



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

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Date: 02 July 2020

REC Substantial Amendment 6

IRAS ID: 281958

Dear REC committee members,

Subject: REC Substantial Amendment 6 for PRINCIPLE Trial in relation to COVID-19

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

Certain documents have been updated or created for the trial.

Summary of key proposed changes to PRINCIPLE Trial: Amendment 6

1 Updating inclusion criteria to reflect current UK government case definition

Rationale: Sudden loss of taste and smell is highly diagnostic of COVID-19 illness. The UK government has updated its definition to include this clinical feature. The inclusion criteria has therefore been expanded to take this into account. Thus, people who are symptomatic and who have this feature will be eligible, provided they meet the age and comorbidity criteria.

2. Updating the rationale and evidence for safety of hydroxychloroquine

Rationale: The MHRA has requested that the protocol be amended to include additional exclusions concerning hydroxychloroquine, and that the rationale for the use of the drug be updated, with a focus on safety.

3. Inclusion of a new arm, doxycycline

Rationale: we propose to include the antibiotic doxycycline in this trial. Doxycycline is currently being prescribed for this condition by many GPs, despite the lack of evidence for or against use of this drug in COVID-19 illness. As this is one of the commonest treatment dilemmas that clinicians face in managing COVID-19 illness, this is a service that the Principle trial can offer. Doxycycline is a widely used and generally very safe drug.

4. 'New Study Invite' wording has been updated to meet the criteria of the Imperial study team who are running the study.

5. Clarification of the recruitment procedure so that it's clear that participants can be recruited in a wide range of environments.

6. Additional social media wording

7. Addition NHS Trusts as sites

8. Including care homes as PICs for the identification of eligible participants

9. We will apply for **section 251** under the general notice under the Health Service Control of Patient Information Regulations 2002, to access participant details, enabling the trial team to directly contact potentially eligible participants from databases such as SGSS.

10. New recruitment materials: advert and radio advert to facilitate recruitment

Yours sincerely,

Dr Hannah Swayze

On behalf of Professor Christopher Butler

Table 1: List of documentation submitted to REC (new documents highlighted in blue)

Document	Version	Date	Key point (described above) documents relate to
Protocol (tracked changes & clean)	4.0	02.07.20	1-3, 5, 9, 10
PIS (tracked changes & clean)	3.1	02.07.20	1
Pictorial PIS (tracked changes & clean)	2.1	02.07.20	1
PIS Appendices (tracked changes & clean)	1.2	02.07.20	3
PRINCIPLE Text Message Info (tracked changes & clean)	3.2	02.07.20	1
Patient Recruitment Letter (tracked changes & clean)	2.1	02.07.20	1
PRINCIPLE Website Advert (tracked changes & clean)	1.2	02.07.20	1

Patient Recruitment Poster (tracked changes & clean)	1.3	02.07.20	1
Social Media Text	1.1	02.07.20	6
Advert	1.0	02.07.20	10
Radio Advert	1.0	02.07.20	10
Doxycycline Medication Card	1.0	02.07.20	3
Doxycycline IMP Label Form_100mg	1.0	02.07.20	3
Doxycycline SmPC	N/A	02.07.20	3
HCQ Medication Card (IMP Participant Information (Hydroxy))	1.1	02.07.20	2
Participant Introductory Letter	1.1	02.07.20	1
New Study Invite	1.1	02.07.20	4
Amendment Tool	SA6	-	All
SA6 Sponsor Approval	SA6	02.07.20	All

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

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Date and Version No: 2nd July 2020 version 4.0

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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.

Protocol signatures continued

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

EudraCT Number: 2020-001209-22

Protocol Date and Version No: v4.0 2nd July 2020

Protocol signature page

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

Principal Investigator
(Please print name)

Signature

**Site name or ID
number**

Date

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1. KEY TRIAL CONTACTS

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2. LAY SUMMARY

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

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

3. SYNOPSIS

Trial Title	Platform Randomised trial of INterventions against COVID-19 In older peoPLE
Internal ref. no. (or short title)	PRINCIPLE
Trial registration	ISRCTN 86534580
Sponsor	University of Oxford
Funder	UKRI/NIHR
Clinical Phase	III
Trial Design	Pragmatic, platform, randomised controlled trial of interventions for COVID-19 in PRIMARY CARE
Trial Participants	Patients ≥50-64 years with comorbidities as detailed in the inclusion criteria below (see section 7.1.1) or aged ≥65 with or without comorbidity, presenting within 14 days since onset of symptoms according to the UK Chief Medical Officer case definition where patients are well enough to remain in the community, which can be found here:

	https://www.gov.uk/government/publications/wuhan-novel-coronavirus-initial-investigation-of-possible-cases/investigation-and-initial-clinical-management-of-possible-cases-of-wuhan-novel-coronavirus-wncov-infection) during a time of prevalent COVID-19, or with a positive test for SARS-CoV-2 infection and symptoms consistent with COVID-19, within 14 days since onset of symptoms		
Sample Size	Approximately 1500 per arm but may be increased if additional arms are introduced and may also be modified in the light of emerging data.		
Planned Trial Period	The trial will start as soon as permissions are in place and procedures and structures implemented. The platform trial will be ongoing until cases of COVID-19 wane to a low level and/or there are no new interventions that require evaluation in pragmatic randomised controlled trial in primary care. March 2022 has been decided as the formal end date at this stage, but this date may need to be amended depending on circumstances prevailing at the time.		
Planned Recruitment period	The first inclusion is planned for as soon as possible, and the duration of the trial will depend on evolving circumstances.		
	Objectives	Outcome Measures	Timepoint (s)
Primary	To assess the effectiveness of trial treatments in reducing the need for hospital admission or death, for patients aged ≥ 50 years with comorbidity, and aged ≥ 65 with or without comorbidity and suspected COVID-19 during a time of prevalent COVID-19 disease	Hospital admission or mortality related to suspected COVID-19	Within 28 days
Secondary	To explore whether trial treatment reduces 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	1-2. Patient reports the day they feel recovered 3. Contacts with health services reported by patients and/or captured by reports of patients' medical records if the practice is a member of the RCGP RSC network 4. Bi-weekly reports from participants' primary care medical records	Daily online symptom scores. Telephone call or text on days 2, 7, 14 and 28 if data is not obtained through the online diary GP notes review if available through Oxford RCGP RSC network; otherwise, other sources of

	6) Oxygen administration 7) Intensive Care Unit admission 8) Mechanical ventilation 9) To determine if effects are specific to those with a positive test for COVID-19 10) Duration of hospital admission 11) Viral shedding Negative effects on well being	5-8 and 10. Patient report/carer report/medical record in primary and secondary care 9. Swab results either at baseline or day 5 for SARS-CoV-2 will indicate an "Intention to Treat Infected" group within the overall cohort for sub analysis. Blood test on recovery (optional) for evidence of historic COVID-19. 11. Follow up swabs at day 5 (if available) will indicate ongoing viral shedding, allowing comparison between groups 12. WHO-5 Well Being Index	routinely collected data after 28 days HES/ONS/EMIS/Medical record data linkage after 28 days if patients have been assessed in hospital Swab result from medical records, the supporting laboratory and/or convalescent blood test for evidence of historic COVID-19 WHO 5 Well Being Index at baseline, day 14, and day 28, either via online diary or telephone
Qualitative sub-study	1. To explore patients' experiences of consulting, being tested and taking (trial) medication for suspected COVID-19. 2. To explore healthcare professionals' views of taking part in research during pandemics.	1. Telephone interviews with patients. 2. Telephone interviews with healthcare professionals.	1. After 28 days. 2. Once practice has completed recruitment.
Intervention(s)	All trial interventions are detailed in the Appendices. Further interventions may be added or replaced during the course of the trial, subject to suitable interventions becoming available and all necessary approvals being obtained.		
Comparator	In the first instance, this will be a two-arm trial, with the intervention arm being usual care plus a trial drug and the comparator being usual care. There will be no placebo control in this study. Additional arms may be added as the trial progresses. These will be detailed in the Appendices. If an intervention arm is shown to be superior, then this will become the new standard of care. However, the primary analysis of subsequent interventions will correspond to the comparison versus the original Usual Care arm.		

4. ABBREVIATIONS

AE	Adverse event
AR	Adverse reaction
CI	Chief Investigator
CRF	Case Report Form
CT	Clinical Trials
CTA	Clinical Trials Authorisation
CTRG	Clinical Trials and Research Governance
DMSC	Data Monitoring Committee / Data Monitoring and Safety Committee
DSUR	Development Safety Update Report
GCP	Good Clinical Practice
GP	General Practitioner
HRA	Health Research Authority
HCP	Healthcare professional
IB	Investigators Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IMP	Investigational Medicinal Product
MHRA	Medicines and Healthcare products Regulatory Agency
NHS	National Health Service
NIHR	National Institute of Health Research
RES	Research Ethics Service
PHE	Public Health England
PI	Principal Investigator
PIL	Participant/ Patient Information Leaflet
R&D	NHS Trust Research and Development Department
RCGP RSC	Royal College of General Practitioners Research Surveillance Centre
REC	Research Ethics Committee
RSI	Reference Safety Information
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SDV	Source Data Verification
SMPC	Summary of Medicinal Product Characteristics
SOP	Standard Operating Procedure

TSC	Trial Steering Committee
SUSAR	Suspected Unexpected Serious Adverse Reactions
TMF	Trial Master File

5. BACKGROUND AND RATIONALE

Introduction

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

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

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

The research team have already conducted the world's first publicly funded platform, open, response-adaptive randomised controlled trial in primary care.(5) 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.(6, 7)

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

Analysis will be by intention-to-treat. However, all participants recruited into the study will be asked to provide a swab (depending on swab availability) so that their COVID-19 status can be ascertained by laboratory analysis. Participants will also be offered a blood test (if available) to check for historic SARS-CoV-2 infection within 6 months of recruitment to the study. We will therefore, in addition to an "intention to treat analysis", conduct an "intention to treat infected" analysis.

