tc + clean]	3.0	19 May 2020
Other [PRINCIPLE_IMP_Label form_azithromycin v1.3 17.05.20 250mg_tc + clean]	1.3	17 May 2020
Participant consent form [PRINCIPLE Consent Form V1.3 18.05.2020_tc + clean]	1.3	18 May 2020
Participant information sheet (PIS) [PRINCIPLE PIS_v3.0 19.05.2020_tc + clean]	3.0	19 May 2020
Participant information sheet (PIS) [PRINCIPLE_Pictorial PIS v2.0_19.05.2020_tc + clean]	2.0	19 May 2020
Participant information sheet (PIS) [PRINCIPLE Information for participants (SWAB)_v1.0_18.05.2020]	1.0	18 May 2020
Participant information sheet (PIS) [PRINCIPLE Information for participants_v1.3 18.05.2020 tc + clean]	1.3	18 May 2020
Research protocol or project proposal [Principle Protocol v3.0 19.05.2020_tc + clean]	3.0	19 May 2020
Sample diary card/patient card [Azithromycin Participant Card_v1.2_17.05.2020_tc + clean]	1.2	17 May 2020
Schedule of Events or SoECAT [SoECAT PRINCIPLE_Trust Eligibility_18MAY20]		
Summary of product characteristics (SmPC) [Azithromycin SmPC (Teva)]		12 July 2019

### **Membership of the Committee**

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

### **Working with NHS Care Organisations**

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

### **Statement of compliance**

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

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

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

### **HRA Learning**

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

<b>20/SC/0158:</b>	<b>Please quote this number on all correspondence</b>
--------------------	---

Yours sincerely

Thomas Fairman  
HRA Approvals Manager

On behalf of

**Mr David Carpenter**  
**Chair**

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

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

*Copy to:*                          *CTRG*





# Health Research Authority

## South Central - Berkshire Research Ethics Committee

### Attendance at Sub-Committee of the REC meeting in correspondence

#### Committee Members:

<i>Name</i>	<i>Profession</i>	<i>Present</i>	<i>Notes</i>
Mr David Carpenter	Retired Social Scientist	Yes	
Dr Mike Proven		Yes	

#### Also in attendance:

<i>Name</i>	<i>Position (or reason for attending)</i>
Alison Doherty	Approvals Administrator

**South Central - Berkshire Research Ethics Committee**

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

20 May 2020

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

Dear Professor Butler

**Study title:** Platform Randomised trial of Interventions against COVID-19 In older peoPLE  
**REC reference:** 20/SC/0158  
**Protocol number:** PRINCIPLE  
**EudraCT number:** 2020-001209-22  
**Amendment number:** SA5  
**Amendment date:** 20 May 2020  
**IRAS project ID:** 281958

Thank you for submitting the above amendment, which was received on 20 May 2020. I can confirm that this is a valid notice of a substantial amendment and will be reviewed by the Sub-Committee of the REC at its next meeting.

**Documents received**

The documents to be reviewed are as follows:

<i>Document</i>	<i>Version</i>	<i>Date</i>
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Schedule of Events or SoECAT [SoECAT PRINCIPLE_Trust Eligibility_18MAY20]		
Summary of product characteristics (SmPC) [Azithromycin SmPC (Tevo)]		12 July 2019

## Notification of the Committee's decision

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

## R&D approval

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


## HRA Learning

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

20/SC/0158:

Please quote this number on all correspondence

Yours sincerely



**Alison Doherty**  
**Approvals Administrator**

Email: [berkshire.rec@hra.nhs.uk](mailto:berkshire.rec@hra.nhs.uk)

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

## RE: PRINCIPLE Substantial Amendment 5 EudraCT: 2020-001209-22

Elaine Chick <elaine.chick@admin.ox.ac.uk>

Wed 5/20/2020 08:54

To: Hannah Swayze <hannah.swayze@phc.ox.ac.uk>

Cc: rpm@oxfordjro.org <rpm@oxfordjro.org>

Dear Hannah

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

- Email documents to the REC that originally reviewed the study. The REC will review the amendments and categorise it. If necessary, they will transfer the amendments internally to HRA for them to review as well.
  - If the amendment does not require HRA review, the REC will state this in their categorisation letter.
  - If it is sent on to the HRA, the HRA will advise you when you can send final REC and HRA approved documents to your local sites.
- Copy in CTRG generic email address ([ctrq@admin.ox.ac.uk](mailto:ctrq@admin.ox.ac.uk)) so the sponsor has final documents and is included in subsequent correspondence

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

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

Best wishes

Elaine



cid:image001.jpg@01D6045A.2891F470

**Elaine Chick**

Deputy Head CTRG, Research Services

University of Oxford

Boundary Brook House, Headington, OX3 7LQ Tel: 01865 616481

[Elaine.chick@admin.ox.ac.uk](mailto:Elaine.chick@admin.ox.ac.uk)

<https://researchsupport.admin.ox.ac.uk/ctrq>

PID14903-A005-SP001-AC001

Participant identifier

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Participant initials

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**Baseline CRF**

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

Symptoms		
Please rate the following symptoms today:		
6.	Fever	No problem / Mild problem / Moderate problem / Major problem
7.	Cough	No problem / Mild problem / Moderate problem / Major problem
8.	Shortness of breath	No problem / Mild problem / Moderate problem / Major problem
9.	Muscle ache	No problem / Mild problem / Moderate problem / Major problem
10.	Nausea / Vomiting	No problem / Mild problem / Moderate problem / Major problem
11.	Have you taken antibiotics since your illness started?	Yes <input type="checkbox"/> No <input type="checkbox"/>

