

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

Internal Reference Number / Short title: PRINCIPLE

Ethics Ref: 20/SC/0158

IRAS Project ID: 281958

EudraCT Number: 2020-001209-22

Date and Version No: 07 April 2020 version 2.0

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No potential conflict of interest

Confidentiality Statement

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

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

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Protocol 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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2. LAY SUMMARY

COVID-19 disproportionately affects people over 50 years old with comorbidities and those over 65 years old. The infection causes considerable morbidity and mortality in this population group in particular, and is having a devastating effect on people's health, and society in the UK and internationally.(1-4) So far, there are no specific treatments for COVID-19 that have been proven in rigorous clinical trials to be effective. Most cases are being managed in the community. It is essential that we urgently identify interventions that may favourably modify progression of the infection. An ideal intervention would be one that is safe, with few side-effects, helps prevent disease progression, and can be administered in the community using existing NHS processes and capability.

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

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

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

3. SYNOPSIS

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

	<p>3) Contacts with the health services</p> <p>4) Consumption of antibiotics</p> <p>5) Hospital assessment without admission</p> <p>6) Oxygen administration</p> <p>7) Intensive Care Unit admission</p> <p>8) Mechanical ventilation</p> <p>9) To determine if effects are specific to those with the infections syndrome but who test positive 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>records where the practice is a member of RSC</p> <p>4. Bi-weekly reports from participants primary care medical records</p> <p>5-8 and 10 patient report/carer report/medical record in primary care and hospital care</p> <p>9. Swab results either at baseline or day 5 for COVID-19 will indicate an "Intention to Treat Infected" group within the overall cohort for sub analysis</p> <p>11. Follow up swabs at day 5 (if available) will indicate ongoing shedding allowing for comparison between groups</p> <p>12. WHO-5 Well Being Index</p>	<p>GP notes review where available through Oxford RCGP RSC network after 28 days</p> <p>HES/ONS/EMIS data linkage after 28 days where patients have been assessed in hospital</p> <p>Swab result available once processed from GP record and from the supporting PHE laboratory</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 patient experiences of consulting, being tested and taking (trial) medication for suspected COVID-19.</p> <p>To explore healthcare professionals' views of taking part in research during pandemics.</p>	<p>1. Telephone interview with patient.</p> <p>Telephone interview with healthcare professional.</p>	<p>1. After 28 days.</p> <p>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 a trial arm that included a study drug is shown to be superior, then that will become the standard of care (usual care) in the trial and any further interventions will be compared against that intervention.		

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 R&D Department
RCGP RSC	Royal College of General Practitioners Research Surveillance Centre
REC	Research Ethics Committee
RSI	Reference Safety Information
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SDV	Source Data Verification
SMPC	Summary of Medicinal Product Characteristics

SOP	Standard Operating Procedure
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 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 at higher risk appear to be people aged 50 and over with comorbidity and those aged 65 and over.(1-3, 13)

We therefore propose a platform trial that has the capability of rapidly evaluating potential drug treatments in the high-risk population group, but that will also be flexible enough to allow the addition of further interventions into the trial platform, should such interventions suitable for pragmatic evaluation in Primary Care become available during the course of the trial. New interventions will not be added into the trial without first obtaining the required permissions.

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

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

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

The study aims to be rapidly initiated, so we can urgently determine if 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 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 caused by the highly infectious SARS-COV2 virus.(4, 15) As of 22 March 2020 in the UK, 5,018 confirmed cases, and 233 deaths have been reported in the UK, and modelling studies suggest the pandemic will worsen rapidly in the UK and elsewhere.(4, 16)

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

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

And/or

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

A pragmatic trial

The aim of PRINCIPLE is to be the national Primary Care platform trial for UK COVID-19, assessing the effectiveness of trial treatments in reducing the need for hospital admission or death for patients with suspected COVID-19 infection aged ≥ 50 years with serious comorbidity, and aged ≥ 65 with or without comorbidity, and during time of prevalent COVID-19 infections in the context of current care delivery. Thus, the trial will need to be as streamlined as possible so that it fits with minimal disruption into routine care during a period of widespread infection and considerable pressure on the NHS and society. In line with common practice for pragmatic trials, this trial will be an open trial with no placebo control. (14, 19-21) 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 design, allows multiple arms to be considered simultaneously, and interventions can be dropped, added and/or replaced as evidence emerges for effectiveness, or lack of it. 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) of evaluation of this outcome measure (if applicable)
Primary Objective To assess effectiveness of trial treatments in reducing the need for hospital admission or death, for patients aged ≥ 50 years with comorbidity, and aged ≥ 65 with or without comorbidity and suspected COVID-19 infection during time of prevalent COVID-19 infections	Hospital admission or mortality related to suspected COVID-19	Within 28 days

<p>Secondary Objectives</p> <p>To explore whether trial treatment reduces</p> <ol style="list-style-type: none"> 1) Duration of severe symptoms 2) Time taken to self-report recovery 3) Contacts with the health services 4) Consumption of antibiotics 5) Hospital assessment without admission 6) Oxygen administration 7) Intensive Care Unit admission 8) Mechanical ventilation 9) To determine if effects are specific to those with the infections syndrome but who test positive for COVID-19 10) Duration of hospital admission 11) Viral shedding 12) Negative effects on well being 	<ol style="list-style-type: none"> 1-2 Patient report on day they feel to have recovered 3. Contacts with health services reported by patients and captured by reports of patients 'medical records where the practice is a member of RSC 4. Bi-weekly reports from participants primary care medical records 5-8 and 10 patient report/carer report/medical record in primary care and hospital care 9. Swab results either at baseline or day 5 for COVID-19 will indicate an "Intention to Treat Infected" group within the overall cohort for sub analysis 11. Follow up swabs (if available) at day 5 will indicate ongoing shedding allowing for comparison between groups 12. WHO-5 Well Being Index 	<p>Daily online symptoms score.</p> <p>Telephone call or text day 7, 14 and 28 if data not being received online</p> <p>GP notes review where available through Oxford RCGP RSC network after 28 days</p> <p>HES/ONS/EMIS data linkage after 28 days where patients have been assessed in hospital</p> <p>Swab result available once processed from GP record and from the supporting PHE laboratory</p> <p>WHO 5 Well Being Index at baseline day 14 and day 28 either via online diary or telephone</p>
<p>Qualitative sub study</p> <ol style="list-style-type: none"> 1) To explore patient experiences of consulting, being tested and taking (trial) medication for suspected COVID-19. <p>To explore healthcare professionals' views of taking part in research during pandemics.</p>	<ol style="list-style-type: none"> 2. Telephone interview with patient. <p>Telephone interview with healthcare professional.</p>	<ol style="list-style-type: none"> 2. After 28 days. <p>Once practice has completed recruitment.</p>

6. TRIAL DESIGN

This will be an open, prospective, individually randomised, platform, controlled clinical trial in community care. The trial will initially be two-arm, 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 is being scaled up. Due to the pandemic, almost all practices in the UK have been asked to join the RCGP RSC Network.

7. PARTICIPANT IDENTIFICATION

7.1 Trial Participants

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

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

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

7.1.1 Inclusion Criteria

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

OR

- Patients aged ≥ 65 with or without comorbidity

7.1.2 Exclusion Criteria

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

8 TRIAL PROCEDURES

8.1 Recruitment

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

People who are concerned about COVID-19 continue to contact their general practices in large numbers. In the first instance, we will ask participating general practices to record whether a person phoning about COVID-19 is potentially eligible for the study. The practice will then ask the person if they are interested in finding out about potential trial participation or seek verbal consent if they are happy to be contacted by the trial team to discuss this further. If they are, information will be provided verbally and online either by the GP surgery or their contact details passed to the trial team who will provide such information on how they might join the study. Full information will be available to view on a web site and subsequently on the Participant Information Sheet (PIS). This information will inform potentially eligible and interested patients about how to access further trial information and consider participation, as well as the procedures involved in joining the study, and what participation would involve. Practices can also choose to screen contacts from the previous (up to) 7 days for potentially eligible participants to be approached to discuss participation.

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

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

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

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

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

During this process, we will ask the potential participant to, if possible, include a phone number 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 a requirement of study participation, merely a suggested mechanism to aid participation for consenting patients.

Eligibility will be checked centrally by a medically qualified clinician or a Research Nurse suitably trained and experienced who has been delegated this responsibility, with appropriate access to the participants' medical records, if they can't access the participants' medical notes, the clinician/delegate will contact the participants' GP for information to enable the study team to confirm eligibility.

Once informed consent has been obtained, 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 treatment allocation they have been randomised to. The participant and GP can review the PIS and completed ICF at any time using a secure log-in access code.

If not sampled face-to-face, all participants will be provided with 2 sampling kits for self-sampling by their practice, study team, Public Health England (PHE) or other central service. 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 PHE standard advice. Once the sample has been taken, they will be asked to place the sample in the provided container, sealed in a double envelope, which will be posted to PHE laboratory according to their standard practice for COVID-19. For trial purposes, we will not store the swabs after testing but PHE may keep the specimen for up to 5 years following their own approved processes. Participants will be informed of their COVID-19 swab result by their GP.

Participants included in the study from a limited locality in London, will 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 Study on patients who also consent into the Imperial College study.

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

The RCGP RSC will report to the central trial office at least twice weekly about healthcare contacts in the participating patient's clinical records, as they are able to download this information centrally for study participants. This will be used as confirmation and a back-up for information obtained directly from study participants and other data sources outlined above. Where notes review is not possible using this route – for example, 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.

8.2 Screening and Eligibility Assessment

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

8.3 Informed Consent

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

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

8.4 Randomisation

Participants will be randomised using a fully validated and compliant web-based randomisation system called Sortition. At the baseline assessment, the recruiter 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. 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, unless 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, it may be issued centrally from the trial team.

Subsequent Visits

There is no requirement for participants to have a research-specific face-to-face visit as part of their study participation, as requiring additional health care contacts should be avoided if at all possible during the COVID-19 pandemic. All subsequent measurements consist of self-completed questionnaires online or through telephone calls from the trial team and primary care and hospital record searches.

Participant follow-up will be primarily online, where they will be asked to complete questions 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 telephone call, at the preference of the participant.

Each day, participants, or their study partner, 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 impact of interventions on this is important.(22)

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

The practice network that will be implementing the trial in the first instance, the Oxford Royal College of General Practitioners Surveillance Network, has the capacity to extract patient information from the clinical records twice a week. This more-or-less real-time ascertainment of primary care will augment information captured from patients themselves, their families or from the hospital records about intensive

care admission and ventilation. Participant records will be accessed up to 3 months following enrolment to ascertain follow up data to day 28 from enrolment. Data will be collected in real time as far as possible, RCGP RCS, EMIS and NHS Digital will be utilised if required. We are engineering a new digital platform to enable daily extracts shortly.

Where notes review is not possible using these routes – for example 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.

8.7 Sample Handling

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

8.8 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 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 sub-study, we may ask the practice 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).

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. 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 permission.

Patient 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 (and result 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.

8.9 Early Discontinuation/Withdrawal of Participants

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

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

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

8.10 Definition of End of Trial

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

9 TRIAL INTERVENTIONS

9.1 Investigational Medicinal Product(s) (IMP) Description

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 Inform process. All GP practices in England are already set up on Inform, as they use this system to order influenza vaccines from Public Health England. GPs will be provided with an envelope by the study team which will be labelled appropriately for trial medication, and they will add the patient's details to this label. This pack, containing instructions on using the medication 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 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.

9.4. Compliance with Trial Treatment

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

9.5. Accountability of the Trial Treatment

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

9.6. Concomitant Medication

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>

<p>Serious Adverse Event (SAE)</p>	<p>A serious adverse event is any untoward medical occurrence that:</p> <ul style="list-style-type: none"> • results in death • is life-threatening • requires inpatient hospitalisation or prolongation of existing hospitalisation • results in persistent or significant disability/incapacity • consists of a congenital anomaly or birth defect*. <p>Other ‘important medical events’ may also be considered a serious adverse event when, based upon appropriate medical judgement, the event may jeopardise the participant and may require medical or surgical intervention to prevent one of the outcomes listed above.</p> <p>NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the 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>
<p>Serious Adverse Reaction (SAR)</p>	<p>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.</p>
<p>Suspected Unexpected Serious Adverse Reaction (SUSAR)</p>	<p>A serious adverse reaction, the nature and severity of which is not consistent with the Reference Safety Information for the medicinal product in question set out:</p> <ul style="list-style-type: none"> • in the case of a product with a marketing authorisation, in the approved summary of product characteristics (SmPC) for that product • in the case of any other investigational medicinal product, in the approved investigator’s brochure (IB) relating to the trial in question.

NB: to avoid confusion or misunderstanding 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 1 night admission to hospital.

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

10.5.2. Procedure for immediate reporting of Serious Adverse Events

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

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

10.5.3 Expectedness

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

10.6 SUSAR Reporting

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

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

10.7 Development Safety Update Reports

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

11 STATISTICS

11.1 Master Statistical Analysis Plan (M-SAP)

The statistical design and pre-specified analyses will be described in detail in a Master Statistical Analysis Plan (M-SAP) drafted by a Trial Statistician and signed off by the CI and Lead/senior statistician. 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 arm, the superior treatment will replace the control arm as the new standard of care, and all subsequent treatments will be compared to the new standard of care. Because the process of dropping and adding treatments may be on-going for an indefinite period of time, platform trials may be better conceived of as a process rather than a singular clinical trial. In the context of the COVID-19 pandemic, the trial may continue as long as the pandemic persists.