The study aims to be rapidly initiated, so we can urgently determine if potential drug treatments that are available for rapid pragmatic evaluation benefit patients. All approved intervention arms will be outlined in an appendix to this protocol. Treatments that are found to be ineffective should not be commissioned, as ineffective treatments put people at unnecessary risk of side-effects and waste resources. We urgently need to know whether potential COVID-19 treatments that are available for rapid pragmatic evaluation might benefit patients and enhance the sustainability of NHS care during this crisis.

COVID 19

Europe is now the centre of the COVID-19 pandemic caused by the highly infectious SARS-CoV-2 virus.(8, 9) 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.(9, 10)

The UK Chief Medical Officer case definition where patients are well enough to remain in the community can be found here: <https://www.gov.uk/government/publications/wuhan-novel-coronavirus-initial-investigation-of-possible-cases/investigation-and-initial-clinical-management-of-possible-cases-of-wuhan-novel-coronavirus-wn-cov-infection>)

A pragmatic trial

The aim of PRINCIPLE is to be the national primary care platform trial for UK COVID-19, assessing the effectiveness of trial treatments in reducing the need for hospital admission or death for patients with suspected COVID-19 aged ≥ 50 years with comorbidity, and aged ≥ 65 with or without comorbidity, and during a time when COVID-19 is prevalent. Thus, the trial will need to be as streamlined as possible so that it fits with minimal disruption into routine care during a period of widespread infection and considerable pressure on the NHS and society. In line with common practice for pragmatic trials, this trial will be an open trial with no placebo control.(5, 11-13) The primary outcome is hospitalisation and death, with the decision to hospitalise being made by clinicians independent of the trial.

Platform trial

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

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

	Objectives	Outcome Measures	Timepoint (s)
Primary	To assess the effectiveness of trial treatments in reducing the need for hospital admission or death, for patients aged ≥ 50 years with comorbidity, and aged ≥ 65 with or without comorbidity and possible COVID-19 during a time of prevalent COVID-19 disease	Hospital admission or mortality related to suspected COVID-19	Within 28 days

Secondary	To explore whether trial treatment reduces 1) Duration of severe symptoms 2) Time taken to self-report recovery 3) Contacts with the health services 4) Consumption of antibiotics 5) Hospital admission without admission 6) Oxygen administration 7) Intensive Care Unit admission 8) Mechanical ventilation 9) o determine if effects are specific to those with a positive test for COVID-19 10) Duration of hospital admission 11) Viral shedding 12) Negative effects on well being	1-2. Patient reports the day they feel recovered 3. Contacts with health services reported by patients and/or captured by reports of patients' medical records if the practice is a member of the RCGP RSC network 4. Bi-weekly reports from participants' primary care medical records 5-8 and 10. Patient report/carer report/medical record in primary and secondary care 9. Swab results either at baseline or day 5 for SARS-CoV-2 will indicate an "Intention to Treat Infected" group within the overall cohort for sub analysis. Blood test on recovery (optional) for evidence of historic COVID-19. 11. Follow up swabs at day 5 (if available) will indicate ongoing viral shedding, allowing comparison between groups 12. WHO-5 Well Being Index	Daily online symptom scores. Telephone call or text on days 2, 7, 14 and 28 if data is not obtained through the online diary GP notes review if available through Oxford RCGP RSC network; otherwise, other sources of routinely collected data after 28 days HES/ONS/EMIS/Medical record data linkage after 28 days if patients have been assessed in hospital Swab result from medical records, the supporting laboratory and/or convalescent blood test for evidence of historic COVID-19 WHO 5 Well Being Index at baseline, day 14, and day 28, either via online diary or telephone
Qualitative sub-study	1. To explore patients' experiences of consulting, being tested and taking (trial) medication for suspected COVID-19.	1. Telephone interviews with patients.	1. After 28 days.

	2. To explore healthcare professionals' views of taking part in research during pandemics.	2. Telephone interviews with healthcare professionals.	2. Once practice has completed recruitment.
Intervention(s)	All trial interventions are detailed in the Appendices. Further interventions may be added or replaced during the course of the trial, subject to suitable interventions becoming available and all necessary approvals being obtained.		
Comparator	In the first instance, this will be a two-arm trial, with the intervention arm being usual care plus a trial drug and the comparator being usual care. There will be no placebo control in this study. Additional arms may be added as the trial progresses. These will be detailed in the Appendices. If an intervention arm is shown to be superior, then this will become the new standard of care. However, the primary analysis of subsequent interventions will correspond to the comparison versus the original Usual Care arm.		

6. TRIAL DESIGN

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

The trial will be implemented in the first instance in practices that are already part of the RCGP RSC Network. Currently, over 500 practices are part of this network, with 100 already offering a sentinel viral swabbing service that is being scaled up.

7. PARTICIPANT IDENTIFICATION

7.1 Trial Participants

Patients ≥ 50 years with comorbidity, and patients aged ≥ 65 with or without comorbidity, presenting in the community within 14 days since onset of symptoms, during a time when COVID-19 is prevalent, or a **positive test** for SARS-CoV-2 infection which was taken fewer than 15 days ago, AND symptoms of COVID-19.

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

7.1.1 Inclusion Criteria

- Participant is willing and able to give informed consent for participation in the study; Participant is willing to comply with all trial procedures;
- SARS-CoV-2 infection (suspected due to symptoms or laboratory confirmed). Onset of symptoms or a **positive test** for SARS-CoV-2 infection with symptoms of COVID-19, must be within the last 14 days.
- *For the purposes of this trial, the prevailing Chief Medical Officer case definition of COVID-19 (as described above) will be used with the following criteria for age.*

- i) 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 a diagnosis of high blood pressure;
 - Known asthma or lung disease;
 - Known diabetes;
 - Known mild hepatic impairment;
 - Known stroke or neurological problem;

OR

- ii) Patients aged ≥ 65 with or without comorbidity

7.1.2 Exclusion Criteria

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

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

Exclusion criteria related to hydroxychloroquine:

- Pregnancy;
- Breastfeeding;
- Known severe hepatic impairment;
- Known severe renal impairment;
- Known porphyria;
- Type 1 diabetes or insulin dependent Type 2 Diabetes mellitus ;
- Known G6PD deficiency;
- Known myasthenia gravis;
- Known severe psoriasis;
- Known severe neurological disorders (especially those with a history of epilepsy—may lower seizure threshold)
- Previous adverse reaction to, or currently taking, hydroxychloroquine or chloroquine
- Patients currently taking the following drugs: penicillamine, amiodarone, ciclosporin, digoxin: the following antimicrobials; azithromycin, clarithromycin, erythromycin, ciprofloxacin, levofloxacin, moxifloxacin, ketoconazole, itraconazole, or mefloquine: the following antidepressants; amitriptyline, citalopram, desipramine, escitalopram, imipramine, doxepin, fluoxetine, wellbutrin, venlafaxine; the following antipsychotics or mood stabilizers; haloperidol, droperidol, lithium, quetiapine, thioridazine, ziprasidone: methadone: sumatriptan, zolmitriptan

- Known congenital or documented QT prolongation
- Known retinal disease

Exclusion criteria related to azithromycin:

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

Exclusion criteria related to doxycycline:

- Pregnancy
- Breastfeeding
- Myasthenia gravis
- Systemic lupus erythematosus
- Previous adverse reaction to, or currently taking, doxycycline or other tetracyclines
- Sucrose intolerance (i.e. rare hereditary problems of fructose intolerance, glucose galactose malabsorption or sucrose-isomaltase insufficiency)
- Already taking antibiotics for an acute condition
- Patients taking the following drugs: ciclosporin, retinoids (acitretin, alitretinoin, isotretinoin, tretinoin), methotrexate, ergotamine, methoxyflurane, lithium.

8 TRIAL PROCEDURES

8.1 Recruitment

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

8.1.1 Face to face

Attending clinicians via GPs, paramedics, hospital emergency departments, clinical care hubs, Hospital at Home facilities, geriatricians, research nurses or other health care professionals can recruit to the trial. They will discuss the study, obtain informed consent, collect data (including participant contact details), complete screening questions and randomise the participant. If required, the clinician will prescribe the medication. At any stage the clinician can revert to the

PC-CTU for the PC-CTU to complete the activity, such as not being able to prescribe, allowing PC-CTU to distribute the medication.