Participant identifier

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Participant initials

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### Baseline CRF

Healthcare Services		
12.	Have you had contact with the following healthcare services since your illness started? Please answer Yes or No.	
12a)	GP	Yes <input type="checkbox"/> No <input type="checkbox"/>
12b)	Other primary Care services (e.g. walk-in services/pharmacist)	Yes <input type="checkbox"/> No <input type="checkbox"/>
12c)	NHS 111	Yes <input type="checkbox"/> No <input type="checkbox"/>
12d)	A&E	Yes <input type="checkbox"/> No <input type="checkbox"/>
12e)	Other	Yes <input type="checkbox"/> No <input type="checkbox"/>
12e. i)	If 'Other' please specify: _____	

Wellbeing							
13.	Please indicate for each of the 5 statements which is closest to how you have been feeling over the past 2 weeks.						
13a)	Over the past 2 weeks...	All of the time	Most of the time	More than half the time	Less than half the time	Some of the time	At no time
13b)	... I have felt cheerful and in good spirits	5	4	3	2	1	0
13c)	... I have felt calm and relaxed	5	4	3	2	1	0
13d)	... I have felt active and vigorous	5	4	3	2	1	0
13e)	... I woke up feeling fresh and rested	5	4	3	2	1	0
13f)	... my daily life has been filled with things that interest me	5	4	3	2	1	0

Completed by: Print name .....Sign .....Date \_\_ / \_\_ / \_\_\_\_

Participant identifier

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Participant initials

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### Eligibility Information CRF

1	Participant's NHS number: _____	
2	Participant is 65 years or older?	Yes <input type="checkbox"/> No <input type="checkbox"/>
	Participant is aged ≥50 with at least one of the comorbidities listed below? <ul style="list-style-type: none"> <li>• Weakened immune system due to a serious illness or infection</li> <li>• Heart disease or hypertension</li> <li>• Asthma or lung disease</li> <li>• Diabetes not treated with insulin</li> <li>• Mild hepatic impairment</li> <li>• Stroke or neurological problem</li> </ul>	Yes <input type="checkbox"/> No <input type="checkbox"/>
3	Participant has had a positive test for COVID-19 infection?	Yes <input type="checkbox"/> No <input type="checkbox"/>
3a)	What date was this test taken?	__ / __ / __
3b)	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 and vomiting.	Yes <input type="checkbox"/> No <input type="checkbox"/>
4	Pregnant or planning on becoming pregnant within the next few weeks?	Yes <input type="checkbox"/> No <input type="checkbox"/>
5	Breastfeeding or planning on starting during the course of the trial?	Yes <input type="checkbox"/> No <input type="checkbox"/>
6	Has porphyria?	Yes <input type="checkbox"/> No <input type="checkbox"/>
7	Has type 1 diabetes or insulin dependent type 2 diabetes mellitus?	Yes <input type="checkbox"/> No <input type="checkbox"/>
8	Has a G6PD deficiency?	Yes <input type="checkbox"/> No <input type="checkbox"/>
9	Has myasthenia gravis?	Yes <input type="checkbox"/> No <input type="checkbox"/>
10	Has severe psoriasis?	Yes <input type="checkbox"/> No <input type="checkbox"/>
11	Has a severe neurological disorder (especially those with a history of epilepsy)?	Yes <input type="checkbox"/> No <input type="checkbox"/>
12	Has a retinal disease (e.g. macular degeneration)?	Yes <input type="checkbox"/> No <input type="checkbox"/>
13	Has a known severe hepatic impairment?	Yes <input type="checkbox"/> No <input type="checkbox"/>
14	Has a known severe renal impairment?	Yes <input type="checkbox"/> No <input type="checkbox"/>
15	Is the patient currently admitted to hospital?	Yes <input type="checkbox"/> No <input type="checkbox"/>
16	Known congenital or documented QT prolongation	Yes <input type="checkbox"/> No <input type="checkbox"/>



Participant identifier

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Participant initials

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### Eligibility Information CRF

17	Allergy to soya or peanuts?	Yes <input type="checkbox"/> No <input type="checkbox"/>
18	Has had a previous adverse reaction to, or are you currently taking, hydroxychloroquine or chloroquine?	Yes <input type="checkbox"/> No <input type="checkbox"/>
19	Is currently taking any of the following drugs:  amiodarone azithromycin ciclosporin digoxin penicillamine any other other macrolides or ketolides	Yes <input type="checkbox"/> No <input type="checkbox"/>
20	Has had a previous adverse reaction to, or is currently taking azithromycin or any other other macrolides or ketolides?	Yes <input type="checkbox"/> No <input type="checkbox"/>
21	Is currently taking any of the following drugs:  amiodarone bromocriptine cabergoline ciclosporin digoxin ergotamine ergometrine hydroxychloroquine or chloroquine methysergide sotalol any ergot derivatives	Yes <input type="checkbox"/> No <input type="checkbox"/>
22	Has previously taken part in the PRINCIPLE trial?	Yes <input type="checkbox"/> No <input type="checkbox"/>
23	Is there any other reason you would exclude this participant? If yes, please provide the reason in the comments box below.	Yes <input type="checkbox"/> No <input type="checkbox"/>

Comments:

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Completed by: Print name ..... Sign ..... Date \_\_ / \_\_ / \_\_