The PRINCIPLE trial will begin as a 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 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 θ_j denote the log odds ratio comparing the odds of hospitalisation/death for persons in treatment group j versus persons in the Usual Care arm. A corresponding Bayesian posterior distribution will be derived for the estimated log odds ratio. The primary analysis for intervention j will test the following hypothesis:

$$H_0: \theta_j \geq 0$$

$$H_1: \theta_j < 0$$

If the Bayesian posterior probability of superiority for a treatment versus Usual Care is sufficiently large (e.g. ≥ 0.99), the null hypothesis will be rejected and the intervention will be deemed superior to Usual Care. The exact threshold of the superiority decision criterion (e.g. 0.99) will be determined *a priori* via simulation to control the one-sided Type I error of the study at approximately 0.025, and will be specified in the M-SAP. The M-SAP will also specify details of the primary analysis when the Usual Care arm is replaced by a superior treatment, and for when the comparison of a treatment versus control 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 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

The first interim analysis will occur when first 100 randomised participants have the opportunity to complete 28 days of follow-up, followed by subsequent weekly interim analyses. At each interim analysis, all enrolled intervention arms will be evaluated for success or futility using the Bayesian primary analysis. If the Bayesian posterior probability of superiority of a given intervention is sufficiently large (e.g. ≥ 0.99), superiority will be declared. If there are additional intervention arms in the study (either currently or subsequently), the superior arm will replace the Usual Care arm as the new standard of care.

If the Bayesian posterior probability of a clinically meaningful treatment effect (≥ 0.05 decrease in the proportion hospitalized/dead) is sufficiently small (e.g. < 0.01) 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 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 M-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 M-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 M-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 M-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 the participant fails to complete data online and after three attempts at contacting the participant/Trial Partner, the RCGP RSC may be utilised to obtain missing data. Data collected will include participant identifiable information and will be accessed at the University of Oxford according to PC-CTU Information Governance policies and GDPR. Data will only be held for the duration of which its required, this will be reviewed annually.

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

12.2 Access to Data

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

12.3 Data Recording and Record Keeping

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

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

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

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

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

16 ETHICAL AND REGULATORY CONSIDERATIONS

16.1 Declaration of Helsinki

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

16.2 Guidelines for Good Clinical Practice

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

16.3 Approvals

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

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

16.4 Other Ethical Considerations

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

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

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

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

16.5 Reporting

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

16.6 Transparency in Research

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

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

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

16.7 Participant Confidentiality

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

16.8 Expenses and Benefits

All participants will be reimbursed with a £20 voucher, to covers the payment of a prescription, should they incur tis as a result of study participation, and a token of recognition of giving their time and contribution to the study. The vast majority of participants will not have to pay a prescription change, should a prescription be issued as a result of trial participation. Most people with the co-morbidities outlines and in the age range required for eligibility, are not required to pay for prescriptions.

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 a MRC call.

17.2 Insurance

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

17.3 Contractual arrangements

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

18 PUBLICATION POLICY

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

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

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

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

20 ARCHIVING

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

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.
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5. Berry SM, Connor JT, Lewis RJ. The platform trial: an efficient strategy for evaluating multiple treatments. *JAMA*. 2015;313(16):1619-20.
6. Butler CC, Connor JT, Lewis RJ, Broglio K, Saville BR, Cook J, et al. Answering patient-centred questions efficiently: Response-adaptive platform trials in primary care. *British Journal of General Practice*. 2018;68(671):294-5.
7. Angus DC, Alexander BM, Berry S, Buxton M, Lewis R, Paoloni M, et al. Author Correction: Adaptive platform trials: definition, design, conduct and reporting considerations (*Nature Reviews Drug Discovery*, (2019), 18, 10, (797-807), 10.1038/s41573-019-0034-3). *Nature Reviews Drug Discovery*. 2019;18(10):808.
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9. Wang M, Cao R, Zhang L, Yang X, Liu J, Xu M, et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. *Cell Res*. 2020;30(3):269-71.
10. 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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13. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet*. 2020.
14. Butler CC, van der Velden AW, Bongard E, Saville BR, Holmes J, Coenen S, et al. Oseltamivir plus usual care versus usual care for influenza-like illness in primary care: an open-label, pragmatic, randomised controlled trial. *The Lancet*. 2020;395(10217):42-52.
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21 APPENDIX A: SCHEDULE OF PROCEDURES

Procedures	Visits					
	Visit timing Day 0	Day 0	Day 0	Day 0	Daily Day 1- 28 incl	Day 29- 3mths
	Screening completed by participant online/phone	Eligibility completed by participant online/phone	Baseline completed by participant online/phone	Eligibility completed by Clinician online/phone	Symptom Diaries completed by participant online/phone	Retrospective data collection by study team
Informed consent	X	X	X	X	X	
Demographics	X	X	X			X
Medical history	X	X	X	X		X
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

22 APPENDIX B: AMENDMENT HISTORY

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

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.

APPENDIX 1: 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 infection causes considerable morbidity and mortality in this population group in particular, and is having a devastating effect on people's health, and society in the UK and internationally.(1-4) So far, there are no specific treatments for COVID-19 that have been proven in rigorous clinical trials to be effective. Clinicians managing suspected COVID-19 infections in the community will make clinical judgement 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 present (<https://www.nice.org.uk/guidance/ng163>).

This usual care arm will follow current NHS care provision, and provide 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 beneficial compared to this usual alone care arm, 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.
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Thompson, Robert Verity, Erik Volz, Haowei Wang, Yuanrong Wang, Patrick GT Walker, Caroline Walters, 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 2: 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.(1, 2) Hydroxychloroquine is a hydroxylated version of the drug chloroquine.(2, 3) 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 (4)19.(2, 5) Hydroxychloroquine is already available within the NHS on prescription for other indications, and has a generally benign safety profile.(6) 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*.(3) Chloroquine is widely distributed in the whole body, including lungs, after oral administration.(2) The EC₉₀ value of chloroquine against the 2019-nCoV in Vero E6 cells was 6.90 µM in one study (1) which can be clinically achievable as demonstrated in the plasma of rheumatoid arthritis patients who received 500 mg administration.(6)

Hydroxychloroquine has been found to be effective against intracellular micro-organisms including malaria and intracellular bacteria *Coxiella burnetii* and *Tropheryma Whipplei*.(3) Both chloroquine and hydroxychloroquine have been shown to have *in vitro* antiviral activity against SARS coronavirus in a number of studies.(3) Most recently activity against SARSCOV2 was shown to be greater for hydroxychloroquine than chloroquine (7).

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 (4), 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>).(2)

2 Outcome measures related to hydroxychloroquine

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

3 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.

3.1 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.

3.2 Storage of IMP

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

3.3 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.

3.3.1 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.

3.3.2 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 4 hour interval be observed between hydroxychloroquine and antacid dosaging. As hydroxychloroquine may enhance the effects of a hypoglycaemic treatment, a decrease in doses of insulin or antidiabetic drugs may be required. Halofantrine prolongs the QT interval and should not be administered with other drugs that have the potential to induce cardiac arrhythmias, including hydroxychloroquine. Also, there may be an increased risk of inducing ventricular arrhythmias if hydroxychloroquine is used concomitantly with other arrhythmogenic drugs, such as amiodarone and moxifloxacin. An increased plasma ciclosporin level was reported when ciclosporin and hydroxychloroquine were co-administered. Hydroxychloroquine can lower the convulsive threshold. Co-administration of hydroxychloroquine with other antimalarials known to lower the convulsion threshold (e.g. mefloquine) may increase the risk of convulsions. Also, the activity of anti-epileptic drugs might be impaired if co-administered with hydroxychloroquine. In a single-dose interaction study, chloroquine has been reported to reduce the bioavailability of praziquantel. It is not

known if there is a similar effect when hydroxychloroquine and praziquantel are co-administered. Per extrapolation, due to the similarities in structure and pharmacokinetic parameters between hydroxychloroquine and chloroquine, a similar effect may be expected for hydroxychloroquine. There is a

theoretical risk of inhibition of intra-cellular α -galactosidase activity when hydroxychloroquine is co-administered with agalsidase.

3.3.3 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.

4 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

1. Wang M, Cao R, Zhang L, Yang X, Liu J, Xu M, et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. *Cell Res.* 2020;30(3):269-71.
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APPENDIX 3: 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.(1) Azithromycin was also used in some of the Chinese observational and interventional studies.

Azithromycin has also been shown to be active *in vitro* against Zika and Ebola viruses,(2-4) and to prevent severe respiratory tract infections when administered to patients suffering viral infection.(5) Inhibition of viral infections by azithromycin may be linked to its suppressive effect on the production of viral interferon.(6) 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.(7-9) 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.(10)

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.(11) 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.(11) Severe pneumonia is more prevalent the older you are and in those with more serious underlying diseases.(12) 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 influenzae*, *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.(13)

For CAP management NICE guidance currently recommends Amoxicillin 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 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.

3.1 Investigational Medicinal Product (IMP) description

Azithromycin 500 mg daily for 3 days. The tablets 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.

The marketing authorisation holders are:

Sandoz Ltd., Frimley Business Park, Frimley, Camberley, Surrey, GU16 7SR, UK. Marketing authorisation numbers PL 04416/0668 PL 04569 0925 PL 04569 0926

Generics [UK] Limited t/a Mylan, Potters Bar, Hertfordshire, EN6 1TL, UK. Marketing authorisation numbers PL 04569/0925 PL 04569/0926

Accord-UK Ltd, (Trading style: Accord), Whiddon Valley, Barnstaple, Devon, EX32 8NS, UK. Marketing authorisation numbers PL 0142/1016 PL 0142/1017

Milpharm Limited, Ares Block, Odyssey Business Park, West End Road, Ruislip, HA4 6QD, UK. Marketing authorisation numbers PL 16363/0461 PL 16363/0462

3.2 Storage of IMP

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

3.3 SmPC precautions and concomitant medication

3.3.1 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 antiarrhythmics (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.

3.3.2 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

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.

3.3.3 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 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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Principle Trial Team

Primary Care Clinical Trials Unit,
Nuffield Department of Primary Care
Health Sciences,
University of Oxford
Radcliffe Observatory Quarter,
Woodstock Road,
Oxford,
OX2 6GG

Date:

Dear Dr _____,

RE:

Name of patient:

Patient's date of birth:

This patient was entered into the PRINCIPLE trial
on (insert date): _____

A copy of your patients consent form can be downloaded at XXXXXXXX/has been sent to you via email. **Please retain the consent form, along with this letter, in your patient's medical record.** Please note that your patient has given consent for us to gather information from their medical notes. If we need you to confirm patient eligibility, a member of the PRINCIPLE research team will contact you to arrange a suitable time and way of doing this.

PRINCIPLE Trial details

Site ID:

PRINCIPLE ID:

Notification of which arm your patient has been randomised to has been sent via our automated systems. If you are not set up on the online systems, the treatment your patient has been randomised to receive will be documented below:

Trial Treatment: _____

Many thanks.

The PRINCIPLE team

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 being informed of my participation within the study.		
7	I agree to take part in the study		
	<i>ADDITIONAL (optional, not required for study participation)</i>	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>		



Signature:

First Name: _____ **Last Name:** _____

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

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

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

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

Participant:

Name: _____ **Date:** ___ / ___ / _____

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



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PRIMARY CARE
HEALTH SCIENCES

Primary Care | ●●●●
Clinical Trials Unit

PRINCIPLE TRIAL: TEXT/PHONE MESSAGE FOR PARTICIPANTS TO CONFIRM THEY HAVE RECEIVED THE TRIAL MEDICATION

This is a message from the PRINCIPLE Trial Team. Please confirm that you have received your trial medication and that it's in good condition? Please reply to this message by sending either YES or NO or click on the link to respond: [LINK](#)



PRINCIPLE TRIAL: TEXT/PHONE MESSAGE FOR PARTICIPANTS TO INVITE THEM TO TAKE PART IN THE QUALITATIVE SUB-STUDY

This is a message from the PRINCIPLE Trial Team to invite you to take part in a an independent study run by a team at Imperial College. The study is for people with COVID-19 and the aim is to follow you up more intensively for immunological reasons and to determine spread within households. If you consent to us providing you with more information about the study please reply YES to this message or NO if you do not consent. Alternatively please click the link to record your response [LINK](#)



PRINCIPLE TRIAL: TEXT/PHONE MESSAGE FOR PARTICIPANTS TO INVITE THEM TO TAKE PART IN THE PROCESS EVALUATION SUB STUDY

This is a message from the PRINCIPLE Trial Team to invite you to take part in a telephone interview to explore your experiences of GP appointments, being tested and taking (trial) medication for suspected COVID-19. Please reply to this message by sending either YES if you are willing to take part or NO if you are not, or click on the link to respond: [LINK](#)



PRINCIPLE TRIAL: TEXT MESSAGE INFORMATION FOR PARTICIPANTS

This is a message from Dr **XX** at **XX** Medical Practice in relation to the COVID-19 outbreak. A clinical trial exploring treatment for the COVID-19 virus is taking place. If you experience **a continuous cough and/or a high temperature** and have had it for **less than 8 days**, please click **here** if you would like to find out more. Please call the Trial Team if you have any questions or do not have access to online systems: 0800 138 0880

Appendix 1—Hydroxychloroquine

Drug Information

Hydroxychloroquine is a drug that is well known and has been used for many years around the world for conditions such as Malaria and Rheumatoid Arthritis, but is not currently used to treat infections like COVID-19.

Side-effects

The common side effects (experienced by less than 10% of people who take the medication) are:

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

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

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

Appendix 2— Azithromycin

Drug Information

Azithromycin is a widely used antibiotic, but is not currently used to treat infections like COVID-19.

Side-effects

The common side effects are:

- * abdominal pain
- * headache
- * nausea
- * vomiting
- * diarrhoea
- * flatulence

May also cause:

- * dizziness
- * insomnia
- * altered taste
- * pins and needles
- * changes in vision or hearing
- * rash
- * itching
- * joint pains
- * fatigue



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.



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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 this drug does work for COVID-19, and that is why we urgently need to do a proper trial so we have the information we need to guide the provision of best care for all.

Aim

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

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

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

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

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

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

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

Do I have to take part?

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

What will happen to me if I take part?

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

Informed Consent

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

Initial Questionnaire

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

Letting Your GP Know

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

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



Flowchart—What Will I Need to Do?

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

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

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

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

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

Follow-up

You should receive a swab kit 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.