8.1.2 Remote recruitment

i) All Health and Social Care professionals will be able to give information verbally or via a trial text, email, poster, social media post, media release, leaflet or letter, to potential participants and their potential study partners (see below). They can also direct interested patients to the online information about the study and/or how to contact the study team. We will also use adverts to promote the trial.

ii) Potential participants may present directly to the study team via the website or telephone. The study team will provide information about potentially joining the trial, the steps involved, and guide them through the consent and enrolment process.

iii) A General Practice may be contacted by a potential participant or the practice may choose to contact patients, preferably by text (or by letter), who they have screened from their GP Practice list and who fall into the correct age and co-morbidity categories. Practices can also choose to screen contacts from the previous 14 days for potentially eligible participants to discuss participation in the study. They will then direct them to the trial enrolment website or seek verbal consent if they are happy to be contacted by the trial team to discuss this further.

iv) We will apply for section 251 under the [general notice under the Health Service Control of Patient Information Regulations 2002](#), to support the response to COVID-19. This notice, which applies only in England and Wales, requires NHS Trusts, Local Authorities and others to process confidential patient information without consent for COVID-19 public health, surveillance and research purposes. The notice provides a temporary legal basis to avoid a breach of confidentiality for COVID-19 purposes. If REC approval is received we will ask NHS agencies, including (but not limited to) 'Test and Trace' to provide a list of patients who may meet the trial inclusion criteria and provide the central trial team with contact details via a secure transfer system.

For all recruitment models:

- Detailed information about the study will be available to view on a website and the Participant Information Sheet (PIS). A summary, pictorial PIS is also available to supplement the full PIS. This information will inform potentially eligible and interested patients of how to access further trial information and consider participation, as well as the procedures involved in joining the study, and what participation would involve.
- Study Partner: during the enrolment process, the study team will ask the potential participant to, if possible, include a phone number and email address for a study partner, who may provide assistance to the study participant in completing trial procedures. Identifying a study partner is not obligatory. A study partner letter may be used in environments such as residential and nursing homes, to provide guidelines on how study partners can support participants in the trial. The letter will be provided to residential and nursing homes, to distribute as required when potential patients self-refer to the trial.

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

8.2 Screening and Eligibility Assessment

An online screening, eligibility and consent procedure will be used. If online access is not possible, a member of the trial team will collect this information during a telephone call. The trial free phone number will also allow potential participants to ask questions about the study and their potential participation, at any stage of the trial.

Participants will be screened after they have read the PIS, by completing an online eligibility questionnaire, presented in lay terms (based on section 7). Eligibility can be checked at study sites or centrally by a medically qualified clinician or a research nurse who is suitably trained and experienced and has been delegated this responsibility, with appropriate access to the participant's medical records. If a participant's medical notes cannot be accessed centrally, the clinician/delegate will contact the participant's GP for information to enable the study team to confirm eligibility to be randomised at least to one intervention, as well as the control arm.

Participants will not be randomised to an arm if an exclusion criterion to that arm applies to them, but will need to have no exclusions relevant to at least one intervention and the usual care arm.

8.3 Informed Consent

If Participants meet the screening criteria, they will be asked to provide informed consent and a screening trial ID number will be assigned. Remote, online consent, or via a telephone call, is required.

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

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

Participants will preferably complete the Informed Consent Form (ICF) online. They will be able to download their consent form for their own records. This online process avoids risks associated with paper documents being handled by people with infection and is efficient during a time of rapid recruitment during a pandemic. The completed ICF may also be printed and delivered to participants along with study materials such as IMP or swabs.

After consent, the participant will enter online baseline information, including their address, contact details and those of a Study Partner.

8.4 Randomisation

Participants will be randomised using a fully validated and compliant web-based randomisation system called Sortition. Once deemed eligible, the clinician or a member of the trial team will randomise the participant. The randomisation process will take only a few moments via the online system and will not delay trial participation. Participants will be randomised to the arm/arms they are eligible for (at least two arms), automatically by Sortition. Full details of response adaptive randomisation are described in section 11.2.4.

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

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

Participants will receive clear instructions on how to self-sample, as per standard advice. Once the sample has been taken, they will be asked to place the sample in the provided container, sealed in a double envelope, which will be posted to a laboratory according to their standard practice for COVID-19 swab testing. For trial purposes, we will not store the swabs after testing but PHE may keep the specimen for up to 5 years following their own approved processes. Participants will be informed of their COVID-19 swab result by their GP or the trial team depending on recruitment route.

If a sample can be taken face-to-face by the general practice or another facility soon after inclusion, the initial self-swab will not be necessary. While the aim is to have a swab result for all patients, if a swab cannot be done for supply or other logistical reasons, this will not exclude the patient from participating in the study. However, they will only be analysed in the intention to treat analysis.

Study materials and any medication participants can also be obtained by the participation, either through collection at a pharmacy or GP practice.

8.7 Subsequent Visits

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

Participants will be sent a link to their online diary, which they will complete for 28 days. They will be asked to rate the severity of a set number of symptoms, record contacts with the health services including hospital admission, record medication use, new infections in the household, and the five questions of WHO-5 on days 14 and 28. The latter instrument has been validated for measuring wellbeing over time. It is becoming increasingly apparent the COVID-19 infection may have a considerable negative impact on well-being; exploring the impact of interventions on this is important.⁽¹⁴⁾ We will capture ethnicity and care home residency at baseline and day 28 (in case it was missed at baseline).

All participants will receive a call from the trial team on day 2/3 to confirm that they have received a swab, participant contact card and trial medication (IMP arm only), and that they understand that they should complete the daily diary for 28 days even if they feel better or their swab result is negative. The trial team calls participants/study partners on days 7, 14 and 28 if they do not have internet access or have not been completing their diary for at least 2 consecutive days prior to the call. The study team will make no more than six attempts to contact the participant/trial partner at each of these follow-up points.

We will also obtain consent to ascertain relevant data from hospital records about length of hospital stay and ICU admission and ventilation, if applicable.

The RCGP RSC will report to the central trial office at regular intervals about healthcare contacts in the participant's clinical records, as they are able to download this information centrally for study participants. This will be used as confirmation and a back-up for information obtained directly from study participants and other data sources outlined above. If notes review is not possible using this route – for example, for patients recruited through an urgent or unscheduled care contact and therefore their registered GP practice has not been involved and does not wish to register with the RCGP RSC, the registered GP surgery will be contacted separately by the trial team to request a limited notes review. Participant records will be accessed up to three months following enrolment to ascertain follow up data from enrolment to day 28. 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.

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

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

8.8 Sample Handling

We will request two biological samples to test for SARS-CoV-2 from all consenting participants, the first at baseline and the second at day 5, as described in section 8.6.

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

8.9 Qualitative Sub-study

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

Recruitment:

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

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

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

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

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

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

Interviews:

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

Patient participant interviews will follow a semi-structured topic guide (Interview Patient Topic Guide) and ask about reasons for consulting and illness perceptions prior to the consultation, experiences of the consultation, the COVID-19 testing process (if applicable, and result if the participant has been notified) and medication adherence. The topic guide will be informed by the Common Sense Model which describes how people perceive and cope with symptoms of illness. HCP interviews will follow the Interview HCP Topic Guide and will ask about experiences of carrying out trial activities, recruiting patients and the work required to set up a clinical trial during a pandemic.

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

8.10 Early Discontinuation/Withdrawal of Participants

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

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

The reason for withdrawal will be recorded on the CRF. Data that has already been collected about the participant will be kept and used. Swabs may be stored outside of the trial remit, for PHE purposes adhering to their retention policy. Optional SARS-CoV-2 blood test samples will not be stored.

8.11 Definition of End of Trial

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

9 TRIAL INTERVENTIONS

9.1 Investigational Medicinal Product(s) (IMP) Description

Trial Drug information can be found in the relevant Appendices.

9.2. Blinding of IMPs

There is no blinding of IMPs in the trial.

9.3. Storage of IMP

GP practices can order a supply of trial medication from Public Health England using the existing ImmForm process. All GP practices in England are already set up on ImmForm, as they use this system to order Influenza vaccines from Public Health England. GPs will be provided with an envelope by the trial team which will be labelled appropriately for trial medication, and they will add the patient's details to this label. This pack, containing instructions on using the medication will be provided to the patient or their representative. Medication may either be issued by the patient's registered GP surgery or by a surgery acting as a hub for a number of local surgeries. Alternatively, study medication will be repackaged by an accredited licensed, central facility and may be delivered to primary care centres or to the Primary Care Clinical Trials Unit for further distribution to study participants as they are included. Distribution of trial packs to study participants will be tracked via courier or call/text message.

Lastly, for trial medications that can be prescribed and issued to patients in the community, clinicians will be able to prescribe trial medication using existing NHS services. Pharmacies will then be able to issue medication that could be delivered to the patient by community pharmacy services or NHS volunteers, or collected from the pharmacy by the participant or someone on their behalf, such as their study partner.

9.4. Compliance with Trial Treatment

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

9.5. Accountability of the Trial Treatment

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

9.6. Concomitant Medication

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

10 SAFETY REPORTING

Daily symptom diaries and participant telephone calls will record any symptoms and side effects from the trial medication. This information will be analysed as part of the whole trial analysis.