Participant identifier

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Participant initials

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### Screening CRF

1.	Are you willing to give informed consent for participation in the study?	Yes <input type="checkbox"/> No <input type="checkbox"/>
2.	Do you have symptoms of possible COVID-19 in the community which have been present for less than 15 days?  <b>Defined:</b> A new continuous cough - this means coughing a lot for more than an hour, or 3 or more coughing episodes in 24 hours (if you usually have a cough, it may be worse than usual) <b>and/or</b> A high temperature - this means you feel hot to touch on your chest or back (you do not need to take your temperature)	Yes <input type="checkbox"/> No <input type="checkbox"/>
2a)	What date did you start to feel unwell with this illness (DD/MMM/YYYY)?	__ / __ / ____
2b)	Are you feeling almost recovered from this illness (i.e. generally much improved and your symptoms are now mild or almost absent)?	Yes <input type="checkbox"/> No <input type="checkbox"/>
3	Have you had a positive test for COVID-19 infection?	Yes <input type="checkbox"/> No <input type="checkbox"/>
3a)	What date was this COVID-19 test taken?	__ / __ / ____
3b)	Are you unwell with symptoms of COVID-19? These symptoms may include, but are not limited to, shortness of breath, general feeling of being unwell,	Yes <input type="checkbox"/> No <input type="checkbox"/>
3c)	What date did you start to feel unwell with this illness?	__ / __ / ____
3d)	Are you feeling almost recovered from this illness (i.e. generally much	Yes <input type="checkbox"/> No <input type="checkbox"/>
4.	Are you aged 65 years old or over?	Yes <input type="checkbox"/> No <input type="checkbox"/>
4a)	Are you aged 50 to 64 years old with at least one of the comorbidities/ conditions listed below?  <ul style="list-style-type: none"> <li>• Weakened immune system due to a serious illness or medication (e.g. chemotherapy)</li> <li>• Heart disease or high blood pressure</li> <li>• Asthma or lung disease</li> <li>• Diabetes not treated with insulin</li> <li>• Liver disease</li> </ul>	Yes <input type="checkbox"/> No <input type="checkbox"/>

Participant identifier

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Participant initials

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### Screening CRF

5	Are you pregnant or planning on becoming pregnant within the next few weeks?	Yes <input type="checkbox"/>	No <input type="checkbox"/>
6	Are you breastfeeding or planning on starting during the course of the trial?	Yes <input type="checkbox"/>	No <input type="checkbox"/>
7	Do you have myasthenia gravis?	Yes <input type="checkbox"/>	No <input type="checkbox"/>
8	Are you currently admitted in hospital?	Yes <input type="checkbox"/>	No <input type="checkbox"/>
9	Do you have a specific heart rhythm abnormality called "prolonged QT syndrome" or condition that prolongs the heart QT interval?	Yes <input type="checkbox"/>	No <input type="checkbox"/>
10	Have you previously participated in the PRINCIPLE trial?	Yes <input type="checkbox"/>	No <input type="checkbox"/>
11	Do you have porphyria?	Yes <input type="checkbox"/>	No <input type="checkbox"/>
12	Do you take insulin for diabetes?	Yes <input type="checkbox"/>	No <input type="checkbox"/>
13	Do you have a G6PD deficiency?	Yes <input type="checkbox"/>	No <input type="checkbox"/>
14	Do you have severe psoriasis?	Yes <input type="checkbox"/>	No <input type="checkbox"/>
15	Do you have a history of epilepsy?	Yes <input type="checkbox"/>	No <input type="checkbox"/>
16	Do you have a disease which affects the retina (e.g. macular degeneration)?	Yes <input type="checkbox"/>	No <input type="checkbox"/>
17	Have you had a previous adverse reaction to, or are you currently taking, hydroxychloroquine or chloroquine?	Yes <input type="checkbox"/>	No <input type="checkbox"/>
18	Are you currently taking any of the following drugs:  amiodarone azithromycin ciclosporin digoxin penicillamine	Yes <input type="checkbox"/>	No <input type="checkbox"/>
19	Are you currently taking antibiotics for a recently diagnosed illness?	Yes <input type="checkbox"/>	No <input type="checkbox"/>
20	Do you have an allergy to soya or peanuts?	Yes <input type="checkbox"/>	No <input type="checkbox"/>
21	Have you had a previous adverse reaction to, or are you currently taking	Yes <input type="checkbox"/>	No <input type="checkbox"/>

Participant identifier

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Participant initials

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### Screening CRF

22	<p>Are you currently taking any of the following drugs:</p> <p>amiodarone</p> <p>bromocriptine</p> <p>cabergoline</p> <p>ciclosporin</p> <p>digoxin</p> <p>ergotamine</p> <p>ergometrine</p> <p>hydroxychloroquine or chloroquine</p> <p>methysergide</p> <p>sotalol</p>	<p>Yes <input type="checkbox"/> No <input type="checkbox"/></p>
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Completed by: Print name .....Sign .....Date \_\_ / \_\_ / \_\_

## **SUMMARY OF PRODUCT CHARACTERISTICS**

### **1 NAME OF THE MEDICINAL PRODUCT**

Azithromycin 250mg Capsules

### **2 QUALITATIVE AND QUANTITATIVE COMPOSITION**

Each capsule contains 250mg azithromycin (as dihydrate).

#### Excipients with known effect

Azithromycin capsules contains sulfur dioxide (E220) which may rarely cause severe hypersensitivity reactions and bronchospasm

For the full list of excipients, see section 6.1.

### **3 PHARMACEUTICAL FORM**

Capsule, hard.