Randomisation

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

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

Swab

The aim is that everyone who takes part in the trial will be asked to take swabs (nose and throat) at the start of the trial and on day 5, if there is a worldwide shortage of swabs we may not be able to test all that take part in the trial, at both or either timepoint . You will receive instructions on how to take your own sample at home using the swab kit. We will also tell you how to post the sample to the labs using the envelopes we provide. In some circumstances, swabbing may not be available due to supply issues.

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

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

Trial Treatment

If you are randomised to the standard care plus trial treatment group, arrangements will be made for the drug to be delivered to you or you may collect/nominate an individual to collect the drug from a local pharmacy, or local GP. You will be told exactly how you will receive the medication. You will also receive instructions on how to take it and for how long 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 7, day 14 and day 28 of the follow up period and ask you a brief set of questions over the phone.

What happens if I am admitted to Hospital?

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

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



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

With any medicine, including ones that are already used within the NHS, there is a risk of side effects. 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 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 15. The decision to withdraw will not affect the standard of care you receive from the NHS in any way, now or in the future.

Expenses and Payments

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



What if there are any problems?

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

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

If you wish to complain about any aspect of the way in which you have been approached or treated, or how your information is handled during the course of this trial, you should contact the trial team on principle@phc.ox.ac.uk or 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 ctr@admin.ox.ac.uk



What will happen to my data?

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

Responsible members of the University of Oxford may be given access to the trial data for monitoring and/or audit of the trial to ensure that the research is complying with applicable regulations.

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

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



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

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

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

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

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

What if relevant new information becomes available during the trial?

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

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

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

What will happen to the results of the trial?

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

Who is organising and funding the research?

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

Who has reviewed the trial?

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

Trial Email Address:

principle@phc.ox.ac.uk







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, University of Oxford

Researchers conducting interviews: Dr Sarah Tonkin-Crine and Dr Aleksandra Borek, University of Oxford

HEALTHCARE PROFESSIONAL INTERVIEW – INVITATION (EMAIL)

Subject: Invitation to a short telephone interview as part of PRINCIPLE trial

Dear [name],

Please forward this invitation, with attached documents, to GPs in your practice.

Your practice is taking part in the PRINCIPLE trial assessing treatments for COVID-19.

We would like to invite 1-2 GPs from your practice, who have been involved in managing patients with suspected COVID-19 and recruiting them to the PRINCIPLE trial to take part in a telephone interview.

The telephone interview will:

- Last 15-30 minutes and can be conducted at the time that suits the GP.
- Be audio-recorded so that we can transcribe the interview for analysis.
- Be confidential so that any identifiable details (e.g., GP or practice names) will be removed or replaced with anonymous IDs.
- Be about GPs' experiences of consulting patients with suspected COVID-19 and their experiences of and views on the trial processes.

We offer a £20 gift voucher for participants.

Attached is a Participant Information Sheet with more information about the study, and information about verbal consent (which will be audio-recorded at the start of the interview).

If you have any questions about the study, or would like to participate, please contact:

[researcher] by email: XXXXX or telephone: xxxxx

Yours sincerely,

[Qualitative research fellow's details]

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, University of Oxford**Researchers conducting interviews:** Dr Sarah Tonkin-Crine and Dr Aleksandra Borek, University of Oxford**HEALTHCARE PROFESSIONAL INTERVIEW – PARTICIPANT INFORMATION SHEET**

We would like to invite you to take part in a telephone interview about your experience of participating in the PRINCIPLE study, which investigated treatments for COVID-19 infection.

Before you decide if you would like to take part, please read this information to understand why this research is being done and what taking part in the interview would involve for you.

If you have questions, would like more information, or would like to take part, contact:

Dr Aleksandra Borek by email: Aleksandra.borek@phc.ox.ac.uk

What is the purpose of this research?

The aim of this interview is to find out healthcare professionals' views and experiences of taking part in the PRINCIPLE trial that aimed to test the impact of selected treatments on recovery from COVID-19. We are interested in finding out what works well and what could be done better to improve future care and future research studies.

Why have I been invited to take part?

You have been invited because you are a healthcare professional who took part in the PRINCIPLE trial. We are intending to interview approximately 25 professionals in total. We will also be interviewing up to 50 patients who took part in the trial.

What will happen to me if I decide to take part?

We would like you to take part in a single telephone interview about your experience. The interview can be done over the telephone (or if you prefer via Skype or Zoom teleconferencing). The interview will be arranged at a time to suit you and should take between 15 and 30 minutes. We will ask you about your experience of taking part in the PRINCIPLE trial, recruiting patients to the trial and your experience of working in primary care during the COVID-19 pandemic.

Consent will be obtained verbally at the start of the interview – please read the Verbal Consent Form available on the PRINCIPLE website [[insert link](#)].

If you are interested in taking part, please contact us using the details at the end of this document.

What are the advantages and disadvantages of taking part?

There are no direct advantages to you. Taking part in interviews about COVID-19 may be distressing for some people. You will be able to skip any interview question if you wish and pause or stop interviews when you wish. Taking part may help us understand how to improve care for, and studies involving, patients with COVID-19.

Will taking part in the interview remain confidential?

Yes. All participants will be given a unique participant number, and the **research data** will be stored with that number, instead of anything that identifies you. Personal details will be held separately and securely on University of Oxford computer network. **The transcript of the audio recording will be de-identified.** To ensure confidentiality, the transcript will not include any names or other defining details that can identify you.

Responsible members of the University of Oxford and the relevant NHS Trusts may be given access to data for monitoring and/or audit of the study to ensure that the research is complying with applicable regulations. Whilst the interview will be treated in confidence, should there be any disclosure relating to the health, safety or wellbeing of yourself or others, it might be necessary to report the matter to appropriate authorities.

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.

We will be using information from you in order to undertake this study and will use the minimum personally-identifiable information possible. We will keep identifiable information about you for less than 3 months after the study has finished. This excludes any research documents with personal information, such as consent forms, which will be held securely at the University of Oxford 10 years after the end of the study.

The audio recording of your interview will be stored securely on the University of Oxford network drive accessed only by the research team. The recording will be sent securely to an independent transcription company who will type up the recording. The company has been assessed and approved for data security by the University of Oxford. Once the recording has been transcribed, it will be deleted by the transcription company and by the research team.

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>. For more details, you can contact Dr Sarah Tonkin-Crine (sarah.tonkin-crine@phc.ox.ac.uk).

What will happen if I don't want to carry on with the interview?

Taking part in the interview is voluntary. You can withdraw from the interview without penalty at any time, without giving a reason and without any negative consequences to you. If you withdraw from the study your data will be deleted, including any data which has been de-identified.

What happens if something goes wrong?

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 study. If you wish to complain or have any concerns, you can contact Dr Sarah Tonkin-Crine (sarah.tonkin-crine@phc.ox.ac.uk). If you remain unhappy or wish to make a formal complaint, please contact the University of Oxford Clinical Trials and Research Governance (CTRG) office on 01865 616480, email ctrg@admin.ox.ac.uk.

What will happen to the results of this interview study?

The results will be published in scientific journals and meetings. A summary of the findings will be made available on the PRINCIPLE study website ([enter website address](#)) and the full report can be made available on request. De-identified transcripts will be stored in an online data repository to be made available for future research where required.

Will I be reimbursed for taking part?

You will be reimbursed £20 in online shopping vouchers for your time to take part in an interview. You will not incur any additional expenses by taking part in this study.

Who is organising and funding the study?

The PRINCIPLE trial ([insert weblink](#)) (including these interviews) is led by researchers at the Nuffield Department of Primary Care Health Sciences at the University of Oxford, who act as research sponsor. It is funded by the UK Research and Innovation / Medical Research Council.

Who has reviewed the study?

All research in the NHS is looked at by an independent group of people, called a Research Ethics Committee (REC), to protect participants' interests. This study has been reviewed and approved by [\[insert ethics committee\]](#).

Where can I get more information?

If you would like to take part in the study or if you have any further questions, please contact:

Contact details: **Dr Aleksandra Borek**
Nuffield Department of Primary Care Health Sciences, University of Oxford
Email: Aleksandra.borek@phc.ox.ac.uk

THANK YOU FOR TAKING THE TIME TO READ THIS INFORMATION

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, University of Oxford

Researchers conducting interviews: Dr Sarah Tonkin-Crine and Dr Aleksandra Borek, University of Oxford

HEALTHCARE PROFESSIONAL INTERVIEW – TOPIC GUIDE

Introduction:

1. Introduce self, and thank the participant for agreeing to take part.
2. Check whether participants have any questions about the Participant Information Sheet or the Verbal Consent Form.
3. State:
 - a. Before we start, I would like to take your consent and I will then make a record of this; the record will be stored securely on the university's computer network. I would then like to record the interview, and the recording with an anonymous ID number will be sent for transcription, and then deleted after transcription.
 - b. The interview will remain confidential unless it is possible that you or someone else is at risk, but this will be discussed with you first. If you disclose any information relating to criminal activity or potential professional malpractice, I will need to discuss this information with my senior clinical investigator who may need to report it to the relevant authorities.
 - c. There are no right or wrong answers and we're interested in your honest views. Participants will have different views and experiences and these differences are important to us and we value your unique perspective.
 - d. Finally, if you'd like me to stop the recorder or if you don't want to answer a question, just let me know.
4. Check if they are happy to give verbal consent.

Topics to be explored in the semi-structured interviews, with example questions:

(Additional questions may be added within the topics below, or asked in response to what the participants say in the interviews)

1. **Healthcare professionals' views on, and experiences of, consulting and providing care to patients with suspected COVID-19 infection;** for example:
 - a. How has your practice adapted your usual way of working during the coronavirus outbreak?
 - b. How have you found these adaptations? What challenges, if any, have there been resulting from these adaptations?
 - c. What information, guidance or training have you received to help you care for patients with suspected COVID-19? How useful did you find this information?

2. **Healthcare professionals' views on, and experiences of, trial processes;** for example:
 - a. Do you know how your practice decided to take part in the PRINCIPLE trial? (How was this decision made?)
 - b. How did you identify patients potentially eligible for the trial in your practice? (Who was responsible?)
 - c. Do you know how patients responded to be invited to the trial? What concerns did they have?
 - d. How did you organise patient tests within the trial in your practice? How did this differ from what you would normally do? What did patients think about this process?
 - e. For patients assigned to the control group, what advice or treatment have you offered to patients as part of usual care?
 - f. For patients assigned to the intervention group(s), how have you managed prescriptions for the relevant medication? (e.g. electronic prescriptions?) What other advice or treatment have you offered these patients?
 - g. Do you have any comments about the trial process, or any suggestions for improving the trial processes?
 - h. Is there anything else that you'd like to tell me that we haven't talked about?

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

REC Number: 20/SC/058

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EudraCT Number: 2020-001209-22

Chief Investigator: Professor Christopher Butler, University of Oxford**Researchers conducting interviews:** Dr Sarah Tonkin-Crine and Dr Aleksandra Borek, University of Oxford**HEALTHCARE PROFESSIONAL INTERVIEW – PARTICIPANT INFORMATION SHEET**

We would like to invite you to take part in a telephone interview about your experience of participating in the PRINCIPLE study, which investigated treatments for COVID-19 infection.

Before you decide if you would like to take part, please read this information to understand why this research is being done and what taking part in the interview would involve for you.

If you have questions, would like more information, or would like to take part, contact:

Dr Aleksandra Borek by email: Aleksandra.borek@phc.ox.ac.uk

What is the purpose of this research?

The aim of this interview is to find out healthcare professionals' views and experiences of taking part in the PRINCIPLE trial that aimed to test the impact of selected treatments on recovery from COVID-19. We are interested in finding out what works well and what could be done better to improve future care and future research studies.

Why have I been invited to take part?

You have been invited because you are a healthcare professional who took part in the PRINCIPLE trial. We are intending to interview approximately 25 professionals in total. We will also be interviewing up to 50 patients who took part in the trial.

What will happen to me if I decide to take part?

We would like you to take part in a single telephone interview about your experience. The interview can be done over the telephone (or if you prefer via Skype or Zoom teleconferencing). The interview will be arranged at a time to suit you and should take between 15 and 30 minutes. We will ask you about your experience of taking part in the PRINCIPLE trial, recruiting patients to the trial and your experience of working in primary care during the COVID-19 pandemic.

Consent will be obtained verbally at the start of the interview – please read the Verbal Consent Form available on the PRINCIPLE website [[insert link](#)].

If you are interested in taking part, please contact us using the details at the end of this document.

What are the advantages and disadvantages of taking part?

There are no direct advantages to you. Taking part in interviews about COVID-19 may be distressing for some people. You will be able to skip any interview question if you wish and pause or stop interviews when you wish. Taking part may help us understand how to improve care for, and studies involving, patients with COVID-19.

Will taking part in the interview remain confidential?

Yes. All participants will be given a unique participant number, and the **research data** will be stored with that number, instead of anything that identifies you. Personal details will be held separately and securely on University of Oxford computer network. **The transcript of the audio recording will be de-identified.** To ensure confidentiality, the transcript will not include any names or other defining details that can identify you.

Responsible members of the University of Oxford and the relevant NHS Trusts may be given access to data for monitoring and/or audit of the study to ensure that the research is complying with applicable regulations. Whilst the interview will be treated in confidence, should there be any disclosure relating to the health, safety or wellbeing of yourself or others, it might be necessary to report the matter to appropriate authorities.

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.

We will be using information from you in order to undertake this study and will use the minimum personally-identifiable information possible. We will keep identifiable information about you for less than 3 months after the study has finished. This excludes any research documents with personal information, such as consent forms, which will be held securely at the University of Oxford 10 years after the end of the study.

The audio recording of your interview will be stored securely on the University of Oxford network drive accessed only by the research team. The recording will be sent securely to an independent transcription company who will type up the recording. The company has been assessed and approved for data security by the University of Oxford. Once the recording has been transcribed, it will be deleted by the transcription company and by the research team.

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>. For more details, you can contact Dr Sarah Tonkin-Crine (sarah.tonkin-crine@phc.ox.ac.uk).