10.1 Adverse Event Definitions

Adverse Event (AE)	Any untoward medical occurrence in a participant to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product.
Adverse Reaction (AR)	An untoward and unintended response in a participant to an investigational medicinal product which is related to any dose administered to that participant. The phrase "response to an investigational medicinal product" means that a causal relationship between a trial medication and an AE is at least a reasonable possibility, i.e. the relationship cannot be ruled out. All cases judged by either the reporting medically qualified professional or the Sponsor as having a reasonable suspected causal relationship to the trial medication qualify as adverse reactions.
Serious Adverse Event (SAE)	A serious adverse event is any untoward medical occurrence that: • results in death • is life-threatening • requires inpatient hospitalisation or prolongation of existing hospitalisation • results in persistent or significant disability/incapacity • consists of a congenital anomaly or birth defect*. Other 'important medical events' may also be considered a serious adverse event when, based upon appropriate medical judgement, the event may jeopardise the participant and may require medical or surgical intervention to prevent one of the outcomes listed above. NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe. *NOTE: Pregnancy is not, in itself an SAE. In the event that a participant or his/her partner becomes pregnant whilst taking part in a clinical trial or during a stage where the foetus could have been exposed to the medicinal product (in the case of the active substance or one of its metabolites having a long half-life) the pregnancy should be followed up by the investigator until delivery

	for congenital abnormality or birth defect, at which point it would fall within the definition of “serious”.
Serious Adverse Reaction (SAR)	An adverse event that is both serious and, in the opinion of the reporting Investigator, believed with reasonable probability to be due to one of the trial treatments, based on the information provided.
Suspected Unexpected Serious Adverse Reaction (SUSAR)	A serious adverse reaction, the nature and severity of which is not consistent with the Reference Safety Information for the medicinal product in question set out: • in the case of a product with a marketing authorisation, in the approved summary of product characteristics (SmPC) for that product • in the case of any other investigational medicinal product, in the approved investigator’s brochure (IB) relating to the trial in question.

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

10.2 Assessment results outside of normal parameters as AEs and SAEs

There are no additional assessment results in this study.

10.3 Assessment of Causality

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

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

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

10.4 Procedures for Reporting Adverse Events

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

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

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

10.5 Reporting Procedures for Serious Adverse Events

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

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

10.5.1. Other events exempt from immediate reporting as SAEs

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

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

10.5.2. Procedure for immediate reporting of Serious Adverse Events

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

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

10.5.3 Expectedness

For SAEs that require reporting, expectedness of SARs will be determined according to the relevant RSI section of the Summary of Product Characteristics/IB. The RSI will be the current

Sponsor and MHRA approved version at the time of the event occurrence. For assessment of expectedness in the Development Safety Update Report, see section 10.7 below.

10.6 SUSAR Reporting

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

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

10.7 Development Safety Update Reports

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

11 STATISTICS

11.1 Master Statistical Analysis Plan (M-SAP)

Details of the statistical design and methods will be described in a Master Statistical Analysis Plan (M-SAP), in which an appendix to the M-SAP titled “Adaptive Design Report” (ADR) provides complete specifications for the primary analysis and pre-specified adaptive algorithm. In addition, the M-SAP will be accompanied by arm-specific appendices to describe any planned deviations from the M-SAP. A broad overview of the design and primary analyses is provided below.

11.2 Open Adaptive Platform Trial

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

The PRINCIPLE trial will begin as a two arm, 1:1 randomised trial but will have the capability to add additional interventions over time. The evaluation of any new interventions will be governed by this master protocol and M-SAP (including adaptive algorithm and decision criteria), with any planned deviations from the master protocol and M-SAP to be specified in arm-specific

appendices. The inclusion of any new interventions will require additional arm-specific appendices to the master protocol and M-SAP.

11.2.1 Primary Endpoint & Analysis

The primary endpoint is hospital admission or death related to suspected COVID-19 infection. The primary analysis will be a Bayesian generalised linear model of the primary outcome regressed on treatment and stratification covariates (age, comorbidity). Let θ_j denote the log odds ratio comparing the odds of hospitalisation/death for persons in treatment group j versus persons in the Usual Care arm. A corresponding Bayesian posterior distribution will be derived for the estimated log odds ratio. The primary analysis for intervention j will test the following hypothesis:

$$\begin{aligned} H_0: \theta_j &\geq 0 \\ H_1: \theta_j &< 0 \end{aligned}$$

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

11.2.2 Adaptive Design

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

11.2.3 Interim Analyses

Per the pre-specified design, the trial will be eligible for the first interim analysis when 200 randomised participants have the opportunity to complete 28 days of follow-up and there are a sufficient number of hospital admissions/deaths. Subsequent interim analyses will be conducted with frequency as specified in the Adaptive Design Report. At each interim analysis, all enrolled intervention arms will be evaluated for success or futility using the Bayesian primary analysis. If the Bayesian posterior probability of superiority of a given intervention is sufficiently large (e.g. ≥ 0.99), superiority will be declared. If there are additional intervention arms in the study (either currently or subsequently), the superior arm will replace the Usual Care arm as the new standard of care.

If the Bayesian posterior probability of a clinically meaningful treatment effect (e.g. $\geq 25\%$ reduction in relative risk of hospitalization/death) is sufficiently small (e.g. < 0.01) the intervention arm will be dropped from the study for futility. If there are no other intervention arms available, the trial will be suspended; otherwise accrual continues to the remaining

treatment arms. The exact futility threshold will be pre-specified in the Adaptive Design Report and determined via simulation.

11.2.4 Allocation & Response Adaptive Randomisation

Initially, randomisation will be fixed 1:1 for a comparison between two trial arms, with stratification by age (less than 65, greater than or equal to 65), and comorbidity (yes/no). If a second intervention arm is added to the study, randomisation allocation will be modified and the additional intervention will be included in the interim analyses (with evaluation for success and futility) as detailed in the Adaptive Design Report. If there are at least 3 arms (2 intervention arms plus Usual Care) in the study, each interim analysis may incorporate modified randomisation probabilities via response adaptive randomisation (RAR). Full details for implementing RAR will be provided in the Adaptive Design Report; the general idea is to allocate more participants to the intervention arms that have the best observed outcomes.

11.2.5 Sample Size Justification

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

11.2.6 Virtual Trial Simulations

Because of the adaptive platform trial structure, there exists no simple formula(s) to calculate power and Type I error (false positive rate). Hence, virtual trial simulations will be used to fully characterize and quantify the power and Type I error of the design. These simulations will be conducted prior to the first interim analysis (with results described in the Adaptive Design Report), and will be used to optimize the adaptive decision criterion and RAR parameters. The simulations will include a comprehensive evaluation of trial performance across a wide range of assumptions (e.g. underlying distribution of outcome in control arm, treatment effect, accrual rates, etc.). This will include summaries regarding the number of subjects required to make a success or futility conclusions for each intervention. For example, we will quantify the probability of claiming superiority at the first and each of the subsequent interim analyses. Complete details of the simulations will be provided in the Adaptive Design Report.

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

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

11.3 Primary Analysis Population

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

11.4 Procedures for Reporting Unplanned Deviation(s) from the Master Statistical Analysis Plan

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

11.5 Qualitative sub-study analysis

11.6

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

12 DATA MANAGEMENT

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

12.1 Source Data

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

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

CRF entries will be considered source data if the CRF is the site of the original recording (e.g. there is no other written or electronic record of data). All documents will be stored safely in confidential

conditions. On all study-specific documents, other than the signed consent, the participant will be referred to by the study participant number/code, not by name.

12.2 Access to Data

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

12.3 Data Recording and Record Keeping

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

Sentry is an online secure data entry system developed in-house at PC-CTU and hosted at Oxford. It is designed to collect sensitive data, such as participant and Trial Partner contact details, and securely retain them separate from a trial's clinical data. Sentry can also act as a central participant portal to manage online eligibility, eConsent and ePRO - acting as an intermediary between the participant and the clinical databases. Sentry is accessed via a secure HTTPS connection and all stored sensitive data is encrypted at rest to AES-256 standards. Participant and Trial Partner data will be kept and stored securely for as long as its required by the study and reviewed on annual basis.

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

For the qualitative sub-study:

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

13 QUALITY ASSURANCE PROCEDURES

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

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

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

13.1 Risk assessment

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

13.2 Monitoring

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

13.3 Trial committees

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

- DMSC - to review the data at each interim analysis as described in the Statistical Analysis section, as the updates to the randomisation scheme occur in order to ensure that the process is working correctly and to review and monitor the accruing data to ensure the rights, safety and wellbeing of the trial participants.
- TSC - the Trial Steering Committee ensure the rights, safety and wellbeing of the trial participants. They will make recommendations about how the study is operating, any ethical or safety issues and any data being produced from other relevant studies that might impact the trial.
- TMG - is responsible for the day-to-day running of the trial, including monitoring all aspects of the trial and ensuring that the protocol is being adhered to. It will include Co-Investigators and will meet weekly in the first instance. A core project team (PT) from within the TMG will meet daily as required for daily operational decision making.

14 PROTOCOL DEVIATIONS

A study related deviation is a departure from the ethically approved study protocol or other study document or process (e.g. consent process or administration of study intervention) or from Good

Clinical Practice (GCP) or any applicable regulatory requirements. Any deviations from the protocol will be documented in a protocol deviation form and filed in the study master file.

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

15 SERIOUS BREACHES

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

- (a) the safety or physical or mental integrity of the trial subjects; or
- (b) the scientific value of the research.