### **4 CLINICAL PARTICULARS**

#### **4.1 Therapeutic indications**

Azithromycin is indicated for the treatment of the following infections when known or likely to be due to one or more susceptible microorganisms (see Section 5.1):

- bronchitis
- community-acquired pneumonia
- sinusitis
- pharyngitis/tonsillitis (see 4.4 regarding streptococcal infections)
- otitis media
- skin and soft tissue infections
- uncomplicated genital infections due to *Chlamydia trachomatis*

Consideration should be given to official guidance regarding the appropriate use of antibacterial agents.

## 4.2 Posology and method of administration

### Posology

*Children over 45 kg body weight and adults, including elderly patients*

The total dosage of azithromycin is 1500 mg which should be given over three days (500 mg once daily).

In uncomplicated genital infections due to *Chlamydia trachomatis*, the dosage is 1000 mg as a single oral dose.

Azithromycin 250 mg capsules are suitable only for children of at least 45 kg body weight for whom the adult dose may be used.

### *Renal insufficiency:*

In patients whose renal function is slightly impaired (creatinine clearance >40 ml/min), dose adjustment is not necessary. No studies have been conducted in patients with a creatinine clearance of <40 ml/min and consequently caution must be exercised in the use of azithromycin for these patients.

### *Hepatic insufficiency:*

Since azithromycin is metabolised in the liver and excreted in the bile, the drug should not be given to patients suffering from severe liver diseases. No studies have been conducted regarding treatment of such patients with azithromycin.

### Method of Administration:

Azithromycin 250 mg capsules should be administered as a single daily dose and should be taken at least 1 hour before or 2 hours after food.

## 4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1 or erythromycin, any macrolide or ketolide antibiotic.

## 4.4 Special warnings and precautions for use

### Hypersensitivity

As with erythromycin and other macrolides, serious allergic reactions, including angioneurotic oedema and anaphylaxis (rarely fatal), dermatologic reactions including acute generalised exanthematous pustulosis (AGEP), Stevens Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) (rarely fatal) and Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) have been reported. Some of these reactions with azithromycin have resulted in recurrent symptoms and required a longer period of observation and treatment.

If an allergic reaction occurs, the drug should be discontinued and appropriate therapy should be instituted. Physicians should be aware that reappearance of the allergic symptoms may occur when symptomatic therapy is discontinued.

**Superinfections:** As with any antibacterial agent, there is a possibility that superinfections could occur (e.g. fungal infections).

Since the liver is the principal route of elimination for azithromycin, the use of azithromycin should be undertaken with caution in patients with significant hepatic disease. Cases of fulminant hepatitis potentially leading to life-threatening liver failure have been reported with azithromycin (see Section 4.8). Some patients may have had pre-existing hepatic disease or may have been taking other hepatotoxic medicinal products.

In case of signs and symptoms of liver dysfunction, such as rapid developing asthenia associated with jaundice, dark urine, bleeding tendency or hepatic encephalopathy, liver function tests/ investigations should be performed immediately. Azithromycin administration should be stopped if liver dysfunction has emerged.

In patients receiving ergot derivatives, ergotism has been precipitated by coadministration of some macrolide antibiotics. There are no data concerning the possibility of an interaction between ergot and azithromycin. However, because of the theoretical possibility of ergotism, azithromycin and ergot derivatives should not be coadministered.

As with any antibiotic preparation, observation for signs of superinfection with non-susceptible organisms, including fungi is recommended.

*Clostridium difficile* associated diarrhoea (CDAD) has been reported with use of nearly all antibacterial agents, including azithromycin, and may range in severity from mild diarrhoea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *C. difficile*.

*C. difficile* produces toxins A and B which contribute to the development of CDAD. Hypertoxin producing strains of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhoea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.

In patients with severe renal impairment (GFR <10 ml/min) a 33% increase in systemic exposure to azithromycin was observed (see Section 5.2).

Prolonged cardiac repolarization and QT interval, imparting a risk of developing cardiac arrhythmia and torsades de pointes, have been seen in treatment with other macrolides. A similar effect with azithromycin cannot be completely ruled out in patients at increased risk for prolonged cardiac repolarization (see Section 4.8) therefore caution is required when treating patients:

- With congenital or documented QT prolongation
- Currently receiving treatment with other active substances known to prolong QT interval such as antiarrhythmics of classes IA and III, cisapride and terfenadine
- With electrolyte disturbance, particularly in cases of hypokalaemia and hypomagnesaemia
- With clinically relevant bradycardia, cardiac arrhythmia or severe cardiac insufficiency

Exacerbations of the symptoms of myasthenia gravis and new onset of myasthenia syndrome have been reported in patients receiving azithromycin therapy (see Section 4.8).

The safety and efficacy of intravenous azithromycin for the treatment of infections in children has not been established.

Safety and efficacy for the prevention or treatment of MAC in children have not been established.

## **4.5 Interaction with other medicinal products and other forms of interaction**

*Antacids:* In a pharmacokinetic study investigating the effects of simultaneously administered antacids on the pharmacokinetics of azithromycin, no overall change has been observed in the bioavailability, although the peak concentrations of azithromycin measured in the plasma fell by 25 %. In patients receiving both azithromycin and antacids, the drugs should not be taken simultaneously. Azithromycin should be taken at least 1 hour before or 2 hours after the antacid.

*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.

*Didanosine (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.

*Digoxin and colchicine:* 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-glycoprotein substrates such as digoxin are administered concomitantly, the possibility of elevated serum digoxin concentrations should be considered. Clinical monitoring, and possibly serum digoxin levels, during treatment with azithromycin and after its discontinuation are necessary.



*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.

*Ergot:* Due to the theoretical possibility of ergotism, the concurrent use of azithromycin with ergot derivatives is not recommended (see Section 4.4).