What will happen if I don't want to carry on with the interview?

Taking part in the interview is voluntary. You can withdraw from the interview without penalty at any time, without giving a reason and without any negative consequences to you. If you withdraw from the study your data will be deleted, including any data which has been de-identified.

What happens if something goes wrong?

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 study. If you wish to complain or have any concerns, you can contact Dr Sarah Tonkin-Crine (sarah.tonkin-crine@phc.ox.ac.uk). If you remain unhappy or wish to make a formal complaint, please contact the University of Oxford Clinical Trials and Research Governance (CTRG) office on 01865 616480, email ctrg@admin.ox.ac.uk.

What will happen to the results of this interview study?

The results will be published in scientific journals and meetings. A summary of the findings will be made available on the PRINCIPLE study website ([enter website address](#)) and the full report can be made available on request. De-identified transcripts will be stored in an online data repository to be made available for future research where required.

Will I be reimbursed for taking part?

You will be reimbursed £20 in online shopping vouchers for your time to take part in an interview. You will not incur any additional expenses by taking part in this study.

Who is organising and funding the study?

The PRINCIPLE trial ([insert weblink](#)) (including these interviews) is led by researchers at the Nuffield Department of Primary Care Health Sciences at the University of Oxford, who act as research sponsor. It is funded by the UK Research and Innovation / Medical Research Council.

Who has reviewed the study?

All research in the NHS is looked at by an independent group of people, called a Research Ethics Committee (REC), to protect participants' interests. This study has been reviewed and approved by [\[insert ethics committee\]](#).

Where can I get more information?

If you would like to take part in the study or if you have any further questions, please contact:

Contact details: **Dr Aleksandra Borek**
Nuffield Department of Primary Care Health Sciences, University of Oxford
Email: Aleksandra.borek@phc.ox.ac.uk

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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, University of Oxford

Researchers conducting interviews: Dr Sarah Tonkin-Crine and Dr Aleksandra Borek, University of Oxford

HEALTHCARE PROFESSIONAL INTERVIEW – TOPIC GUIDE

Introduction:

1. Introduce self, and thank the participant for agreeing to take part.
2. Check whether participants have any questions about the Participant Information Sheet or the Verbal Consent Form.
3. State:
 - a. Before we start, I would like to take your consent and I will then make a record of this; the record will be stored securely on the university's computer network. I would then like to record the interview, and the recording with an anonymous ID number will be sent for transcription, and then deleted after transcription.
 - b. The interview will remain confidential unless it is possible that you or someone else is at risk, but this will be discussed with you first. If you disclose any information relating to criminal activity or potential professional malpractice, I will need to discuss this information with my senior clinical investigator who may need to report it to the relevant authorities.
 - c. There are no right or wrong answers and we're interested in your honest views. Participants will have different views and experiences and these differences are important to us and we value your unique perspective.
 - d. Finally, if you'd like me to stop the recorder or if you don't want to answer a question, just let me know.
4. Check if they are happy to give verbal consent.

Topics to be explored in the semi-structured interviews, with example questions:

(Additional questions may be added within the topics below, or asked in response to what the participants say in the interviews)

1. **Healthcare professionals' views on, and experiences of, consulting and providing care to patients with suspected COVID-19 infection;** for example:
 - a. How has your practice adapted your usual way of working during the coronavirus outbreak?
 - b. How have you found these adaptations? What challenges, if any, have there been resulting from these adaptations?
 - c. What information, guidance or training have you received to help you care for patients with suspected COVID-19? How useful did you find this information?

2. **Healthcare professionals' views on, and experiences of, trial processes;** for example:
 - a. Do you know how your practice decided to take part in the PRINCIPLE trial? (How was this decision made?)
 - b. How did you identify patients potentially eligible for the trial in your practice? (Who was responsible?)
 - c. Do you know how patients responded to be invited to the trial? What concerns did they have?
 - d. How did you organise patient tests within the trial in your practice? How did this differ from what you would normally do? What did patients think about this process?
 - e. For patients assigned to the control group, what advice or treatment have you offered to patients as part of usual care?
 - f. For patients assigned to the intervention group(s), how have you managed prescriptions for the relevant medication? (e.g. electronic prescriptions?) What other advice or treatment have you offered these patients?
 - g. Do you have any comments about the trial process, or any suggestions for improving the trial processes?
 - h. Is there anything else that you'd like to tell me that we haven't talked about?

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, University of Oxford**Researchers conducting interviews:** Dr Sarah Tonkin-Crine and Dr Aleksandra Borek, University of Oxford

PATIENT INTERVIEW – TOPIC GUIDE

Introduction:

1. Introduce self, and thank the participant for agreeing to take part.
2. Check whether participants have any questions about the Participant Information Sheet or the Verbal Consent Form.
3. State:
 - a. Before we start, I would like to take your consent and I will then make a record of this; the record will be stored securely on the university's computer network. I would then like to record the interview, and the recording with anonymous ID number will be sent for transcription, and then deleted after transcription.
 - b. The interview will remain confidential unless it is possible that you or someone else is at risk, but this will be discussed with you first.
 - c. There are no right or wrong answers and we're interested in your honest views. Participants will have different views and experiences and these differences are important to us and we value your unique perspective.
 - d. Finally, if you'd like me to stop the recorder or if you don't want to answer a question, just let me know.
4. Check if they are happy to give verbal consent.

Topics to be explored in the semi-structured interviews, with example questions:

(Additional questions may be added within the topics below, or asked in response to what the participants say in the interviews)

1. **Patients' views on, and experiences of, consulting for and managing symptoms of suspected COVID-19 infection;** for example:
 - Can you tell me about what led you to contact your general practice when you were ill? What concerns prompted you to consult? Did you have any specific concerns about COVID-19? How long had you had your symptoms for before (asking for) the consultation?
 - How was the consultation done (phone, online)? How did you find it?
 - What advice did you receive on how to manage your symptoms? To what extent was the information and advice provided helpful?
 - What did you think would be the consequences of having the symptoms of COVID-19? (Did you have any concerns about physical consequences? Any about social consequences?)
 - How confident did you feel about being able to manage your symptoms and recovery?

2. Patients' views on, and experiences of, the trial processes; for example:

- How did you find out about the PRINCIPLE trial? How sufficient did you find the information provided to help you decide whether to take part or not?
- What did you think about participating in the trial? (What encouraged you to take part? What discouraged you from taking part? Did you have any particular concerns about taking part? Were they addressed?)
- How did you feel about being assigned to the intervention/control group? (choose as required)
- What do you think of the testing process? How did you feel about being tested by COVID-19? How easy or difficult was it to follow the test instructions?
- How did you find out about the result of the test? How did you feel about the result?
- INTERVENTION GROUP ONLY: When did you receive and start taking the medication? How confident did you feel about being able to take it as instructed? What did you think the medication would do?
- CONTROL GROUP ONLY: How did you care for yourself during your illness? Did you take any medication to help with your symptoms or recovery?
- Is there anything else about any medication or managing your illness that you'd like to share with me?
- How long did you think you think your symptoms would last? [Intervention group: To what extent did you expect the duration of your illness to be affected by the medication?]
- How did you find having to complete the daily diary of symptoms? (How easy or difficult was it? Did you complete it online or by phone?)
- Is there anything else about the trial that you'd like to share?

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, University of Oxford**Researchers conducting interviews:** Dr Sarah Tonkin-Crine and Dr Aleksandra Borek, University of Oxford

PATIENT INTERVIEW – VERBAL CONSENT

Please read the Participant Information Sheet – Patient Interview [\[add link\]](#) if you haven't already done so.

If you agree to participate, at the start of the telephone interview the researcher will read out the following statements and ask if you agree. Your verbal consent will be audio-recorded and a record will be made.

		Tick box
1.	Do you agree to being audio recorded?	
2.	Do you confirm that you have read and understand the Participant Information Sheet for Interviews [version, date] for the above study? Do you confirm that you have had the opportunity to consider the information, ask questions and have had these answered satisfactorily?	
3.	Do you understand that your participation is voluntary and that you are free to withdraw at any time without giving any reason, without my legal rights being affected?	
4.	Do you understand that research data collected during the study may be looked at by designated individuals from the University of Oxford, regulatory authorities or from the NHS Trusts where it is relevant to you taking part in this study? Do you give permission for these individuals to access my data?	
5.	Do you agree to take part in this study?	



WRITTEN RECORD OF VERBAL CONSENT

Date of consent:

Name of the Participant giving consent:

Name of the Researcher recording consent:

Signature of Researcher:

A copy of this record will be emailed to the participant.

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

Email: **XXXX**

MHRA

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

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

09/04/2020

Dear Prof C Butler

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

Our Reference:	CTA 21584/0426/001-0003
Eudract Number:	2020-001209-22
Product:	Plaquenil-Hydroxychloroquine, Azithromycin
Protocol Number:	PRINCIPLE
Substantial Amendment Code Number:	Code Number: SA2 Version: Date: 2020/04/07

ACKNOWLEDGEMENT OF AMENDMENT

Thank you for your notice of amendment, received on 09/04/2020. The information you provided to support your request is complete and therefore your request is valid.

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

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

Yours sincerely,

Submissions
MHRA



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

Chief Investigator: Professor Chris Butler

Tel: +44 (0)1865 289670

Email: christopher.butler@phc.ox.ac.uk

Address: Primary Care Clinical Trials Unit

Gibson Building, 1st Floor, Radcliffe Observatory Quarter, Woodstock Road, Oxford. OX2 6GG

Date: 8th April 2020

REC Substantial Amendment 2

IRAS ID: 281958

Dear REC committee members,

Subject: REC Substantial Amendment 2 for PRINCIPLE Trial in relation to COVID-19

Please find attached the Notification of a Substantial Amendment for the trial entitled: Platform Randomised trial of INterventions against COVID-19 In older people (PRINCIPLE). The amendments are described and justified below.

The protocol and other associated documents have been updated/created in line with the key changes detailed below.

Summary of key proposed changes to PRINCIPLE Trial: Amendment 2.

1 Inclusion of a third trial arm in the PRINCIPLE platform trial.

Rationale: The PRINCIPLE trial aims to determine the effectiveness of interventions that are suitable for patients at higher risk of complications from COVID who are managing in the community at the time of enrolment. The goal is to identify interventions that will reduce the need for hospital admission and speed recovery, and which could be rapidly scaled up.

The current comparison is:

1. Usual care

Vs.

2. Usual care plus hydroxychloroquine 200mg twice a day for 7 days.

PRINCIPLE is a platform trial, conducted under a master protocol that which allows for the addition of further arms as the trial progresses. We have been interacting with many GPs and also with the UK-wide Primary Care Research Network, and all are crying out for evidence about the role of antibiotics in exactly the sort of patients we are recruiting in this COVID-19 priority trial.

Azithromycin has antiviral properties, treats community acquired pneumonia, exacerbations of chronic obstructive airways disease, and so might prevent the need for hospitalisation and speed recovery (please see summary in Appendix 1: Usual care plus azithromycin arm). Azithromycin is already used in primary care and could be made widely available, if effective. This drug has been considered by the "Expert Review of Covid-19 Therapeutics for Immediate Deployment" convened by Sir Patrick Vallance, and was given the green light for deployment as a new arm in the PRINCIPLE Trial by the Urgent Public Health Prioritisation group on 5.04.2020. Azithromycin and antibiotics are already being widely prescribed in the UK and in other countries for patients eligible for PRINCIPLE, despite no evidence for benefit from randomised controlled trials.

Thus, we would like to make the trial:

1. Usual care

Vs.

2. Usual care plus hydroxychloroquine 200mg twice a day for 7 days.

Vs

3. Usual care plus azithromycin 500mg daily for 3 days.

We are obviously concerned about antimicrobial stewardship, and the potentially unnecessary use of antibiotics and the development of antimicrobial resistance. However, there is in-vitro evidence for antiviral action of azithromycin, due to which it is already being widely used in Italy and other settings for COVID-19 and evaluating it under current circumstances will be of considerable importance. Antibiotics are being widely prescribed for this condition in the UK. Many serious sequelae of COVID-19 arise from secondary bacterial infection. If proven to be effective, then the drug can be deployed for patient benefit and to enhance care sustainability. However, if the trial demonstrates no benefit, then that would lead to major gains in antibiotic stewardship as well, and avoid putting patients at unnecessary risk from side effects of the drug. To facilitate ease of review, and in common with protocols for platform trials, we have included the new intervention arm as an appendix (Appendix 1: Usual care plus azithromycin arm). Amendments not related to this arm are detailed in the master protocol and summarised below.

2. Study medication may be repackaged and distributed by an accredited licensed, central facility, who will compile study packs for participants. Once signed off by a Qualified Person, study packs will then be delivered to the Primary Care Clinical Trials Unit, or clinical sites, for further distribution to study participants as soon as they are included.

Rationale: So far, we have only been able to get swabs, information materials and study drug to participants by first delivering to their general practice, who then distribute to enrolled participants (or their representative). Hydroxychloroquine is delivered to practices in boxes containing 60 tablets in total, but subdivided into 4 sachets of 15 tablets each. The current protocol allows a medically qualified person in the practice to take one sachet of 15 tablets from the box and repackage it in a properly labelled envelope and issue it to patients (according to randomisation). If all of this could all be done centrally, and delivered to the patient directly, it would bypass the GP practice, thereby increasing efficiency by removing an extra step in the trial process. Furthermore, it would take a considerable administrative and delivery burden off front line clinicians and practices. This would also allow patients recruited through COVID-19 'Hot Hub' practices and NHS 111 to have study materials delivered directly to them (see below). If we do have a central facility issuing medication and study materials directly to patients, that would not stop practices already set up continuing to use existing processes to deliver the study, so study drug would not be wasted.

3. Inclusion of a second swab at Day 5.

Where possible, we also now intend to obtain a swab from participants on day 5 to estimate viral shedding between study arms. Our secondary outcomes rely on patient self-report to a large measure, and having an objective virologic end point will add to study rigour, and also provide information about the impact of trial interventions on viral shedding, which will be of considerable public health importance. While there are concerns nationally regarding shortages of swabs, PHE are resolving these and have prioritised swab supply for PRINCIPLE. Should this be insufficient we have



contingency plans through alternative international sources. If, despite this, swabs are in short supply, we will prioritise the enrolment swab.