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

16 ETHICAL AND REGULATORY CONSIDERATIONS

16.1 Declaration of Helsinki

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

16.2 Guidelines for Good Clinical Practice

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

16.3 Approvals

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

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

16.4 Other Ethical Considerations

If a particular arm is deemed futile and dropped, no further participants will be randomised to this arm and anyone who is currently on this arm will be informed it has been dropped. Once a particular intervention has been declared superior and effective, that will become the comparator arm (i.e. standard care).

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

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

16.5 Reporting

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

16.6 Transparency in Research

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

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

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

16.7 Participant Confidentiality

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

16.8 Expenses and Benefits

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

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

17 FINANCE AND INSURANCE

17.1 Funding

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

17.2 Insurance

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

17.3 Contractual arrangements

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

18 PUBLICATION POLICY

The Investigators (those listed on the protocol and others to be decided at publication) will be involved in reviewing drafts of the manuscripts, abstracts, press releases and any other publications arising from the study. Authors will acknowledge the study funders. Authorship will be determined in accordance with the ICMJE guidelines and other contributors will be acknowledged.

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

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

20 ARCHIVING

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

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22 APPENDIX A: SCHEDULE OF PROCEDURES

Procedures	Visits						
	Visit timing Day 0	Day 0	Day 0	Day 0	Daily Day 1-28 incl	Day 29-3mths	Day 28-6 months
	Screening completed by participant online/phone	Eligibility completed by participant online/phone	Baseline completed by participant online/phone	Eligibility completed by Clinician online/phone	Symptom Diaries completed by participant online/phone	Retrospective data collection by study team	Contacted by study team if consent provided
Informed consent	X	X	X	X	X		
Demographics	X	X	X			X	
Medical history	X	X	X	X		X	
Swab	When available, preferably by self-swabbing at study entry and 5 days after inclusion				When available, preferably by self-swabbing at study entry and 5 days after inclusion		
Concomitant medications		X				X	
Eligibility assessment	X	X					
Randomisation				X			

Dispensing of trial drugs				X	X		
Daily Questionnaire					X		
WHO 5 Well Being Index	X				Day 14 and day 28		
Telephone interview (for subset of patient participants)					X		
Compliance					X		
Adverse event assessments					X*	X	
Optional SARS-CoV-2 blood test							X

- Those randomised on day 7 will receive a telephone call from the trial team to collect and information about cardiovascular Adverse Events (please see hydroxychloroquine appendix)

23 APPENDIX B: AMENDMENT HISTORY

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made
1	1.1		Emma Ogburn; Chris Butler; Gail Hayward	Inclusion criteria: change 'known heart disease' to 'Known heart disease and/or hypertension'; Exclusion criteria: exclude patients taking the following drugs: penicillamine, amiodarone, ciclosporin, chloroquine. Update section 9.6 to include vision changes and lowering of blood sugar. Update change in Funder and update Investigator list to reflect UKRI funder bid.
2	2.0		Emma Ogburn; Chris Butler; Gail Hayward, Hannah Swayze	Inclusion of TSC; central facility to distribute patient packs; addition of third arm; update of secondary outcomes to include WHO wellbeing questions; qualitative sub study; sign posting to other RCGP RSC study; eligibility confirmation by research nurse.
3	2.1		Hannah Swayze; Chris Butler; Emma Ogburn; Gail Hayward	Trial rationale; secondary outcomes to include blood test; 14 days of covid-19 symptoms; call to participant at day 2; poster
4	2.1		<i>No changes to the protocol</i>	
5	3.0		Hannah Swayze; Chris Butler; Emma Ogburn; Gail Hayward	Updated Azithromycin information; broadening of inclusion criteria; first interim analysis; primary analysis details; care home materials; administrative and typographical updates; study partner letter; recruitment via social media, care homes and pharmacies; GPs prescribe trial medication; eligibility to at least one intervention arm as well as the

				control arm; ICF may be sent to participants.
6			Chris Butler; Emma Ogburn; Gail Hayward; Ben Saville; Ly-Mee Yu; Hannah Swayze	Updating inclusion criteria; updating the rationale and evidence for safety of hydroxychloroquine; inclusion of a new arm, doxycycline; AE reporting for hydroxychloroquine arm; typographical clarifications

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

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

24 APPENDIX C: USUAL CARE ARM

1. Background and rationale

COVID-19 disproportionately affects people over 50 years old with comorbidities and those over 65 years old. The disease causes considerable morbidity and mortality in this population group in particular, and is having a devastating effect on people's health, and society in the UK and internationally.(1-3, 9) So far, there are no specific treatments for COVID-19 that have been proven in rigorous clinical trials to be effective. Clinicians managing suspected COVID-19 in the community will make clinical judgements about best treatment based on the clinical situation, but care is usually supportive to begin with, unless patients deteriorate and require hospital admission (<https://www.nice.org.uk/guidance/ng163>). The National Institute for Health and Care Excellence does not recommend the immediate use of antibiotics unless there are signs of pneumonia (<https://www.nice.org.uk/guidance/ng163>).

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

2. Changes to outcome measures

None

3. Detail of intervention

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

a. Investigational Medicinal Product (IMP) description

Not applicable

b. Storage of IMP

Not applicable

4. Safety reporting

Mechanisms for safety reporting are outlined in the trial protocol.

25 APPENDIX D: USUAL CARE PLUS HYDROXYCHLOROQUINE ARM

1. Background and rationale

a. Evidence for potential Hydroxychloroquine benefits in COVID-19

A candidate intervention for COVID-19, a drug called hydroxychloroquine, has become available following early evaluation in some studies in China.(15, 16) Hydroxychloroquine is a hydroxylated version of the drug chloroquine.(16, 17) Both agents are commonly in use as anti-malarials, and are used in a variety of auto-immune diseases. They have received significant recent interest as potential modifiers of disease activity in COVID-19. (16, 18, 19) Hydroxychloroquine is already available within the NHS on prescription for other indications, and has a generally benign safety profile.(20) 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*.(17) Chloroquine is widely distributed in the whole body, including lungs, after oral administration.(16) The EC₉₀ value of chloroquine against the 2019-nCoV in Vero E6 cells was 6.90 µM in one study (15) which can be clinically achievable as demonstrated in the plasma of rheumatoid arthritis patients who received 500 mg administration.(20)

Hydroxychloroquine has been found to be effective against intracellular micro-organisms including malaria and intracellular bacteria *Coxiella burnetii* and *Tropheryma Whipplei*.(17) Both chloroquine and hydroxychloroquine have been shown to have *in vitro* antiviral activity against SARS coronavirus in a number of studies.(17) Most recently activity against SARSCOV2 was shown to be greater for hydroxychloroquine than chloroquine (21).

Key publications that have relevance to the safety and rationale for use of hydroxychloroquine in the PRINCIPLE Trial:

1. The Mahévas study was an observational study that assessed whether hydroxychloroquine reduced the need for transfer to ICU in patients already sick enough to be hospitalised.(22) It focussed on sicker patients with hypoxic pneumonia, some requiring ITU care. It did not find a difference in transfers to ICU. So the question and population in the Mahevas study are very different compared to PRINCIPLE. Most importantly, unlike PRINCIPLE, the Mahevas study is **not a randomised clinical trial**. Numbers were relatively small (n=181), and it is at high risk of bias due to the observational design.

Regarding safety, those receiving hydroxychloroquine were prescribed 600mg per day, whereas the dose in the PRINCIPLE trial is 400mg per day; 18% of those who received hydroxychloroquine in the Mahévas study were also on azithromycin (which can be arrhythmogenic), and this combination is not possible in PRINCIPLE because of the additive risk. Moreover, PRINCIPLE excludes several other drug combinations that could be arrhythmogenic. In the Mahevas study, eight patients (10%) who were taking hydroxychloroquine experienced electrocardiographic changes that required discontinuation of hydroxychloroquine. Critically, those in the control

group did not have ECGs done, so we don't know if there was indeed a difference between groups, and we cannot therefore attribute the ECG changes to hydroxychloroquine. COVID-19 itself, or drug interactions, may well have been underlying reasons. The authors state, "Although hydroxychloroquine is considered safe in the context of systemic lupus erythematosus, these adverse events might be explained by the use of high dose hydroxychloroquine in patients older than 75 years with renal impairment and frequent drug interactions. We cannot rule out the possibility that these cardiac effects attributed to hydroxychloroquine were caused by COVID-19, especially given electrocardiograms were unavailable during follow-up in the control group."

2. The Tang study was a hospital-based, randomised study and included 150 patients; randomisation was done using sealed envelopes.(23) The trial found no difference in the proportion of patients with two sequential negative swab results.

Regarding safety, 75 participants received hydroxychloroquine 1200 mg daily for 3 days and then 800 mg for either 2 or 3 weeks. Again, the dose used in this study was much higher than the dose being used in PRINCIPLE (initially three times, and subsequently twice as high as PRINCIPLE). However, 63% and 64% of patients in the hydroxychloroquine and control groups respectively also received other antiviral agents. In PRINCIPLE, we are not evaluating the combination of antiviral agents and hydroxychloroquine. Importantly, this study did not find evidence of cardiac arrhythmias associated with hydroxychloroquine use. The authors state, "Events of cardiac arrhythmia, such as prolonged QT interval were not observed in our trial, possibly because of the relatively mild to moderate disease of patients investigated or the short term period of follow-up."