Pharmacokinetic studies have been conducted between azithromycin and the following drugs known to undergo significant cytochrome P450 mediated metabolism.

*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).

*Carbamazepine:* In a pharmacokinetic interaction study conducted in healthy volunteers, azithromycin had no significant effect on the plasma levels of carbamazepine or its active metabolite.

*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.

*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 coadministration 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 carefully monitored, and the dose should be adjusted accordingly.

*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.

*Fluconazole:* Coadministration 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.

*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 conducted 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

*Nelfinavir:* Coadministration 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 drug. 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 (see Section 4.8).

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

*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.

*Theophylline:* Azithromycin did not affect the pharmacokinetics of theophylline when healthy volunteers received azithromycin and theophylline simultaneously. The combined use of theophylline and other macrolide antibiotics has sometimes led to an increased serum level of theophylline.

*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.

*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.

## **4.6 Fertility, Pregnancy and lactation**

### Pregnancy

Animal reproduction studies have been performed at doses up to moderately maternally toxic dose concentrations. These studies demonstrated that azithromycin crosses the placenta, but have revealed no evidence of harm to the foetus. There are, however, no adequate and well controlled studies in pregnant women. Since animal studies are not always predictive of human response, azithromycin should be used during pregnancy only if clearly needed, and if adequate alternatives are not available.

### Breast-feeding

There are no data on secretion in breast milk. As many drugs are excreted in human milk, azithromycin should not be used in the treatment of a lactating woman unless the physician feels that the potential benefits justify the potential risks to the infant.

## **4.7 Effects on ability to drive and use machines**

Dizziness has been reported, which may affect the ability to drive or operate machinery.

## **4.8 Undesirable effects**

The table below lists the adverse reactions identified through clinical trial experience and post-marketing surveillance by system organ class and frequency. Adverse reactions identified from post-marketing experience are included in *italics*. The frequency grouping is defined using the following convention: Very common ( $\geq 1/10$ ); Common ( $\geq 1/100$  to  $< 1/10$ ); Uncommon ( $\geq 1/1,000$  to  $< 1/100$ ); Rare ( $\geq 1/10,000$  to  $< 1/1,000$ ); Very Rare ( $< 1/10,000$ ); and Not known (cannot be estimated).

from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

**Adverse reactions possibly or probably related to azithromycin based on clinical trial experience and post-marketing surveillance:**

<b>System Organ Class</b>	<b>Adverse reaction</b>	<b>Frequency</b>
<b>Infections and Infestations</b>	Candidiasis, oral candidiasis, vaginal infection	Uncommon
	<i>Pseudomembranous colitis</i> (see Section 4.4)	Not known
<b>Blood and Lymphatic System Disorders</b>	Leukopenia, neutropenia	Uncommon
	<i>Thrombocytopenia, haemolytic anaemia</i>	Not known
<b>Immune System Disorders</b>	Angioedema, hypersensitivity	Uncommon
	<i>Anaphylactic reaction</i> (see Section 4.4)	Not known
<b>Metabolism and Nutrition Disorders</b>	Anorexia	Common
<b>Psychiatric Disorders</b>	Nervousness	Uncommon
	Agitation	Rare
	<i>Aggression, anxiety</i>	Not known
<b>Nervous System Disorders</b>	Dizziness, headache, paraesthesia, dysgeusia	Common
	Hypoaesthesia, somnolence, insomnia	Uncommon
	<i>Syncope, convulsion, psychomotor hyperactivity, anosmia, ageusia, parosmia</i>	Not known
	<i>Myasthenia gravis</i> (see Section 4.4)	
<b>Eye Disorders</b>	Visual impairment	Common
<b>Ear and Labyrinth Disorders</b>	Deafness	Common
	Hearing impaired, tinnitus	Uncommon
	Vertigo	Rare
<b>Cardiac Disorders</b>	Palpitations	Uncommon
	<i>Torsades de pointes</i> (see Section 4.4), <i>arrhythmia</i> (see Section 4.4) <i>including ventricular tachycardia</i>	Not known
<b>Vascular Disorders</b>	<i>Hypotension</i>	Not known
<b>Gastrointestinal Disorders</b>	Diarrhoea, abdominal pain, nausea, flatulence	Very common
	Vomiting, dyspepsia	Common
	Gastritis, constipation	Uncommon
	<i>Pancreatitis, tongue discolouration</i>	Not known
<b>Hepatobiliary Disorders</b>	Hepatitis	Uncommon
	Hepatic function abnormal	Rare
	<i>Hepatic failure</i> (see Section 4.4)*, <i>hepatitis fulminant, hepatic necrosis, jaundice cholestatic</i>	Not known
<b>Skin and Subcutaneous Tissue Disorders</b>	Rash, pruritus	Common
	Stevens-Johnson syndrome, photosensitivity reaction, urticaria	Uncommon
	Acute generalised exanthematous pustulosis (AGEP)	Rare
	<i>Toxic epidermal necrolysis, erythema multiforme, Drug reaction with eosinophilia and systemic symptoms</i>	Not known

	(DRESS).	
<b>Musculoskeletal and Connective Tissue Disorders</b>	Arthralgia	Common
<b>Renal and Urinary Disorders</b>	Renal failure acute, nephritis interstitial	Not known
<b>General Disorders and Administration Site Conditions</b>	fatigue	Common
	Chest pain, oedema, malaise, asthenia	Uncommon
<b>Investigations</b>	Lymphocyte count decreased, eosinophil count increased, blood bicarbonate decreased	Common
	Aspartate aminotransferase increased, alanine aminotransferase increased, blood bilirubin increased, blood urea increased, blood creatinine increased, blood potassium abnormal	Uncommon
	<i>Electrocardiogram QT prolonged</i> (see Section 4.4)	Not known

\*which has rarely resulted in death

#### Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: [www.mhra.gov.uk/yellowcard](http://www.mhra.gov.uk/yellowcard) or search for MHRA Yellow Card in the Google Play or Apple App Store.