4. Inclusion of a trial process evaluation

This is, to say the least, an unusual clinical trial conducted in unusual circumstances. The experiences of participants and contributing clinicians will be of great interest to understanding the results that this trial produces, and also to those who might be planning analogous research. We therefore propose to include a process evaluation of the trial, which will involve interviews with a limited number of patients who have completed the trial, and involve interviews with a limited number of patients who have completed the trial, and their respective clinician. This will be a 'light-touch' evaluation which will not interfere with the trial itself or impact negatively upon care delivery.

5. Inclusion of the WHO-5 Mental Health Wellbeing questionnaire

It is becoming increasingly apparent that a major impact of COVID-19 infection is on mental health and well-being. We therefore plan to determine whether interventions have an effect on this outcome which we will measure using the WHO mental health well-being questionnaire which is a validated five question scale. This is an efficient questionnaire which will not add significantly to the respondent burden, but will generate unique and critically important data to allow us to make a far more holistic assessment of the impact of interventions.

6. Offer of opportunity for a sub sample to be more intensively tested and their household contacts to be tested.

Colleagues at Imperial College, in collaboration with the Oxford RCGP RSC, are planning a study of people with COVID-19 and to follow them up more intensively for immunological reasons and to determine spread within households. This will be governed by an approved, separate protocol. However, we plan to offer patients in a limited geographical area in London, who consent to be part of PRINCIPLE, to be put in touch with the research team at Imperial College to discuss participation in that study further. In this way, PRINCIPLE might benefit from obtaining an additional set of objective measures relating to immunological response to treatment (or not) with the PRINCIPLE study interventions.

7. Inclusion of a Trial Steering Committee

Based on a discussion we had with the Data Monitoring and Safety Committee (DMSC) on 2nd April 2020, we have decided to have a Trial Steering Committee to the trial. This is because due to the nature of the study design that treatment allocation will not be blinded to the DMSC. The DMSC would prefer to have an independent committee that they could report their recommendation to.

8. Permission to open in Scotland, Northern Ireland and Wales.

Please see Table 1 below for a list of all documents submitted for your review (those highlighted are new documents).

Yours sincerely,

Dr Hannah Swayze

On behalf of Professor Christopher Butler

Table 1: List of documentation submitted to REC

Document	Version	Date
Protocol	2.0	07.04.20
Protocol (tracked changes)	2.0	07.04.20
PIS	2.0	08.04.20
PIS Appendices	1.0	07.04.20
Participant Consent Form	1.1	07.04.20
PRINCIPLE GP letter (and tracked changes)	1.1	07.04.20
Test Message Info	1.1	07.04.20
PRINCIPLE_Baseline CRF (and tracked changes version)	1.1	07.04.20
PRINCIPLE_Eligibility CRF (and tracked changes version)	1.4	08.04.20
PRINCIPLE_Screening CRF (and tracked changes version)	1.4	08.04.20
PRINCIPLE_Daily Diary (and tracked changes version)	1.1	07.04.20
PRINCIPLE_Call CRF (and tracked changes version)	1.1	07.04.20
PRINCIPLE_IMP_Label form (250mg)	1.0	07.04.20
PRINCIPLE_IMP_Label form (500mg)	1.0	07.04.20
Participant new study invite	1.0	07.04.20
Participant Process evaluation invite	1.0	07.04.20
PRINCIPLE Information for participants (and tracked changes version)	1.1	08.04.20
Azithromycin Participant card	1.0	07.04.20
Participant Medication Receipt	1.0	07.04.20
Azithromycin SmPC	N/A	
PRINCIPLE_Interviews_HCP_Invitation	1.0	08.04.20
PRINCIPLE_Interviews_HCP_PIS	1.0	08.04.20
PRINCIPLE_Interviews_HCP_Topic	1.0	08.04.20
PRINCIPLE_Interviews_HCP_Verbal Consent	1.0	08.04.20
PRINCIPLE_Interviews_Patient_PIS	1.0	08.04.20
PRINCIPLE_Interviews_Patient_Topic Guide	1.0	08.04.20
PRINCIPLE_Interviews_Patient_Verbal Consent	1.0	08.04.20

Hannah Swayze

From: berkshire.rec@hra.nhs.uk <noreply@harp.org.uk>
Sent: 14 April 2020 16:16
To: Christopher Butler; CTRG Sponsorship Correspondence
Cc: Hannah Swayze
Subject: IRAS PROJECT ID 281958, REC Reference 20/SC/0158 Confirmation of favourable opinion for substantial amendment
Attachments: IRAS 281958 SL32_Favourable_opinion_of_a_substantial_amendment-9.pdf

Dear Dr Butler

IRAS project ID:	281958
REC reference:	20/SC/0158
Short Study title:	PRINCIPLE
Date complete amendment submission received:	09 April 2020
Amendment No./ Sponsor Ref:	SA2
Amendment Date:	07 April 2020
Amendment Type:	Substantial
Outcome of HRA Assessment	This email also constitutes HRA and HCRW Approval for the amendment, and you should not expect anything further.

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

HRA and HCRW Approval Status

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

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

User Feedback

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

<http://www.hra.nhs.uk/about-the-hra/governance/quality-assurance/>.

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

20/SC/0158/AM02 Please quote this number on all correspondence

Kind regards

Alison Doherty

Approvals Administrator

Health Research Authority

Bristol REC Centre | Whitefriars | BS1 2NT

T. 020 7104 8049

E. berkshire.rec@hra.nhs.uk

W. www.hra.nhs.uk

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



MHRA

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

09/04/2020

Dear Prof C Butler,

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

Our Reference:	CTA 21584/0426/001-0003
Eudract Number:	2020-001209-22
Product:	Plaquenil-Hydroxychloroquine, Azithromycin
Protocol number:	PRINCIPLE
Substantial Amendment Code Number:	Code Number: SA2 Version: Date: 2020/04/07

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 09/04/2020.

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

14 April 2020

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

Dear Dr Butler

Study title: Platform Randomised trial of INterventions against COVID-19 In older peOPLE
REC reference: 20/SC/0158
Protocol number: PRINCIPLE
EudraCT number: 2020-001209-22
Amendment number: SA2
Amendment date: 07 April 2020
IRAS project ID: 281958

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

Ethical opinion

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

Approved documents

The documents reviewed and approved at the meeting were:

<i>Document</i>	<i>Version</i>	<i>Date</i>
Annex 2: Notification of Amendment [AmendmentFormMHRAEudract_ReadyForSubmission (1)]	SA2	07 April 2020
Cover Letter [REC SA2 cover letter 07.04.20]		07 April 2020
GP/consultant information sheets or letters [PRINCIPLE GP letter v1.1 07APR20_tc]	1.1	07 April 2020
Letter from sponsor [SA2 Sponsor Approval 09.04.20]		09 April 2020
Letters of invitation to participant [PRINCIPLE TRIAL - Participant new study invite v1.0 07.04.2020]	1.0	07 April 2020
Other [PRINCIPLE TRIAL - Participant Medication Receipt v1.0	1.0	07 April 2020

07.04.2020]		
Other [PRINCIPLE TRIAL - Process evaluation invite v1.0 07.04.2020]	1.0	07 April 2020
Other [PRINCIPLE TRIAL - text message info version 1.1 07.04.2020]	1.1	07 April 2020
Other [PRINCIPLE_Baseline_v1.1_07Apr2020]	1.1	07 April 2020
Other [PRINCIPLE_Call CRF_v1.1_07Apr2020]	1.1	07 April 2020
Other [PRINCIPLE_Eligibility Information CRF_v1.4_08Apr2020]	1.4	08 April 2020
Other [PRINCIPLE_Screening_v1.4_08Apr2020]	1.4	08 April 2020
Other [MHRA Notice of Acceptance of Amendment]		09 April 2020
Participant consent form [PRINCIPLE Consent Form V1.1_07.4.2020_TT]	1.1	07 April 2020
Participant information sheet (PIS) [Substudy PIS]	1	08 April 2020
Research protocol or project proposal [Principle Protocol v2.0 07.04.2020 tracked]	2.0	07 April 2020
Sample diary card/patient card [PRINCIPLE_Daily Diary_v1.1_07Apr2020]	1.1	07 April 2020

Membership of the Committee

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

Working with NHS Care Organisations

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

Statement of compliance

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

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

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

HRA Learning

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

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



Mr David Carpenter
Chair

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

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

Copy to: N/A N/A CTRG

South Central - Berkshire Research Ethics Committee

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

Committee Members:

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

Also in attendance:

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

Hannah Swayze

From: Elaine Chick
Sent: 09 April 2020 11:46
To: Hannah Swayze
Cc: rpm@oxfordjro.org; Emma Ogburn
Subject: FW: PRINCIPLE Substantial Amendment 2 EudraCT: 2020-001209-22

Dear Hannah

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

- Email documents to the REC that originally reviewed the study. The REC will review the amendments and categorise it. If necessary, they will transfer the amendments internally to HRA for them to review as well.
 - If the 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 (ctrg@admin.ox.ac.uk) so the sponsor has final documents and is included in subsequent correspondence

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

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

Best wishes
Elaine



Elaine Chick

Deputy Head CTRG, Research Services
University of Oxford

Boundary Brook House, Headington, OX3 7LQ Tel: 01865 616481 Elaine.chick@admin.ox.ac.uk
<https://researchsupport.admin.ox.ac.uk/ctrg>

PID14903-A002-SP001-AC001

Participant identifier

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Participant initials

--	--	--

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"/>
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.	What date did you start to feel unwell with this illness (DD/MMM/YYYY)?	_ _ / _ _ _ / _ _ _ _
12.	Have you taken antibiotics since your illness started?	Yes <input type="checkbox"/> No <input type="checkbox"/>

Participant identifier

--	--	--	--	--	--	--

Participant initials

--	--	--

Baseline CRF

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

Wellbeing							
14.	Please indicate for each of the 5 statements which is closest to how you have been feeling over the past 2 weeks.						
14a)	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
14b)	... I have felt cheerful and in good spirits	5	4	3	2	1	0
14c)	... I have felt calm and relaxed	5	4	3	2	1	0
14d)	... I have felt active and vigorous	5	4	3	2	1	0
14e)	... I woke up feeling fresh and rested	5	4	3	2	1	0
14f)	... my daily life has been filled with things that interest me	5	4	3	2	1	0

Completed by: Print nameSignDate __/ __/ ____

Participant identifier

--	--	--	--	--	--	--

Participant initials

--	--	--

Day 7, 14 and 28 Call CRF

6.	Has anybody else in your/participant's house become unwell today with a respiratory illness?	Yes	<input type="checkbox"/>	No	<input type="checkbox"/>
----	--	-----	--------------------------	----	--------------------------

As you/participant do not feel recovered, please can you rate the following symptoms:

7.	Fever	No problem / Mild problem / Moderate problem / Major problem
8.	Cough	No problem / Mild problem / Moderate problem / Major problem
9.	Shortness of breath	No problem / Mild problem / Moderate problem / Major problem
10.	Muscle ache	No problem / Mild problem / Moderate problem / Major problem
11.	Nausea / Vomiting	No problem / Mild problem / Moderate problem / Major problem

12.	Do you have any other symptoms with your current illness:		

Other Healthcare Services

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

Notification of Death—TRIAL TEAM USE ONLY

14.	Has the trial team been notified of the participant's death?	Yes	<input type="checkbox"/>	No	<input type="checkbox"/>
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Participant identifier

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Participant initials

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Day 7, 14 and 28 Call CRF

Wellbeing (to be completed on days 14 and 28 ONLY)

15.	Please indicate for each of the 5 statements which is closest to how you have been feeling over the past 2 weeks.						
15a)	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
15b)	... I have felt cheerful and in good spirits	5	4	3	2	1	0
15c)	... I have felt calm and relaxed	5	4	3	2	1	0
15d)	... I have felt active and vigorous	5	4	3	2	1	0
15e)	... I woke up feeling fresh and rested	5	4	3	2	1	0
15f)	... my daily life has been filled with things that interest me	5	4	3	2	1	0

Completed by: Print nameSignDate __ / __ / __

Participant identifier

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Participant initials

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Daily Diary

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

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

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

Participant identifier

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Participant initials

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Daily Diary

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

Completed by: Print nameSignDate __ / __ / __

Participant identifier

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Participant initials

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Daily Diary

Healthcare Services		
13.	Have you had contact with the following healthcare services in the last 24 hours? Please answer Yes or No.	
13a.	GP	Yes <input type="checkbox"/> No <input type="checkbox"/>
13b.	Other primary Care services (e.g. walk-in services/pharmacist)	Yes <input type="checkbox"/> No <input type="checkbox"/>
13c.	NHS 111	Yes <input type="checkbox"/> No <input type="checkbox"/>
13d.	A&E	Yes <input type="checkbox"/> No <input type="checkbox"/>
13f.	Other	Yes <input type="checkbox"/> No <input type="checkbox"/>
13f. i)	If 'Other' please specify: _____	
14	Hospital	Yes <input type="checkbox"/> No <input type="checkbox"/>
14a.	If yes, what date did you go to hospital (DD/MMM/YYYY)?	_ _ / _ _ _ / _ _ _ _
14b.	Were you admitted overnight?	Yes <input type="checkbox"/> No <input type="checkbox"/>
14c.	How many nights did you stay in hospital?	<input style="width: 20px;" type="text"/> <input style="width: 20px;" type="text"/> nights
14d.	Did you stay in an Intensive Care Unit during your stay in hospital?	Yes <input type="checkbox"/> No <input type="checkbox"/>
14e.	Did you receive oxygen while in hospital?	Yes <input type="checkbox"/> No <input type="checkbox"/>
14f.	Did you receive mechanical ventilation while in hospital?	Yes <input type="checkbox"/> No <input type="checkbox"/>