3. The Mehra study published in the Lancet on 22.05.2020 reported an association between hydroxychloroquine use and cardiac events and mortality amongst patients hospitalised with COVID-19.(24) The *observational* study design is inherently susceptible to bias, the study data integrity has been queried given the homogeneity of the baseline characteristics, the adequacy of the adjustment for confounders cannot be assessed from the published methods, and the registries used are in a different patient population compared to PRINCIPLE. Patients were much sicker and more advanced in the illness than in PRINCIPLE. The authors themselves state that "*Randomised clinical trials will be required before any conclusion can be reached regarding benefit or harm of these agents (hydroxychloroquine and chloroquine) in COVID-19 patients.*" The authors also state "These data do not apply to the use of any treatment regimen used in the ambulatory, out-of-hospital setting." This study has proved hugely controversial on social media, with a number of methodological and data integrity concerns already raised, for example:

1. There were inadequate adjustments for known and measured confounders (disease severity, temporal effects, site effects, dose used).
2. The authors have not adhered to standard practices in the machine learning and statistics community. They have not released their code or data. There is no data/code sharing and availability statement in the paper. The Lancet was among the many signatories on the Wellcome statement on data sharing for COVID 19 studies.
3. There was no ethics review.
4. There was no mention of the countries or hospitals that contributed to the data source, no acknowledgments to their contributions. A request to the authors for information on the contributing centres was denied.
5. Data from Australia are not compatible with government reports (too many cases for

just five hospitals, more in-hospital deaths than had occurred in the entire country during the study period). Surgisphere (the data company) have since claimed this was an error of classification.

6. Data from Africa indicate over 40% of all COVID-19 cases and deaths in the continent occurred in *Surgisphere*-associated hospitals which had sophisticated electronic patient data recording, and patient monitoring able to detect and record “non-sustained [at least 6 secs] or sustained ventricular tachycardia or ventricular fibrillation”. This seems unlikely.
7. Unusually small reported variances in baseline variables, interventions and outcomes between continents
8. Mean daily doses of hydroxychloroquine that are 100 mg higher than FDA recommendations, whilst 66% of the data are from North American hospitals.
9. Implausible ratios of chloroquine to hydroxychloroquine use in some continents.
10. The tight 95% confidence intervals reported for the hazard ratios are unlikely. For instance, for the Australian data this would need about double the numbers of recorded deaths that were reported in the paper.

This paper has now been retracted, and the data cannot be verified.

4. The Geleris study was an observational study of 1,376 consecutive COVID-19 patients at a New York hospital to determine whether hydroxychloroquine use was associated with intubation or death, as a primary composite outcome.(25) 811 (58.9%) of these patients received hydroxychloroquine. The authors excluded patients who were intubated, died, or who were transferred to another facility within 24 hours after presentation to the emergency department from the analyses. A propensity score matching model (C-statistic of 0.81) was used to ensure that groups were similar at baseline.

Regarding safety, multivariable adjusted analyses with inverse probability weighting revealed no significant association between treatment with hydroxychloroquine and intubation or death (HR 1.04 (95% CI 0.82 – 1.32)). Whilst the patient population in this study is different to that of PRINCIPLE, it is interesting that the findings contrast with those of a recent Lancet study published by Mehra *et al*. One possible reason for the difference is that patients receiving interventions like hydroxychloroquine in the study by Mehra *et al* were sicker than those in the study’s control group. This may have arisen through use of crude measures to account for baseline disease severity (qSOFA score and SpO₂ < 94%) in their propensity score matching model, and may also explain the big differences seen in patients requiring mechanical ventilation between controls (7.7%) and those in intervention groups (20-21.6%).

5. Boulware and colleagues conducted a Covid-19 postexposure prophylaxis, placebo controlled randomised trial of hydroxychloroquine in 821 asymptomatic patients; 11.8% of those taking hydroxychloroquine vs 14.3 of those taking placebo experienced a new illness compatible with COVID-19 (absolute difference -2.4%) but this difference was not statistically significant, indicating no evidence of benefit from the hydroxychloroquine. (26)

Regarding safety, While side effects were more common with hydroxychloroquine than with placebo (40.1% vs. 16.8%), no serious adverse reactions were reported.

Earlier studies of hydroxychloroquine for COVID-19

1. Chen and colleagues conducted a *randomised* controlled trial to test the effectiveness of hydroxychloroquine in 30 adult patients who tested positive for COVID-19 in China.(27) Patients in the treatment group received 400mg of hydroxychloroquine for 5 days, while the control group received usual care. The result of a nasopharyngeal swab on Day 7 was used as the primary outcome. The intention- to- treat analysis revealed that the treatment group did not differ from the control group in the number of patients testing negative for COVID-19 on Day 7 (13 versus 14 patients), nor the duration of illness (all $P>0.05$).

Regarding safety, the authors report three adverse events in the control group (one patient with abnormal liver function and anaemia, and one patient with abnormal renal function), and four adverse events in the treatment group (two patients with diarrhoea, one with lethargy, and one patient with abnormal liver function tests), which the authors argue were not linked to treatment with HCQ. One patient in the treatment group deteriorated significantly and thus HCQ was stopped on Day 4 of the treatment. This study was under-powered according to their own calculations.

2. Gautret and colleagues presented the results of an open- label, non-randomised trial with 36 patients diagnosed with COVID-19 in French hospitals.(28) Six participants were asymptomatic, 22 had upper respiratory tract infection symptoms, and eight had lower respiratory tract infection symptoms. The twenty patients in the treatment group received HCQ 200mg three times a day for 10 days. Patients declining to take part in the study and not meeting the inclusion criteria were assigned to the control group and received usual care. Six of the patients in the treatment group additionally received azithromycin to prevent bacterial superinfection. The primary outcome was SARS- CoV-2 carriage at Day 6 on nasopharyngeal swabs. Patients treated with hydroxychloroquine were significantly more likely to test negative for SARS- CoV-2 on Day 6 compared with controls (70% versus 12.5% virologically cured, $p<0.001$). All patients treated with hydroxychloroquine and azithromycin tested negative on Day 6.

Regarding safety, the authors did not report any safety data, stating that this would follow in a subsequent publication. Aside from a lack of adverse event reporting, there are many problems with the study methodology including the non-randomized design, under-powered sample size, lack of intention-to-treat analysis, and absence of medium to long-term follow-up data.

3. Chen and colleagues conducted a *randomised* clinical trial of adult patients admitted to hospital with confirmed COVID-19.(7) Sixty two patients were randomly assigned to usual care ($n=31$) or hydroxychloroquine (200 mg BD) for five days in addition to usual care ($n=31$). The authors report that there were 'significant differences' in time to clinical recovery (TTCR) between the two groups, with TTCR defined as the return of body temperature and cough relief, maintained for more than 72 hours. They also report that all four patients who 'progressed to severe disease' were in the control group. The reporting of empirical data by the authors is limited and unclear. They did not include a power calculation, but presumably this study was under-powered to detect differences between groups. No medium to long-term follow-up data is presented.

Regarding safety, the authors report that two mild adverse events occurred (a rash and a headache), both of which were in patients receiving hydroxychloroquine. No patients receiving usual care experienced adverse events.

In summary

The large scale hospital based Recovery trial has recently announced that they found no benefit from hydroxychloroquine (as yet unpublished). No safety concerns have been reported by the Principle Trial. A post exposure prophylaxis study found no benefit from hydroxychloroquine, but also found no safety concerns. These studies address a different research question and focus on different patient populations in comparison to the Principle Trial. Evidence about early treatment of COVID-19 in the community is urgently needed: the potential application of the findings of the PRINCIPLE Trial of community treatment is considerable, and the 'reach' of the study is now nation-wide. Our study population are patients in the community and our trial question is about early treatment. Outcome data from studies with sicker hospitalised patients may not apply to our study population

A key, controversial observational study (Mehra et al) reported that those taking hydroxychloroquine had worse outcomes and suffered more cardiac events than those not taking hydroxychloroquine. However, major doubts have been expressed about the data integrity of this study and insufficient detail in the paper to judge the adequacy of the methods employed to adjust for the inevitable confounders in an observational study. Hydroxychloroquine is not a licensed drug for treating COVID-19. Patients doing well are therefore less likely to be prescribed this drug. When a patient is causing their clinical team more concern or their condition is deteriorating, the chances of them being prescribed hydroxychloroquine will be greater. Adjustment for potential confounders has been inadequate in the observational studies. Critically, these studies cannot adjust for the clinician's sense of how the patient is faring over time. The Mehra study has been retracted and can't be relied upon.

The deficiencies and differences in all of these studies highlight the need for well-conducted, adequately powered randomised clinical trials, to provide definitive evidence of the safety and effectiveness of hydroxychloroquine for the early community treatment COVID-19 illness. PRINCIPLE will assess whether hydroxychloroquine is safe and effective if given earlier in the course of illness and in patients with milder symptoms not requiring hospital admission.