## 4.9 Overdose

The undesirable effects at doses in excess of those recommended were similar to those after normal doses. The typical symptoms of an overdose with macrolide antibiotics include reversible loss of hearing, severe nausea, vomiting and diarrhoea. In cases of overdose, administration of medicinal charcoal and general symptomatic treatment as well as measures to support vital functions are indicated where necessary.

# 5 PHARMACOLOGICAL PROPERTIES

## 5.1 Pharmacodynamic properties

ATC code: J01FA10

### Mechanism of action:

Azithromycin is a macrolide antibiotic belonging to the azalide group. The molecule is constructed by adding a nitrogen atom to the lactone ring of erythromycin A.

The mechanism of action of azithromycin is based upon the suppression of bacterial protein synthesis by binding to the ribosomal 50S sub-unit and inhibition of peptide translocation.

### Mechanism of resistance:

Resistance of gram-positive organisms to the macrolides usually involves an alteration of the antimicrobial binding site. The MLSB type of resistance, which may be constitutive or induced by exposure to certain macrolides in staphylococci and which is inducible in streptococci, is mediated by a variety of acquired genes (*erm* family) encoding methylases targeted at the peptidyl transferase centre of 23S ribosomal RNA. Methylation impedes binding of antibacterials to the ribosome and gives rise to cross-resistance to macrolides (all macrolides when constitutive), lincosamides and type B streptogramins but not to type A streptogramins. Less frequent mechanisms of resistance include antimicrobial degradation by inactivating enzymes such as esterase and active efflux of the antimicrobial from the bacteria.

Gram negative organisms may be intrinsically resistant to the macrolides because of the inability of the macrolide to effectively penetrate the outer cell membrane; macrolides having a better penetration may have activity against some gram-negative organisms. Gram-negative organisms may also produce ribosomal methylase or macrolide inactivating enzymes.

### ***Breakpoints***

The CLSA susceptibility breakpoints for typical bacterial pathogens are:

- susceptible  $\leq 2$  mg/l; resistant  $\geq 8$  mg/l
- *Haemophilus* spp.: susceptible  $\leq 4$  mg/l
- *Streptococcus pneumoniae* and *Streptococcus pyogenes*:

susceptible  $\leq 0.5$  mg/l; resistant  $\geq 2$  mg/l

### ***Susceptibility***

The prevalence of acquired resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of the agent in at least some types of infections is questionable.

Commonly susceptible species
Aerobic Gram-positive microorganisms
<b>Staphylococcus aureus</b> Methicillin-susceptible

<i>Streptococcus pneumoniae</i> Penicillin-susceptible
<i>Streptococcus pyogenes</i>
<b>Aerobic Gram-negative microorganisms</b>
<b>Haemophilus influenzae</b> <i>Haemophilus parainfluenzae</i>
<i>Legionella pneumophila</i>
<i>Moraxella catarrhalis</i>
<i>Pasteurella multocida</i>
<b>Anaerobic microorganisms</b>
<b>Clostridium perfringens</b>
<b>Peptococcus and Peptostreptococcus spp.</b>
<b>Other microorganisms</b>
<b>Chlamydia trachomatis</b>
<b>Species for which acquired resistance may be a problem</b>
<b>Aerobic Gram-positive microorganisms</b>
<b>Streptococcus pneumoniae</b> Penicillin-intermediate* Penicillin-resistant*
<i>Staphylococci MRSA, MRSE**</i>
<b>Inherently resistant organisms</b>
<b>Aerobic Gram-positive microorganisms</b>
<b>Enterococcus faecalis</b>
<b>Anaerobic microorganisms</b>
Bacteroides fragilis group

\* Pneumococci that have some degree of reduced susceptibility to penicillin are more likely to be macrolide-resistant than penicillin-susceptible strains

\*\* Methicillin-resistant staphylococci have a very high prevalence of acquired resistance to macrolides and are rarely susceptible to azithromycin.

#### Paediatric population

Following the assessment of studies conducted in children, the use of azithromycin is not recommended for the treatment of malaria, neither as monotherapy nor combined with chloroquine or artemisinin based drugs, as non-inferiority to anti-malarial drugs recommended in the treatment of uncomplicated malaria was not established.

## **5.2 Pharmacokinetic properties**

### Absorption

Bioavailability after oral administration is approximately 37%. Peak concentrations in the plasma are attained 2-3 hours after taking the medicinal product.

#### Distribution

Orally administered azithromycin is widely distributed throughout the body.

In pharmacokinetic studies it has been demonstrated that the concentrations of azithromycin measured in tissues are noticeably higher (as much as 50 times) than those measured in plasma, which indicates that the agent strongly binds to tissues.

Binding to serum proteins varies according to concentration and ranges from 12% at 0.5 microgram/ml up to 52% at 0.05 microgram/ml. The mean volume of distribution at steady state ( $VV_{ss}$ ) has been calculated to be 31.1 l/kg.

#### Elimination

Terminal plasma elimination half-life closely reflects the elimination half-life from tissues of 2-4 days.