Participant identifier

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Participant initials

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Daily Diary

Wellbeing (to be completed on days 14 and 28 ONLY)							
15.	Please indicate for each of the 5 statements which is closest to how you have been feeling over the past 2 weeks.						
15a)	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
15b)	... I have felt cheerful and in good spirits	5	4	3	2	1	0
15c)	... I have felt calm and relaxed	5	4	3	2	1	0
15d)	... I have felt active and vigorous	5	4	3	2	1	0
15e)	... I woke up feeling fresh and rested	5	4	3	2	1	0
15f)	... my daily life has been filled with things that interest me	5	4	3	2	1	0

Completed by: Print nameSignDate __ / __ / __

Participant identifier

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Participant initials

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Eligibility Information CRF

1.	Participant's NHS number: _____	
3.	<p>Participant is ≥65 years old, or aged ≥50 with at least one of the comorbidities listed below?</p> <ul style="list-style-type: none"> • Weakened immune system due to a serious illness or infection • Heart disease or hypertension • Asthma or lung disease • Diabetes not treated with insulin • Mild hepatic impairment • Stroke or neurological problem 	Yes <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.	<p>Has had a previous adverse reaction to any of the following, that you are aware of:</p> <ul style="list-style-type: none"> • Azithromycin • Chloroquine • Hydroxychloroquine • Any other macrolides or ketolides 	Yes <input type="checkbox"/> No <input type="checkbox"/>

Participant identifier

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Participant initials

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Eligibility Information CRF

13.	<p>Is currently taking any of the following:</p> <ul style="list-style-type: none"> • Amiodarone • Azithromycin • Chloroquine • Ciclosporin • Digoxin • Hydroxychloroquine • Penicillamine • Sotalol • Any other macrolides or ketolides • Any ergot derivatives (e.g. bromocriptine, cabergoline, ergotamine, ergometrine, methysergide) 	Yes <input type="checkbox"/> No <input type="checkbox"/>
14.	Has a retinal disease (e.g. macular degeneration)?	Yes <input type="checkbox"/> No <input type="checkbox"/>
15.	Has a known severe hepatic impairment?	Yes <input type="checkbox"/> No <input type="checkbox"/>
16.	Has a known severe renal impairment?	Yes <input type="checkbox"/> No <input type="checkbox"/>
17.	Is the patient currently taking antibiotics for an acute condition?	Yes <input type="checkbox"/> No <input type="checkbox"/>
18.	Is the patient currently admitted to hospital?	Yes <input type="checkbox"/> No <input type="checkbox"/>
19.	Known congenital or documented QT prolongation	Yes <input type="checkbox"/> No <input type="checkbox"/>
20.	Allergy to soya or peanuts	Yes <input type="checkbox"/> No <input type="checkbox"/>
21.	Has previously taken part in the PRINCIPLE trial?	Yes <input type="checkbox"/> No <input type="checkbox"/>
22.	Comments: _____ _____	

Completed by: Print nameSignDate __/__/____

Participant identifier

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Participant initials

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Screening CRF

1.	Are you are willing to give informed consent for participation in the study?	Yes <input type="checkbox"/> No <input type="checkbox"/>
2.	<p>Do you have symptoms of possible COVID-19 in the community which have been present for less than 8 days?</p> <p>Defined: A new continuous cough - this means coughing a lot for more than an hour, or 3 or more coughing episodes in 24 hours (if you usually have a cough, it may be worse than usual)</p> <p><i>and/or</i></p> <p>A high temperature - this means you feel hot to touch on your chest or back (you do not need to take your temperature)</p>	Yes <input type="checkbox"/> No <input type="checkbox"/>
3.	<p style="color: red;">Are you aged 65 years old or over, or aged 50 years or older with at least one of the comorbidities/conditions listed below?</p> <ul style="list-style-type: none"> • Weakened immune system due to a serious illness or medication (e.g. chemotherapy) • Heart disease or hypertension • Asthma or lung disease • Diabetes not treated with insulin • Liver disease • Stroke or neurological problem 	Yes <input type="checkbox"/> No <input type="checkbox"/>
4.	Are you pregnant or planning on becoming pregnant within the next few weeks?	Yes <input type="checkbox"/> No <input type="checkbox"/>
5.	Are you breastfeeding or planning on starting during the course of the trial?	Yes <input type="checkbox"/> No <input type="checkbox"/>
6.	Do you have porphyria?	Yes <input type="checkbox"/> No <input type="checkbox"/>
7.	Do you take insulin for diabetes?	Yes <input type="checkbox"/> No <input type="checkbox"/>
8.	Do you have a G6PD deficiency?	Yes <input type="checkbox"/> No <input type="checkbox"/>
9.	Do you have myasthenia gravis?	Yes <input type="checkbox"/> No <input type="checkbox"/>
10.	Do you have severe psoriasis?	Yes <input type="checkbox"/> No <input type="checkbox"/>

Participant identifier

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Participant initials

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Screening CRF

11.	Do you have a history of epilepsy?	Yes <input type="checkbox"/> No <input type="checkbox"/>
12.	Have you had a previous allergic (adverse reaction) to any of the following: <ul style="list-style-type: none"> • Azithromycin • Chloroquine • Hydroxychloroquine • Any other antibiotics (not including penicillin) 	Yes <input type="checkbox"/> No <input type="checkbox"/>
13.	Are you currently taking any of the following: <ul style="list-style-type: none"> • Amiodarone • Chloroquine • Ciclosporin • Digoxin • Hydroxychloroquine • Penicillamine • Sotalol 	Yes <input type="checkbox"/> No <input type="checkbox"/>
14.	Do you have a disease which affects the retina of the eye (e.g. macular degeneration)?	Yes <input type="checkbox"/> No <input type="checkbox"/>
15.	Are you currently taking antibiotics for a recently diagnosed illness?	Yes <input type="checkbox"/> No <input type="checkbox"/>
16.	Are you currently admitted in hospital?	Yes <input type="checkbox"/> No <input type="checkbox"/>
17.	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"/>
18.	Do you have an allergy to soya or peanuts?	Yes <input type="checkbox"/> No <input type="checkbox"/>
19.	Have you previously participated in the PRINCIPLE trial?	Yes <input type="checkbox"/> No <input type="checkbox"/>

Completed by: Print nameSignDate __ / __ / __



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**. Azithromycin can come in 250mg or 500mg tablets. If you have been given 250mg tablets, you should take TWO tablets a day for 3 days, a total of 6 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.

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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PRIMARY CARE
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.



Instructions for participants

Thank you for taking part in the PRINCIPLE trial.

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

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

Contact us

If you have any questions, please contact us on:

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

Telephone: 0800 138 0880

Summary

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

Azithromycin 500mg Tablets

Summary of Product Characteristics Updated 25-Sep-2019 | Sandoz Limited

1. Name of the medicinal product

Azithromycin 500 mg Tablets

2. Qualitative and quantitative composition

Each film-coated tablet contains: 500 mg of azithromycin (as monohydrate)

Excipient(s) with known effect:

Each tablet contains 0.36 mg soya lecithin.

For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Film-coated tablet

White to off-white, oblong, film-coated tablet, deep break line on one side and score line on other side. The tablet can be divided into equal doses.

4. Clinical particulars

4.1 Therapeutic indications

Azithromycin tablets can be applied for the treatment of the following infections, when caused by microorganisms sensitive to azithromycin (see sections 4.4 and 5.1):

- acute bacterial sinusitis (adequately diagnosed)
- acute bacterial otitis media (adequately diagnosed)
- pharyngitis, tonsillitis
- acute exacerbation of chronic bronchitis (adequately diagnosed)
- mild to moderately severe community acquired pneumonia
- skin and soft tissue infections
- uncomplicated *Chlamydia trachomatis* urethritis and cervicitis

Considerations should be given to official guidance on the appropriate use of antibacterial agents.

4.2 Posology and method of administration

Posology

Adults

In uncomplicated *Chlamydia trachomatis* urethritis and cervicitis the dose is 1000 mg as a single oral dose.

For all other indications the dose is 1500 mg, to be administered as 500 mg per day for three consecutive days. As an alternative the same total dose (1500 mg) can also be administered over a period of five days with 500 mg on the first day and 250 mg on the second to the fifth day.

Elderly people

The same dose as in adult patients is used for older people. Since elderly people can be patients with ongoing proarrhythmic conditions a particular caution is recommended due to the risk of developing cardiac arrhythmia and torsades de pointes (see section 4.4).

Paediatric population

Azithromycin tablets should only be administered to children weighing more than 45 kg when normal adult dose should be used. For children under 45 kg other pharmaceutical forms of azithromycin, e.g. suspensions, may be used.

In patients with renal impairment: No dose adjustment is necessary in patients with mild to moderate renal impairment (GFR 10-80 ml/min) (see section 4.4).

In patients with hepatic impairment: A dose adjustment is not necessary for patients with mild to moderately impaired liver function (see section 4.4).

Method of administration

Azithromycin Tablets should be given as a single daily dose. The tablets may be taken with food.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Hypersensitivity

As with erythromycin and other macrolides, rare 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 medicinal product 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.

Since 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 ergotamine derivatives, ergotism has been precipitated by coadministration of some macrolide antibiotics. There are no data concerning the possibility of an interaction between ergotamine derivatives and azithromycin. However, because of the theoretical possibility of ergotism, azithromycin and ergot derivatives should not be co-administered (see section 4.5).

Cardiovascular events

Prolonged cardiac repolarisation and QT interval, imparting a risk of developing cardiac arrhythmia and torsades de pointes, have been seen in treatment with other macrolides including azithromycin (see section 4.8). Therefore as the following situations may lead to an increased risk for ventricular arrhythmias (including torsade de pointes) which can lead to cardiac arrest, azithromycin should be used with caution in patients with ongoing proarrhythmic conditions (especially women and elderly patients) such as patients:

- With congenital or documented QT prolongation.
- Currently receiving treatment with other active substances known to prolong QT interval such as antiarrhythmics of class IA (quinidine and procainamide) and class III (dofetilide, amiodarone and sotalol), cisapride and terfenadine; antipsychotic agents such as pimozone; antidepressants such as citalopram; and fluoroquinolones such as moxifloxacin and levofloxacin
- With electrolyte disturbance, particularly in cases of hypokalaemia and hypomagnesaemia
- With clinically relevant bradycardia, cardiac arrhythmia or severe cardiac insufficiency.

Epidemiological studies investigating the risk of adverse cardiovascular outcomes with macrolides have shown variable results. Some observational studies have identified a rare short term risk of arrhythmia, myocardial infarction and cardiovascular mortality associated with macrolides including azithromycin. Consideration of these findings should be balanced with treatment benefits when prescribing azithromycin.

Clostridium difficile associated diarrhoea (CDAD) has been reported with the 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 antimicrobial agents. In case of CDAD anti-peristaltics are contraindicated.

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).

Safety and efficacy for the prevention or treatment of *Mycobacterium avium* complex in children have not been established.

The following should be considered before prescribing azithromycin:

Azithromycin film-coated tablets are not suitable for treatment of severe infections where a high concentration of the antibiotic in the blood is rapidly needed.

Azithromycin is not the first choice for the empiric treatment of infections in areas where the prevalence of resistant isolates is 10% or more (see section 5.1).

In areas with a high incidence of erythromycin A resistance, it is especially important to take into consideration the evolution of the pattern of susceptibility to azithromycin and other antibiotics.

As for other macrolides, high resistance rates of *Streptococcus pneumoniae* (> 30 %) have been reported for azithromycin in some European countries (see section 5.1). This should be taken into account when treating infections caused by *Streptococcus pneumoniae*.

Pharyngitis/ tonsillitis

Azithromycin is not the substance of first choice for the treatment of pharyngitis and tonsillitis caused by *Streptococcus pyogenes*. For this and for the prophylaxis of acute rheumatic fever penicillin is the treatment of first choice.

Sinusitis

Often, azithromycin is not the substance of first choice for the treatment of sinusitis.

Acute otitis media

Often, azithromycin is not the substance of first choice for the treatment of acute otitis media.

Skin and soft tissue infections

The main causative agent of soft tissue infections, *Staphylococcus aureus*, is frequently resistant to azithromycin. Therefore, susceptibility testing is considered a precondition for treatment of soft tissue infections with azithromycin.

Infected burn wounds

Azithromycin is not indicated for the treatment of infected burn wounds.

Sexually transmitted disease

In case of sexually transmitted diseases a concomitant infection by *T. palladium* should be excluded.

Neurological or psychiatric diseases

Azithromycin should be used with caution in patients with neurological or psychiatric disorders.

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

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

Azithromycin Tablets contains soya lecithin which might be a source of soya protein and should therefore not be taken in patients allergic to soya or peanut due to the risk of hypersensitivity reactions.

Azithromycin Tablets contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

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 (see section 4.8).

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 (see section 4.4).

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.

4.6 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 (see section 5.3). 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.

Breast-feeding

Azithromycin has been reported to be secreted into human breast milk, but there are no adequate and well-controlled clinical studies in nursing women that have characterized the pharmacokinetics of azithromycin excretion into human breast milk.

Because it is not known whether azithromycin may have adverse effects on the breast-fed infant, nursing should be discontinued during treatment with azithromycin. Among other things diarrhoea, fungus infection of the mucous membrane as well as sensitisation is possible in the nursed infant. It is recommended to discard the milk during treatment and up until 2 days after discontinuation of treatment. Nursing may be resumed thereafter.

Fertility

In fertility studies conducted in rat, reduced pregnancy rates were noted following administration of azithromycin. The relevance of this finding to humans is unknown.

4.7 Effects on ability to drive and use machines

There is no evidence to suggest that azithromycin may have an effect: on a patient's ability to drive or operate machinery. Visual impairment and vision blurred may have an effect on a patient's ability to drive or operate machinery (section 4.8).