2. Eligibility criteria specifically related to hydroxychloroquine

Inclusion criteria: None

Exclusion criteria:

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

Patients currently taking the following drugs: penicillamine, amiodarone, ciclosporin, digoxin: the following antimicrobials; azithromycin, clarithromycin, erythromycin, ciprofloxacin, levofloxacin, moxifloxacin, ketoconazole, itraconazole, or mefloquine: the following antidepressants; amitriptyline, citalopram, desipramine, escitalopram, imipramine, doxepin, fluoxetine, wellbutrin, venlafaxine; the following antipsychotics or mood stabilizers; haloperidol, droperidol, lithium, quetiapine, thioridazine, ziprasidone: methadone: sumatriptan, zolmitriptan

- Known congenital or documented QT prolongation
- Known retinal disease

3. Outcome measures related to hydroxychloroquine

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

4. Detail of intervention

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

a. Investigational Medicinal Product (IMP) description

Hydroxychloroquine sulphate 200 milligram (mg) tablets. The tablets are for oral administration. One tablet (200mg) hydroxychloroquine to be taken twice daily for 7 days by mouth (14 tablets in total).

Special instructions: Each dose should be taken with a meal or glass of milk. Antacids may reduce absorption of hydroxychloroquine so it is advised that a 4-hour interval be observed between taking hydroxychloroquine and an antacid.

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

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

b. Storage of IMP

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

c. SmPC precautions and concomitant medication

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

i. Precautions

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

Hydroxychloroquine occasionally causes blurred vision, which typically resolves once the medication is stopped. Participants will be advised via the Participant Information documents that if they develop any problems with vision, they should stop taking the medication immediately, seek clinical advice, and not drive or operate any heavy machinery.

ii. Concomitant medication

Hydroxychloroquine sulfate has been reported to increase plasma digoxin levels. Serum digoxin levels should be closely monitored in participants receiving concomitant treatment.

Hydroxychloroquine sulfate may also be subject to several of the known interactions of chloroquine even though specific reports have not appeared. These include: potentiation of its direct blocking action at the neuromuscular junction by aminoglycoside antibiotics; inhibition of its metabolism by cimetidine which may increase plasma concentration of the antimalarial; antagonism of effect of neostigmine and pyridostigmine; reduction of the antibody response to primary immunisation with intradermal human diploid-cell rabies vaccine.

As with chloroquine, antacids may reduce absorption of hydroxychloroquine so it is advised that a four hour interval be observed between hydroxychloroquine and antacid dosaging.

As hydroxychloroquine may enhance the effects of a hypoglycaemic treatment, a decrease in doses of insulin or antidiabetic drugs may be required.

Halofantrine prolongs the QT interval and should not be administered with other drugs that have the potential to induce cardiac arrhythmias, including hydroxychloroquine. Also, there may be an increased risk of inducing ventricular arrhythmias if hydroxychloroquine is used concomitantly with other arrhythmogenic drugs, such as amiodarone and moxifloxacin.

An increased plasma ciclosporin level was reported when ciclosporin and hydroxychloroquine were co-administered.

Hydroxychloroquine can lower the convulsive threshold. Co-administration of hydroxychloroquine with other antimalarials known to lower the convulsion threshold (e.g. mefloquine) may increase the risk of convulsions. Also, the activity of anti-epileptic drugs might be impaired if co-administered with hydroxychloroquine. In a single-dose interaction study, chloroquine has been reported to reduce the bioavailability of praziquantel. It is not known if there is a similar effect when hydroxychloroquine and praziquantel are co-administered. Per extrapolation, due to the similarities in structure and pharmacokinetic parameters between hydroxychloroquine and chloroquine, a similar effect may be expected for hydroxychloroquine.

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

iii. Pregnancy and Breastfeeding

A moderate amount of data on pregnant women (between 300 – 1000 pregnancy outcomes), including prospective studies in long-term use with large exposure, have not observed a

significant increased risk of congenital malformations or poor pregnancy outcomes. Hydroxychloroquine crosses the placenta. Only limited non-clinical data are available for hydroxychloroquine, data on chloroquine have shown developmental toxicity at high supratherapeutic doses and a potential risk of genotoxicity in some test systems. Therefore, hydroxychloroquine sulfate should be avoided in pregnancy except when, in the judgement of the physician, the individual potential benefits outweigh the potential hazards. Careful consideration should be given to using hydroxychloroquine during lactation, since it has been shown to be excreted in small amounts in human breast milk, and it is known that infants are extremely sensitive to the toxic effects of 4-aminoquinolines. Pregnancy and breastfeeding are exclusion criteria for the hydroxychloroquine arm of the PRINCIPLE trial.

5. Safety reporting

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

Common symptoms of hydroxychloroquine include abdominal pain; appetite decreased; diarrhoea; emotional lability; headache; nausea; skin reactions; vision disorders; and vomiting. Mechanisms for safety reporting are outlined in the trial protocol.

We will call all participants randomised to hydroxychloroquine on day 7 to ask about cardiovascular AEs. Our team of clinicians will review any AEs relating to cardiovascular symptoms from the day 7 call, and assess whether these may be related to hydroxychloroquine. If AEs are thought to be related and it's deemed necessary by the assessing clinician, the participant's GP will be contacted to arrange a face-to-face visit for further clinical evaluation.

26 APPENDIX E: USUAL CARE PLUS AZITHROMYCIN ARM

1. Background and rationale

a. Evidence for potential Azithromycin benefits in COVID-19

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

Firstly, Azithromycin appears to have some anti-viral mechanisms. In COVID-19, Azithromycin appears to inhibit viral replication and therefore reduces shedding. In the small open observational trial of Gautret *et al* the addition of azithromycin to hydroxychloroquine (HCQ) (at 200 tds for 10 days) in 6 of the 14 HCQ subjects of the total 36 COVID-19 patients in the study significantly reduced viral shedding at 3 days to 15% (one subject) versus 70% in the HCQ arm and 95% in the indirect control arm, with no shedding at 6 days in the combination arm versus 50% and 90% respectively.(28) Azithromycin was also used in some Chinese observational and interventional studies.

Azithromycin has also been shown to be active *in vitro* against Zika and Ebola viruses,(29-31) and to prevent severe respiratory tract infections when administered to patients suffering viral infection.(32) Inhibition of viral infections by azithromycin may be linked to its suppressive effect on the production of viral interferon.(33) 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.(34-36) 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.(37)

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

An important secondary pathway to severe illness and death with COVID-19 may be secondary infection and sepsis in the immune-compromised state, especially secondary community or hospital acquired pneumonia. Older people are more susceptible to pneumonia because of comorbidities, a weakened immune system and are therefore more likely to die.(38) 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.(38) Severe pneumonia is more prevalent the older you are and in those with more serious underlying diseases.(39) The leading cause of death is respiratory insufficiency. Death has been shown to increase in those not responding to initial antimicrobials, and consequently, the initial selection of the agent is important.

Common causative organisms in the elderly admitted to the hospital with pneumonia include *Haemophilus influenza*, *Staphylococcus aureus*, *Streptococcus pneumoniae*, and *Mycoplasma pneumoniae*. In severe pneumonia, *S. aureus*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa* have been identified as common causative organisms. Older patients often have polymicrobial infections, which may be a factor in non-responders. Assessment of 12,945 US

Medicare inpatients over 65 with pneumonia found that initial treatment with a second-generation cephalosporin plus macrolide (HR, 0.71; 95% CI, 0.52-0.96), a non-pseudomonas third-generation cephalosporin plus a macrolide (HR, 0.74; 0.60-0.92), or a fluoroquinolone alone (HR, 0.64; 0.43-0.94) was associated with lower 30-day mortality.(40)

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

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

2 Changes to outcome measures

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

3 Eligibility criteria specifically related to azithromycin

Inclusion criteria: No changes

Exclusion criteria:

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

4 Detail of intervention

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

a. Investigational Medicinal Product (IMP) description

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

Special instructions:

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

The marketing authorisation holder is: Teva UK Limited, Brampton Road, Hampden Park, Eastbourne, East Sussex, BN22 9AG, UK.

Marketing authorisation number: PL 00289/1570

b. Storage of IMP

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

c. SmPC precautions and concomitant medication

i. Precautions

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

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

ii. Concomitant medications

Effects of other medicinal products on azithromycin:

Antacids

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

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

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

Fluconazole

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

Nelfinavir

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

Rifabutin

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

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

Terfenadine

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

Cimetidine

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

Effect of azithromycin on other medicinal products:

Ergotamine derivatives

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

Digoxin and colchicine (P-gp substrates)

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

Coumarin-Type Oral Anticoagulants

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

monitoring prothrombin time when azithromycin is used in patients receiving coumarin-type oral anticoagulants.

Cyclosporin

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

Theophylline

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

Trimethoprim/sulfamethoxazole

Coadministration of trimethoprim/sulfamethoxazole DS (160 mg/800 mg) for 7 days with azithromycin 1200 mg on Day 7 had no significant effect on peak concentrations total exposure or urinary excretion of either trimethoprim or sulfamethoxazole. Azithromycin serum concentrations were similar to those seen in other studies.