Approximately 12% of an intravenously administered dose of azithromycin is excreted unchanged in urine within the following three days. Particularly high concentrations of unchanged azithromycin have been found in human bile. In the same source, 10 metabolites were also detected, which were formed through N- and O-demethylation, hydroxylation of desosamine- and aglycone rings and degradation of cladinose conjugate. Comparison of the results of liquid chromatography and microbiological analyses has shown that the metabolites of azithromycin are not microbiologically active.

In animal tests, high concentrations of azithromycin have been found in phagocytes. It has also been established that during active phagocytosis higher concentrations of azithromycin are released than are released from inactive phagocytes. Consequently, in animal tests the azithromycin concentrations measured in inflammation foci were high.

### **5.3 Preclinical safety data**

In animal tests in which the dosages used amounted to 40 times the clinical therapeutic dosages, azithromycin was found to have caused reversible phospholipidosis, but as a rule, no true toxicological consequences were observed which were associated with this.

#### *Carcinogenic potential:*

Long-term studies in animals have not been performed to evaluate carcinogenic potential as the drug is indicated for short-term treatment only, and there were no signs indicative of carcinogenic activity.

#### *Mutagenic potential:*



There was no evidence of a potential for genetic and chromosome mutations in in-vivo and in-vitro test models.

*Reproductive toxicity:*

In animal studies of the embryotoxic effects of the substance, no teratogenic effect was observed in mice and rats. In rats, azithromycin dosages of 100 and 200 mg/kg bodyweight/day led to mild retardation of foetal ossification and maternal weight gain. In peri- and post-natal studies in rats, mild retardation was observed following treatment with 50 mg/kg/day azithromycin and above.

## **6 PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

Capsule contents:

Cellulose microcrystalline,  
Sodium laurilsulfate,  
Magnesium stearate,

Capsule Shell:

Gelatin,  
Titanium dioxide (E-171),  
FD & C Blue 2 (E-132),  
Indigo carmine (E-132),  
Sulfur dioxide.

### **6.2 Incompatibilities**

Not applicable.

### **6.3 Shelf life**

3 years

**6.4 Special precautions for storage**

This medicine does not require any special storage conditions.

**6.5 Nature and contents of container**

Blisterpack PVC/PVDC/Aluminium.

Pack sizes 2, 4, 6 or 100 capsules. Not all pack sizes may be marketed.

**6.6 Special precautions for disposal**

None

**7 MARKETING AUTHORISATION HOLDER**

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

**8 MARKETING AUTHORISATION NUMBER(S)**

PL 00289/1570

**9      DATE OF FIRST AUTHORISATION/RENEWAL OF THE  
AUTHORISATION**

29/07/2008

**10     DATE OF REVISION OF THE TEXT**

12/07/2019

Study Title	Principle
EudraCT No	2020-001209-22
Version Number, Date	1.3 17.05.20

Description of information needed	Label Text
<b>Name, address and telephone number of the sponsor</b> (the main contact for information on the product, clinical trial and emergency unblinding)	University of Oxford Joint Research Office 1st floor, Boundary Brook House Churchill Drive, Headington Oxford OX3 7GB Tel: +44 (0)1865572224 Fax: +44 (0)1865572228
<b>Pharmaceutical dosage form, route of administration, quantity of dosage units,</b> and in the case of open trials, the name/identifier and strength/potency;	Azithromycin (250mg) capsules  The capsules are for oral administration.
<b>Batch and/or code number</b> to identify the contents and packaging operation;	
<b>Trial reference code</b> allowing identification of the <u>trial, site, investigator and sponsor</u> if not given elsewhere;	PRINCIPLE trial. University of Oxford Chief Investigator: Prof. Chris Butler
<b>Trial subject identification number</b> /treatment number and where relevant, the visit number;	
<b>Kit/Pack number</b>	
<b>Investigator</b> (if not included previously)	
<b>Directions for use</b> (reference may be made to a leaflet or other explanatory document intended for the trial subject or person administering the product)	Take two 250mg tablets (making 500mg in total) azithromycin once a day for 3 days by mouth (6 capsules in total)  Special instructions: Azithromycin must be taken at least 1 hour before or 2 hours after antacids. Azithromycin must be taken at least 1 hour before or 2 hours after food.
<b>“For clinical trial use only”</b> or similar wording;	For clinical trial use only
<b>Storage conditions</b>	Store below 25°C
<b>Period of use</b> (use-by date, expiry date or re-test date as applicable), in month/year format and in a manner that avoids any ambiguity	3 days  Expiry date: month/year  Shelf life is 36 months.
<b>“keep out of reach of children”</b> except when the product is for use in trials	Keep out of reach of children



where the product is not taken home by subjects	
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Study Title	Principle
EudraCT No	2020-001209-22
Version Number, Date	1. <del>30</del> <del>1707.054</del> .20

Description of information needed	Label Text
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<b>Pharmaceutical dosage form, route of administration, quantity of dosage units, and in the case of open trials, the name/identifier and strength/potency;</b>	Azithromycin (250mg) <del>capsule</del> tablets.  The <del>capsule</del> tablets are for oral administration.
<b>Batch and/or code number</b> to identify the contents and packaging operation;	
<b>Trial reference code</b> allowing identification of the <u>trial, site, investigator and sponsor</u> if not given elsewhere;	PRINCIPLE trial. University of Oxford Chief Investigator: Prof. Chris Butler
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<b>“For clinical trial use only”</b> or similar wording;	For clinical trial use only
<b>Storage conditions</b>	Store below 25°C
<b>Period of use</b> (use-by date, expiry date or re-test date as applicable), in month/year format and in a manner that avoids any ambiguity	3 days  Expiry date: month/year  Shelf life is <del>36</del> 24 months.