4.8 Undesirable effects

The table below lists the adverse reactions identified through clinical 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 ($< 1/10,000$); 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:

System Organ Class	Frequency	Adverse reaction
Infections and infestations	Uncommon	Candidiasis Vaginal infection Pneumonia Fungal infection Bacterial infection Pharyngitis Gastroenteritis Respiratory disorder Rhinitis Oral candidiasis
	Not known	<i>Pseudomembranous colitis</i> (see section 4.4)
Blood and lymphatic system disorders	Uncommon	Leukopenia Neutropenia Eosinophilia
	Not known	Thrombocytopenia Haemolytic anaemia
Immune system disorders	Uncommon	Angioedema Hypersensitivity
	Not known	<i>Anaphylactic reaction</i> (see section 4.4)
Metabolism and nutrition disorders	Uncommon	Anorexia
Psychiatric disorders	Uncommon	Nervousness Insomnia
	Rare	Agitation Depersonalisation
	Not known	<i>Aggression</i> <i>Anxiety</i> Delirium Hallucination
Nervous system disorders	Common	Headache
	Uncommon	Dizziness

		Somnolence Dysgeusia Paraesthesia
	Not known	<i>Syncope, convulsion</i> Hypoaesthesia <i>Psychomotor hyperactivity</i> <i>Anosmia</i> <i>Ageusia</i> <i>Parosmia</i> <i>Myasthenia gravis</i> (see section 4.4).
Eye disorders	Uncommon	Visual impairment
	Not known	Blurred vision
Ear and labyrinth disorders	Uncommon	Ear disorder Vertigo
	Not known	Hearing impairment including deafness and/or tinnitus
Cardiac disorders	Uncommon	Palpitations
	Not known	<i>Torsades de pointes</i> (see section 4.4) <i>Arrhythmia</i> (see section 4.4) including <i>ventricular tachycardia</i> <i>electrocardiogram QT prolonged</i> (see section 4.4)
Vascular disorders	Uncommon	Hot flush
	Not known	<i>Hypotension</i>
Respiratory, thoracic and mediastinal disorders	Uncommon	Dyspnoea Epistaxis
Gastrointestinal disorders	Very common	Diarrhoea
	Common	Vomiting Abdominal pain Nausea
	Uncommon	Constipation Flatulence Dyspepsia Gastritis Dysphagia Abdominal distension Dry mouth Eructation Mouth ulceration Salivary hypersecretion
	Not known	<i>Pancreatitis</i> <i>Tongue discolouration</i>

Hepatobiliary disorders	Uncommon	Hepatitis
	Rare	Hepatic function abnormal Jaundice cholestatic
	Not known	<i>Hepatic failure</i> (which has rarely resulted in death) (see section 4.4)* <i>Hepatitis fulminant</i> <i>Hepatic necrosis</i>
Skin and subcutaneous tissue disorders	Uncommon	Rash Pruritus Urticaria Dermatitis Dry skin Hyperhidrosis
	Rare	Photosensitivity reaction Acute generalised exanthematous pustulosis (AGEP)
	Not known	Steven-Johnson syndrome <i>Toxic epidermal necrolysis</i> <i>Erythema multiforme</i>
Musculoskeletal and connective tissue disorders	Uncommon	Osteoarthritis Myalgia Back pain Neck pain
	Not known	Arthralgia
Renal and urinary disorders	Uncommon	Dysuria Renal pain
	Not known	Renal failure acute Nephritis interstitial
Reproductive system and breast disorders	Uncommon	Metrorrhagia Testicular disorder
General disorders and administration site conditions	Uncommon	Oedema Asthenia Malaise Fatigue Face oedema Chest pain Pyrexia Pain Peripheral oedema
Investigations	Common	Lymphocyte count decreased Eosinophil count increased Blood bicarbonate decreased Basophils increased

	Uncommon	Monocytes increased Neutrophils increased Aspartate aminotransferase increased Alanine aminotransferase increased Blood bilirubine increased Blood urea increased Blood creatinine increased Blood potassium abnormal Blood alkaline phosphatase increased Chloride increased Glucose increased Platelets increased Hematocrit decreased Bicarbonate increased Abnormal sodium
Injury and poisoning	Uncommon	Post procedural complication

* which has rarely resulted in death

Adverse reactions possibly or probably related to Mycobacterium Avium Complex prophylaxis and treatment based on clinical trial experience and post-marketing surveillance. These adverse reactions differ from those reported with immediate release or the prolonged release formulations, either in kind or in frequency:

System Organ Class	Frequency	Adverse reaction
Metabolism and nutrition disorders	Common	Anorexia
Nervous system disorders	Common	Dizziness Headache Paraesthesia Dysgeusia
	Uncommon	Hypoaesthesia
Eye disorders	Common	Visual impairment
Ear and labyrinth disorders	Common	Deafness
	Uncommon	Hearing impaired Tinnitus
Cardiac disorders	Uncommon	Palpitations
Gastrointestinal disorders	Very common	Diarrhoea Abdominal pain Nausea Flatulence Abdominal discomfort Loose stools
Hepatobiliary disorders	Uncommon	Hepatitis
Skin and subcutaneous tissue disorders	Common	Rash Pruritus
	Uncommon	Steven-Johnson syndrome

		Photosensitivity reaction
Musculoskeletal and connective tissue disorders	Common	Arthralgia
General disorders and administration site conditions	Common	Fatigue
	Uncommon	Asthenia Malaise

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 (www.mhra.gov.uk/yellowcard) or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Adverse events experienced in higher than recommended doses were similar to those seen at normal doses. In the event of overdosage general symptomatic and general supportive measures are indicated as required.

5. Pharmacological properties

5.1 Pharmacodynamic properties

General properties

Pharmacotherapeutic group: antibacterials for systemic use; macrolids; azithromycin, ATC code: J01FA10

Mode of action:

Azithromycin is an azalide, a sub-class of the macrolid antibiotics. By binding to the 50S-ribosomal sub-unit, azithromycin avoids the translocation of peptide chains from one side of the ribosome to the other. As a consequence of this, RNA-dependent protein synthesis in sensitive organisms is prevented.

PK/PD relationship

For azithromycin the AUC/MIC is the major PK/PD parameter correlating best with the efficacy of azithromycin.

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.

Mechanism of resistance:

Resistance to azithromycin may be inherent or acquired. There are three main mechanisms of resistance in bacteria: target site alteration, alteration in antibiotic transport and modification of the antibiotic.

Complete cross resistance exists among *Streptococcus pneumoniae*, beta-haemolytic streptococcus of group A, *Enterococcus faecalis* and *Staphylococcus aureus*, including methicillin resistant *S. aureus* (MRSA) to erythromycin, azithromycin, other macrolides and lincosamides.

Breakpoints

EUCAST (European Committee on Antimicrobial Susceptibility Testing)

Pathogens	susceptible (mg/l)	resistant (mg/l)
<i>Staphylococcus</i> spp.	≤ 1	> 2
<i>Streptococcus</i> spp. (Group A, B, C, G)	≤ 0.25	> 0.5
<i>Streptococcus pneumoniae</i>	≤ 0.25	> 0.5
<i>Haemophilus influenzae</i>	≤ 0.12	> 4
<i>Moraxella catarrhalis</i>	≤ 0.5	> 0.5
<i>Neisseria gonorrhoeae</i>	≤ 0.25	> 0.5

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.

Pathogens for which resistance may be a problem: prevalence of resistance is equal to or greater than 10% in at least one country in the European Union.

Table of susceptibility

Commonly susceptible species
Aerobic Gram-negative microorganisms
<i>Haemophilus influenzae</i> *
<i>Moraxella catarrhalis</i> *
Other microorganisms
<i>Chlamydophila pneumoniae</i>
<i>Chlamydia trachomatis</i>
<i>Legionella pneumophila</i>
<i>Mycobacterium avium</i>
<i>Mycoplasma pneumonia</i> *
Species for which acquired resistance may be a problem
Aerobic Gram-positive microorganisms
<i>Staphylococcus aureus</i> *
<i>Streptococcus agalactiae</i>
<i>Streptococcus pneumoniae</i> *
<i>Streptococcus pyogenes</i> *
Other microorganisms
<i>Ureaplasma urealyticum</i>
Inherently resistant organisms
Aerobic Gram-positive microorganisms
<i>Staphylococcus aureus</i> – methicillin resistant and erythromycin resistant strains
<i>Streptococcus pneumoniae</i> – penicillin resistant strains
Aerobic Gram-negative microorganisms
<i>Escherichia coli</i>
<i>Pseudomonas aeruginosa</i>
<i>Klebsiella</i> spp.
Anaerobic Gram-negative microorganisms
<i>Bacteroides fragilis</i> group

* Clinical effectiveness is demonstrated by sensitive isolated organisms for approved clinical indications.

5.2 Pharmacokinetic properties

Absorption

After oral administration the bioavailability of azithromycin is approximately 37%. Peak plasma levels are reached after 2-3 hours (C_{max} after a single dose of 500 mg orally was approximately 0.4 mg/l).

Distribution

Kinetic studies have shown markedly higher azithromycin levels in tissue than in plasma (up to 50 times the maximum observed concentration in plasma) indicating that the active substance is heavily tissue bound (steady state distribution volume of approximately 31 l/kg). Concentrations in target tissues such as lung, tonsil, and prostate exceed the MIC₉₀ for likely pathogens after a single dose of 500 mg.

In experimental *in vitro* and *in vivo* studies azithromycin accumulates in the phagocytes, freeing is stimulated by active phagocytosis. In animal studies this process appeared to contribute to the accumulation of azithromycin in the tissue.

In serum the protein binding of azithromycin is variable and depending on the serum concentration varies from 50% in 0.05 mg/l to 12% in 0.5 mg/l.

Excretion

Plasma terminal elimination half-life closely reflects the tissue depletion half-life of 2 to 4 days. About 12% of an intravenously administered dose is excreted in the urine unchanged over a period of 3 days; the majority in the first 24 hours. Biliary excretion of azithromycin, predominantly in unchanged form, is a major route of elimination.

The identified metabolites (formed by N- and O- demethylising, by hydroxylising of the desosamine and aglycone rings, and by the splitting of the cladinose conjugate) are microbiologically inactive.

After a 5 day treatment slightly higher (29%) AUC values were seen in the elderly volunteers (>65 years of age) compared to the younger volunteers (< 45 years of age). However these differences are not regarded as clinically relevant; therefore a dose adjustment is not recommended.

Pharmacokinetics in special populations

Renal insufficiency

Following a single oral dose of azithromycin 1 g, mean C_{max} and AUC₀₋₁₂₀ increased by 5.1% and 4.2% respectively, in subjects with mild to moderate renal impairment (glomerular filtration rate of 10-80 ml/min) compared with normal renal function (GFR > 80 ml/min). In subjects with severe renal impairment, the mean C_{max} and AUC₀₋₁₂₀ increased 61% and 33% respectively compared to normal.

Hepatic insufficiency

In patients with mild to moderate hepatic impairment, there is no evidence of a marked change in serum pharmacokinetics of azithromycin compared to normal hepatic function. In these patients, urinary recovery of azithromycin appears to increase perhaps to compensate for reduced hepatic clearance.

Elderly

The pharmacokinetics of azithromycin in elderly men was similar to that of young adults; however, in elderly women, although higher peak concentrations (increased by 30-50%) were observed, no significant accumulation occurred.

Infants, toddlers, children and adolescents

Pharmacokinetics have been studied in children aged 4 months – 15 years taking capsules, granules or suspension. At 10 mg/kg on day 1 followed by 5 mg/kg on days 2-5, the C_{max} achieved is slightly lower than adults with 224 ug/l in children aged 0.6-5 years and after 3 days dosing and 383 ug/l in those aged 6-15 years. The t_{1/2} of 36 h in the older children was within the expected range for adults.

5.3 Preclinical safety data

In high-dose animal studies, giving active substance concentrations 40 fold higher than those expected in clinical practice, azithromycin has been noted to cause reversible phospholipidosis, generally without discernible toxicological consequences. There is no evidence that this is of relevance to the normal use of azithromycin in humans.

Carcinogenic potential:

Long-term studies in animals have not been performed to evaluate carcinogenic potential.

Mutagenic potential:

Azithromycin has shown no mutagenic potential in standard laboratory tests: mouse lymphoma assay, human lymphocyte clastogenic assay, and mouse bone marrow clastogenic assay.

Reproductive toxicity:

No teratogenic effects were observed in animal studies of embryotoxicity in mice and rats. In rats, azithromycin doses of 100 and 200 mg/kg bodyweight/day led to mild retardations in foetal ossification and in maternal weight gain. In peri-/postnatal studies in rats, mild retardations following treatment with 50 mg/kg/day azithromycin and above were observed.

6. Pharmaceutical particulars

6.1 List of excipients

Core:

Microcrystalline cellulose
Pregelatinised maize starch
Sodium starch glycolate Type A
Colloidal anhydrous silica
Sodium laurilsulfate
Magnesium stearate

Coating:

Polyvinyl alcohol
Titanium dioxide (E 171)
Talc
Soya Lecithin
Xanthan Gum.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

The tablets are packed in PVC/PVDC/Aluminium blisters and inserted in a carton.

Pack sizes:

2, 3, 6, 12, 24, 30, 50, and 100 film-coated tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. Marketing authorisation holder

Sandoz Ltd.,
Frimley Business Park,
Frimley,
Camberley,
Surrey, GU16 7SR,UK

8. Marketing authorisation number(s)

PL 04416/0668

9. Date of first authorisation/renewal of the authorisation

Date of first authorisation: 01/09/2006

Date of latest renewal: 25/01/2010

10. Date of revision of the text

10/09/2019

Company Contact Details

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Certificate No: UK MIA(IMP) 18693 Insp GMP/IMP 18693/11204-0015

Medicines and Healthcare products Regulatory Agency

CERTIFICATE OF GMP COMPLIANCE OF A MANUFACTURER

Part 1

Issued following an inspection in accordance with Art. 15 of Directive 2001/20/EC.

The competent authority of the United Kingdom confirms the following:

The manufacturer	FISHER CLINICAL SERVICES UK LIMITED
Site address	LANGHURSTWOOD ROAD HORSHAM RH12 4QD UNITED KINGDOM

Has been inspected under the national inspection programme in connection with manufacturing authorisation no. MIA(IMP) 18693 in accordance with Art. 13 of Directive 2001/20/EC transposed in the following national legislation: The Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031).