"keep out of reach of children" except when the product is for use in trials where the product is not taken home by subjects	Keep out of reach of children
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**To:** Participating Organisation

**Subject: IRAS Number 281958; Azithromycin update and SA5 Notification of Amendment Category A**

Dear Participating Organisation,

**RE: IRAS Number 281958; PRINCIPLE; i) Azithromycin update and ii) Amendment Reference - SA5**

**i) Azithromycin update**

Further to the email sent on 23<sup>rd</sup> May 2020, we can confirm that currently, participants will be randomised to Usual Care OR Azithromycin + Usual Care. If randomised to the treatment arm, Azithromycin and the swab kit (dependent on availability) will be sent by Oxford CTU directly to the participant.

**In exceptional circumstances and when the CTU team are informed** (eg. bank holidays) GPs can prescribe the Azithromycin via normal NHS processes and send to the participant. This process has been approved in Protocol v3.0. Participants that pay for prescriptions are reimbursed from the study team with a voucher. If GPs do prescribe Azithromycin, the CTU would need to be immediately informed so that the participant does not receive the medication from both the GP and CTU.

You will not need to order the drug via ImmForm and the process for eligibility review will not change. Azithromycin details, including eligibility criteria are described in the protocol, and the manufacturer's SmPC is enclosed with this amendment.

PRINCIPLE is a Platform trial and so the PIS already contains information in the appendices on all drugs being investigated, including Azithromycin.

**Usual Care Participant Packs:**

- These packs contain the Participant Booklet, Participant ID card and swab (if available)
- If you have received usual care materials from the trial team (if you are a site or recruiter), please continue with your current arrangements for sending the usual care packs to participants.

**ii) Substantial Amendment 5**

We have submitted and received REC, HRA and MHRA approvals for an amendment for the PRINCIPLE study. Please find attached, the categorisation email, approvals and amendment package. Please read the documents carefully as these provide information on how this amendment should be implemented, as well as what the amendment entails.

When will this amendment be implemented?

This amendment has been categorised as **category A**. In line with the HRA categorisation email and [UK wide policy on the handling of amendments](#), your site has 2 calendar days from the date of this notification to raise an objection about the amendment. If we do not hear from you, we will assume that the amendment may be implemented at your site. If you need more



time to consider the amendment please contact us prior to the 2 day deadline and we will assist with any queries you may have.

#### What is the impact on research activities at sites?

This amendment impacts the research activities undertaken at NHS organisations. The main changes for attention are

No.	Amendment	Rationale
1	<b>Eligibility Criteria:</b> Broadening of inclusion criteria  <b>Inclusion of a positive SARS-CoV-2 test in the presence of symptoms</b>	As we understand more about the clinical presentation of this devastating illness, we have come to recognise that some patients with COVID-19 illness do not mount a fever response, and do not necessarily cough in the early stages of the illness. Patients who test positive for the illness, may be very unwell in other ways, including shortness of breath, gastro-intestinal symptoms, neurological symptoms, new incontinence, and so forth. This is particularly true of older people, many of whom are frail and in care homes, where the disease is extracting a terrible toll. At the moment, many care home residents will be excluded from participating, according to our current inclusion criteria. Adding in the <b>inclusion of a positive SARS-CoV-2 test in the presence of symptoms</b> will allow people with these presentations to be eligible.
2	<b>Eligibility Criteria:</b> Participants can take part in the study if they are eligible to be randomised to <b>at least one intervention arm as well as the control arm.</b>	For example, those who are already taking an antibiotic will be eligible to be randomised to HCQ or Usual Care. Those who are not already on an antibiotic will be eligible to be randomised to HCQ or AZ or Usual Care.
3	Additional study materials to facilitate recruitment, such as at Care and Residential Homes	We wish to use additional study materials to help Care Home staff give their residents the opportunity to participate in the trial. This is an especially important area for COVID-19 disease and we should be doing all we can to make it possible for this population to be included in the trial: <ul style="list-style-type: none"> <li>i) Care Home Staff poster</li> <li>ii) Participant Introductory Letter</li> <li>iii) Medication Letter to inform care home of residents' trial drug.</li> <li>iv) Study Partner Leaflet</li> </ul>
4	Social Media Post	To facilitate participant recruitment.
5	GPs will be able to prescribe trial medication using existing NHS services	If required, GPs will be able to prescribe, and pharmacies issue, trial medication using existing NHS services, to facilitate the process of providing participants with IMP.
1	Azithromycin SmPC	Manufacturer (Teva) for Azithromycin has been confirmed and the associated SmPC is enclosed.

*Please see the NoSA for full details.*

Is there any impact on funding/agreements?

This amendment **does not impact** the funding/agreement that have previously been agreed.

What is the HRA Approval status of the amendment?

All approvals have been received. If you are able to notify us ahead of the 2 day period that you are able to accommodate this amendment it will enable us to implement sooner.

If you need to discuss the impact of the amendment at your site please do not hesitate to contact the PRINCIPLE Trial Team.

Kind regards

The PRINCIPLE Trial Team

## IRAS Number 281958; Azithromycin update and SA5 Notification of Amendment Category A

Hannah Swayze <hannah.swayze@phc.ox.ac.uk>

Tue 26/05/2020 11:35

Cc: PRINCIPLE Study <principle@phc.ox.ac.uk>

 1 attachments (30 MB)

SA5 CRN.zip;

Dear All,

Please can you kindly circulate the email below and attached zip folder to your sites. It's regarding the recent amendment and the process for Azithromycin distribution.

Please let us know if you have any questions.

Many thanks for your help,

Hannah

Dear Participating Organisation,

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