From the knowledge gained during inspection of this manufacturer, the latest of which was conducted on 21/01/2019, it is considered that it complies with the principles and guidelines of Good Manufacturing Practice laid down in Directive 2003/94/EC.

This certificate reflects the status of the manufacturing site at the time of the inspection noted above and should not be relied upon to reflect the compliance status if more than three years have elapsed since the date of that inspection. However, this period of validity may be reduced or extended using regulatory risk management principles by an entry in the Restrictions or Clarifying remarks field.

This certificate is only valid when presented with all pages and both parts 1 and 2.

The authenticity of this certificate may be verified in EudraGMDP. If it does not appear please contact the issuing authority.





Certificate No: UK MIA(IMP) 18693 Insp GMP/IMP 18693/11204-0015

Part 2

Human Investigational Medicinal Products for phase I, II, III clinical trials

1. MANUFACTURING OPERATIONS

1.1 Sterile products

1.1.3 Batch Certification

1.2 Non-sterile products

1.2.1 Non-sterile products (processing operations for the following dosage forms)

1.2.1.1 Capsules, hard shell

1.2.2 Batch Certification

1.3 Biological medicinal products

1.3.2 Batch certification (list of product types)

1.3.2.1 Blood products

1.3.2.2 Immunological products

1.3.2.3 Cell therapy products

1.3.2.4 Gene therapy products

1.3.2.5 Biotechnology products

1.3.2.6 Human or animal extracted products

1.3.2.8 Other biological medicinal products

IMPs

1.4 Other products or manufacturing activity

1.4.1 Manufacture of

1.4.1.1 Herbal products

1.4.1.2 Homeopathic products

1.5 Packaging

1.5.1 Primary packaging

1.5.1.1 Capsules, hard shell

1.5.1.2 Capsules, soft shell

1.5.1.8 Other solid dosage forms

1.5.1.12 Suppositories

1.5.1.13 Tablets

1.5.1.14 Transdermal patches

1.5.2 Secondary packaging

1.6 Quality control testing

Not Authorised





2. IMPORTATION OF MEDICINAL PRODUCTS

2.1 Quality control testing of imported medicinal products

Not Authorised

2.2 Batch certification of imported medicinal products

2.2.1 Sterile Products

2.2.1.1 Aseptically prepared products

2.2.1.2 Terminally sterilised products

2.2.2 Non-sterile products

2.2.3 Biological medicinal products

2.2.3.1 Blood products

2.2.3.2 Immunological products

2.2.3.3 Cell therapy products

2.2.3.4 Gene therapy products

2.2.3.5 Biotechnology products

2.2.3.6 Human or animal extracted products

2.3 Other importation activities

2.3.1 Site of Physical Importation





Certificate No: UK MIA(IMP) 18693 Insp GMP/IMP 18693/11204-0015

3. MANUFACTURING OPERATIONS

- 3.1 Manufacture of Active Substance by Chemical Synthesis**
Not Authorised
- 3.2 Processing Activities of Active Substance from Natural Sources**
Not Authorised
- 3.3 Manufacture of Active Substance using Biological Processes**
Not Authorised
- 3.4 Manufacture of sterile active substance**
Not Authorised
- 3.5 General Finishing Steps**
Not Authorised
- 3.6 Quality Control Testing**
Not Authorised
- 4 Other Activities**
Not Authorised





Certificate No: UK MIA(IMP) 18693 Insp GMP/IMP 18693/11204-0015

Any restrictions or clarifying remarks related to the scope of this certificate:

N/A

1. Building(s)/Area(s)

N/A

2. Room(s)

N/A

3. Line(s) Equipment(s)

N/A

4. QC testing

N/A

5. Medicinal Product(s)/IMP(s)

N/A

**Name of the authorised person of the
Competent Authority of the United Kingdom**

Dr A J Gray
Head of Inspectorate
inspectionplanning@mhra.gov.uk

Date: 22/03/2019





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

Chief Investigator: Professor Chris Butler (Professor of Primary Care)

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Title of Trial: PRINCIPLE: Platform Randomised trial of INTERventions against COVID-19 In older people

Protocol Number: PRINCIPLE

EudraCT Number: 2020-001209-22

IRAS ID: 281958

IMP: Hydroxychloroquine and Azithromycin

Chief Investigator: Professor Christopher Butler

Sponsor: University of Oxford

CESP Submission Number: 1158632

Date: 9th April 2020

Dear Colleague,

Subject: MHRA Substantial Amendment 2 submission for PRINCIPLE Trial in relation to COVID-19

Please find attached an application for the clinical trial authorisation for the platform randomised trial PRINCIPLE. The following documents are included:

- Cover letter for PRINCIPLE
- IRAS Substantial Amendment Form (pdf and xml)
- Protocol version 2.0, 07.04.20
- Protocol version 2.0, 07.04.20 (tracked changes)
- GMP IMP CERT of GMP Compliance 22mar2019
- MIA (IMP) 18693 v 39
- Azithromycin SmPC
- PRINCIPLE_IMP_Label form_azithromycin v1.0 07.04.20 250mg
- PRINCIPLE_IMP_Label form_azithromycin v1.0 07.04.20 500mg
- MHRA Products Form

The changes to the Protocol are detailed and justified below.

Summary of key proposed changes to PRINCIPLE Trial: Amendment 2:

1 Inclusion of a third trial arm in the PRINCIPLE platform trial.

Rationale: The PRINCIPLE trial aims to determine the effectiveness of interventions that are suitable for patients at higher risk of complications from COVID who are managing in the community at the



time of enrolment. The goal is to identify interventions that will reduce the need for hospital admission and speed recovery, and which could be rapidly scaled up.

The current comparison is:

1. Usual care
- Vs.
2. Usual care plus hydroxychloroquine 200mg twice a day for 7 days.

PRINCIPLE is a platform trial, conducted under a master protocol that which allows for the addition of further arms as the trial progresses. We have been interacting with many GPs and also with the UK-wide Primary Care Research Network, and all are crying out for evidence about the role of antibiotics in exactly the sort of patients we are recruiting in this COVID-19 priority trial. Azithromycin has antiviral properties, treats community acquired pneumonia, exacerbations of chronic obstructive airways disease, and so might prevent the need for hospitalisation and speed recovery (please see summary in Appendix 1: Usual care plus azithromycin arm). Azithromycin is already used in primary care and could be made widely available, if effective. This drug has been considered by the “Expert Review of Covid-19 Therapeutics for Immediate Deployment” convened by Sir Patrick Vallance, and was given the green light for deployment as a new arm in the PRINCIPLE Trial by the Urgent Public Health Prioritisation group on 5.04.2020. Azithromycin and antibiotics are already being widely prescribed in the UK and in other countries for patients eligible for PRINCIPLE, despite no evidence for benefit from randomised controlled trials.

Thus, we would like to make the trial:

1. Usual care
- Vs.
2. Usual care plus hydroxychloroquine 200mg twice a day for 7 days.
- Vs
3. Usual care plus azithromycin 500mg daily for 3 days.

We are obviously concerned about antimicrobial stewardship, and the potentially unnecessary use of antibiotics and the development of antimicrobial resistance. However, there is in-vitro evidence for antiviral action of azithromycin, due to which it is already being widely used in Italy and other settings for COVID-19 and evaluating it under current circumstances will be of considerable importance. Antibiotics are being widely prescribed for this condition in the UK. Many serious sequelae of COVID-19 arise from secondary bacterial infection. If proven to be effective, then the drug can be deployed for patient benefit and to enhance care sustainability. However, if the trial demonstrates no benefit, then that would lead to major gains in antibiotic stewardship as well, and avoid putting patients at unnecessary risk from side effects of the drug. To facilitate ease of review, and in common with protocols for platform trials, we have included the new intervention arm as an appendix (Appendix 1: Usual care plus azithromycin arm). Amendments not related to this arm are detailed in the master protocol and summarised below.

2. Study medication may be repackaged and distributed by an accredited licensed, central facility, who will compile study packs for participants. Once signed off by a Qualified Person, study packs will then be delivered to the Primary Care Clinical Trials Unit, or clinical sites, for further distribution to study participants as soon as they are included.

Rationale: So far, we have only been able to get swabs, information materials and study drug to participants by first delivering to their general practice, who then distribute to enrolled participants

(or their representative). Hydroxychloroquine is delivered to practices in boxes containing 60 tablets in total, but subdivided into 4 sachets of 15 tablets each. The current protocol allows a medically qualified person in the practice to take one sachet of 15 tablets from the box and repackage it in a properly labelled envelope and issue it to patients (according to randomisation). If all of this could all be done centrally, and delivered to the patient directly, it would bypass the GP practice, thereby increasing efficiency by removing an extra step in the trial process. Furthermore, it would take a considerable administrative and delivery burden off front line clinicians and practices. This would also allow patients recruited through COVID-19 'Hot Hub' practices and NHS 111 to have study materials delivered directly to them (see below). If we do have a central facility issuing medication and study materials directly to patients, that would not stop practices already set up continuing to use existing processes to deliver the study, so study drug would not be wasted.

2 Inclusion of a second swab at Day 5.

Where possible, we also now intend to obtain a swab from participants on day 5 to estimate viral shedding between study arms. Our secondary outcomes rely on patient self-report to a large measure, and having an objective virologic end point will add to study rigour, and also provide information about the impact of trial interventions on viral shedding, which will be of considerable public health importance. While there are concerns nationally regarding shortages of swabs, PHE are resolving these and have prioritised swab supply for PRINCIPLE. Should this be insufficient we have contingency plans through alternative international sources. If, despite this, swabs are in short supply, we will prioritise the enrolment swab.

3 Inclusion of a trial process evaluation

This is, to say the least, an unusual clinical trial conducted in unusual circumstances. The experiences of participants and contributing clinicians will be of great interest to understanding the results that this trial produces, and also to those who might be planning analogous research. We therefore propose to include a process evaluation of the trial, which will involve interviews with a limited number of patients who have completed the trial, and involve interviews with a limited number of patients who have completed the trial, and their respective clinician. This will be a 'light-touch' evaluation which will not interfere with the trial itself or impact negatively upon care delivery.

4 Inclusion of the WHO-5 Mental Health Wellbeing questionnaire

It is becoming increasingly apparent that a major impact of COVID-19 infection is on mental health and well-being. We therefore plan to determine whether interventions have an effect on this outcome which we will measure using the WHO mental health well-being questionnaire which is a validated five question scale. This is an efficient questionnaire which will not add significantly to the respondent burden, but will generate unique and critically important data to allow us to make a far more holistic assessment of the impact of interventions.

5 Offer of opportunity for a sub sample to be more intensively tested and their household contacts to be tested.

Colleagues at Imperial College, in collaboration with the Oxford RCGP RSC, are planning a study of people with COVID-19 and to follow them up more intensively for immunological reasons and to determine spread within households. This will be governed by an approved, separate protocol. However, we plan to offer patients in a limited geographical area in London, who consent to be part of PRINCIPLE, to be put in touch with the research team at Imperial College to discuss participation in that study further. In this way, PRINCIPLE might benefit from obtaining an additional set of



objective measures relating to immunological response to treatment (or not) with the PRINCIPLE study interventions.

6 Inclusion of a Trial Steering Committee

Based on a discussion we had with the Data Monitoring and Safety Committee (DMSC) on 2nd April 2020, we have decided to have a Trial Steering Committee to the trial. This is because due to the nature of the study design that treatment allocation will not be blinded to the DMSC. The DMSC would prefer to have an independent committee that they could report their recommendation to.

7 Permission to open in Scotland, Northern Ireland and Wales.

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

Yours sincerely,

Dr Hannah Swayze

On behalf of Professor Christopher Butler (Chief Investigator)

Study Title	Principle
EudraCT No	2020-001209-22
Version Number, Date	1.0 07.04.20

Description of information needed	Label Text
Name, address and telephone number of the sponsor (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
Pharmaceutical dosage form, route of administration, quantity of dosage units, and in the case of open trials, the name/identifier and strength/potency;	Azithromycin (250mg) tablets. The tablets are for oral administration.
Batch and/or code number to identify the contents and packaging operation;	
Trial reference code 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
Trial subject identification number /treatment number and where relevant, the visit number;	
Investigator (if not included previously)	
Directions for use (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 tablets in total) Special instructions: Azithromycin must be taken at least 1 hour before or 2 hours after antacids.
“For clinical trial use only” or similar wording;	For clinical trial use only
Storage conditions	Store below 25°C
Period of use (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 Shelf life is 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



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

IMP Label, Version/Date: v1.0 07.04.2020, EudraCT number:2020-001209-22

Professor Christopher Butler IRAS Project number: 281958 REC Reference: REC No:20/SC/0158

Study Title	Principle
EudraCT No	2020-001209-22
Version Number, Date	V1.0, 07.04.20

Description of information needed	Label Text
Name, address and telephone number of the sponsor (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
Pharmaceutical dosage form, route of administration, quantity of dosage units, and in the case of open trials, the name/identifier and strength/potency;	Azithromycin (500mg) tablets. The tablets are for oral administration.
Batch and/or code number to identify the contents and packaging operation;	
Trial reference code 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
Trial subject identification number /treatment number and where relevant, the visit number;	
Investigator (if not included previously)	
Directions for use (reference may be made to a leaflet or other explanatory document intended for the trial subject or person administering the product)	Take one tablet (500mg) azithromycin once a day for 3 days by mouth (3 tablets in total) Special instructions: Azithromycin must be taken at least 1 hour before or 2 hours after antacids.
“For clinical trial use only” or similar wording;	For clinical trial use only
Storage conditions	Store below 25°C
Period of use (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 Shelf life is 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



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

IMP Label, Version/Date: v1.0 07.04.2020, EudraCT number:2020-001209-22

Professor Christopher Butler IRAS Project number: 281958 REC Reference: REC No:20/SC/0158