Zidovudine

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

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

Astemizole, alfentanil

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

Atorvastatin

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

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

Carbamazepine

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

Cisapride

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

Cetirizine

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

Didanosins (Dideoxyinosine)

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

Efavirenz

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

Indinavir

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

Methylprednisolone

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

Midazolam

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

Sildenafil

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

Triazolam

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

iii. Fertility, pregnancy and lactation

Pregnancy

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

5 Safety reporting

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

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

26 APPENDIX F: USUAL CARE PLUS DOXYCYCLINE ARM

1. Background and rationale

a. Evidence for potential doxycycline benefits in COVID-19

Doxycycline may be beneficial in the treatment of COVID-19 patients, and especially those in the at-risk or age range of the PRINCIPLE trial.

The rationale for testing doxycycline is based on three reasons:

Firstly, doxycycline may have direct antiviral activity against SARS-CoV-2 based on computer modelling. Analysing all the proteins encoded by SARS-CoV-2 genes and then predicting potential targets by performing target-based virtual ligand screening, doxycycline ranked in the group of compounds with the highest binding affinity to 3CLpro (3-chymotrypsin-like protease). 3CLpro is the main protease in SARS-CoV-2 which is critical in the life-cycle of the virus (41).

Secondly, doxycycline has known anti-inflammatory effects in various human diseases by inhibiting mitogen-activated protein kinase (MAPK) and SMAD pathways (42), as well as potent antioxidant properties(43). Doxycycline reduces the hyperinflammation associated with severe COVID-19 by antagonising metalloproteinases such as MMP9 that are linked with lung injury, including SARS and ARDS(44).

Lastly, from extensive experience in other infectious diseases, doxycycline has broad antimicrobial activity and is efficacious against a broad spectrum of bacteria including atypical bacteria and other pathogens including intracellular plasmodia, chlamydia, rickettsia, and RNA viruses like Dengue fever and chikungunya.

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

An important secondary pathway to severe illness and death with COVID-19 may be secondary infection and sepsis in the immune-compromised state, especially secondary community or hospital acquired pneumonia. Older people are more susceptible to pneumonia because of comorbidities, a weakened immune system and are therefore more likely to die.(38) 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.(38) Severe pneumonia is more prevalent the older you are and in those with more serious underlying diseases.(39) The leading cause of death is respiratory insufficiency. Death has been shown to increase in those not responding to initial antimicrobials, and consequently, the initial selection of the agent is important. Common causative organisms in the elderly admitted to the hospital with pneumonia include *Haemophilus influenza*, *Staphylococcus aureus*, *Streptococcus pneumoniae* and less commonly, atypical organisms, such as *Mycoplasma pneumoniae* and *Klebsiella pneumoniae*. All these organisms fall under doxycycline's antimicrobial spectrum.

We are aware that currently NICE, in their COVID-19 rapid guideline, advocates that clinicians offer oral doxycycline for treatment of suspected pneumonia in people who can or wish to be

treated in the community if: the likely cause is bacterial or; it is unclear whether the cause is bacterial or viral and symptoms are more concerning or; they are at high risk of complications (older or frail patients, pre-existing comorbidity or have a history of severe illness following previous lung infection).(45) Doxycycline will have at least as broad a spectrum of action as azithromycin in terms of bacterial infections with the potential anti-viral and anti-inflammatory effects.

Doxycycline for acute cough and community acquired pneumonia is recommended in the British National Formulary at a dose of Doxycycline 200mg stat then 100mg daily for the next 4 days. However, its use in COVID-19 is not proven and therefore important to address in this trial. Given the potential anti-inflammatory properties of doxycycline, we will use a slightly extended 7 day course.

2. Changes to outcome measures

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

3. Eligibility criteria specifically related to doxycycline

Inclusion criteria: No changes

Exclusion criteria:

- Pregnancy
- Breastfeeding
- Myasthenia gravis
- Systemic lupus erythematosus
- Previous adverse reaction to, or currently taking, doxycycline or other tetracyclines
- Sucrose intolerance (i.e. rare hereditary problems of fructose intolerance, glucose galactose malabsorption or sucrose-isomaltase insufficiency)
- Already taking antibiotics for an acute condition
- Patients taking the following drugs: ciclosporin, retinoids (acitretin, alitretinoin, isotretinoin, tretinoin), methotrexate, ergotamine, methoxyflurane, lithium.

4. Detail of intervention

Participants randomised to the usual care plus doxycycline arm will receive usual clinical care as per NHS guidelines, plus a course of oral doxycycline for 7 days. We will use the IMP distribution methods described in the protocol to deliver IMP to participants.

a. Investigational Medicinal Product (IMP) description

Doxycycline 100mg capsules. Participants in this arm will take 200mg on the first day (as a single dose or in divided doses with a twelve hour interval) followed by 100mg a day for 6 days (7 day course in total). The capsules are for oral administration.

Special instructions:

Capsules should be swallowed whole with plenty of fluid, while sitting or standing. Capsules should be taken during meals, well before going to bed. Due to the risk of photosensitivity, patients should be advised to avoid exposure to sunlight or sun lamps.

The marketing authorisation holder is:

Accord-UK Ltd (Trading style: Accord), Whiddon Valley, Barnstaple, Devon, EX32 8NS
Marketing authorisation number: PL 0142/0407

b. Storage of IMP

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

c. SmPC precautions and concomitant medication

i. Precautions

Doxycycline is a commonly prescribed antibiotic with an established safety profile. The SmPC states that in elderly patients “doxycycline may be prescribed in the usual dose with no special precautions. No dosage adjustment is necessary in the presence of renal impairment”.

ii. Concomitant medications

Warfarin

There have been reports of prolonged prothrombin time in patients taking warfarin and doxycycline. Tetracyclines depress plasma prothrombin activity and reduced dosage of concomitant anti-coagulants may be necessary

5. Safety reporting

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

Common side effects of doxycycline include: Angioedema; diarrhoea; headache; Henoch-Schönlein purpura; hypersensitivity; nausea/vomiting; pericarditis; skin and photosensitivity reaction; dyspnoea; hypotension; peripheral oedema; tachycardia.

PRINCIPLE Trial, EudraCT: 2020-001209-22 Substantial Amendment 6

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

Thu 7/2/2020 15:24

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

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

 1 attachments (407 KB)

281958_Substantial Amendment 6_29Jun2020_Locked02Jul20_140718.pdf;

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 amendment as required.

Please find attached the PDF version of the signed and locked amendment tool.

Please submit this signed amendment tool, together with the tracked and clean copies of all amended documents, to the REC via the online amendment submission portal (for further guidance please refer to the HRA training video: [how to complete online submission of amendments](#)).

When you have received the submission confirmation, please email this, with the final documents you submitted, to the CTRG generic email address (ctr@admin.ox.ac.uk).

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

Please send a copy of the approval letter(s) to the CTRG generic email address (ctr@admin.ox.ac.uk) once you have received it/them. Please do not implement your amendment until all approval(s) are in place.

Let me know if you have any questions, or need any further information.

Kind regards,

Elaine

PID14903-A008-SP001-AC001

Elaine Chick

Deputy Head | Clinical Trials and Research Governance (CTRG)
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Joint Research Office
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researchsupport@admin.ox.ac.uk



Guidance (FAQs) for Clinical Research during the COVID-19 national emergency can be found on: <https://researchsupport.admin.ox.ac.uk/ctrq>

Online submission of amendments and a new amendment tool went live across the UK on **Tuesday 2 June 2020**.

Substantial and non-substantial amendment forms will no longer be accepted. See [amendment tool and full guidance](#).

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

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

Date:

Hello,

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

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

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

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

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

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

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

Yours Sincerely

The PRINCIPLE Study Team, University of Oxford

VOLUNTEERS NEEDED

Do you have suspected or confirmed
COVID-19?

Are you aged 65 or over? Or 50 to 64 with underlying health conditions? with symptoms within the past 14 days?

Please visit www.principletrial.org to find out how to take part
in an **Urgent Public Health Clinical Trial** for
COVID-19 Treatments



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Clinical Trials Unit

Advert, v1.0, 02.07.20.
IRAS: 281958, REC:
20/SC/058



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

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

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

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

- i) **You have symptoms of COVID-19 (a new continuous cough or a high temperature or a loss of, or change in, normal sense of taste or smell), and have had them for less than 15 days.**

OR

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

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

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

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

Yours Sincerely

[insert practice name]



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

Patient Recruitment Letter Version/Date: v2.1 2nd July 2020, EudraCT number:2020-001209-22

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



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Clinical Trials Unit

PRINCIPLE Radio Advert

COVID-19 has affected the lives of everybody within the UK and the rest of the world. Finding safe and effective treatments has been the drive of researchers at the University of Oxford and right now, you have an opportunity to help. PRINCIPLE is a national priority trial to find treatments for COVID-19. We are looking for volunteers aged 65 or over, OR aged between 50 and 64 with an underlying health condition. To be eligible to take part, you must be unwell with Covid-19 symptoms, and have had them for less than 14 days. No face to face visits are needed. Please help us fight COVID-19 by visiting our website www.principletrial.org.

PRINCIPLE Trial – Social Media Post – version 1

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

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

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

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

<http://www.principletrial.org>

PRINCIPLE Trial – Social Media Post – version 2

PRINCIPLE is an Urgent Public Health clinical trial investigating treatments for people aged over 50, with COVID-19 symptoms. More details at www.principletrial.org or click [HERE](#) to register as a patient from PRACTICE NAME.

PRINCIPLE TRIAL: TEXT MESSAGE INFORMATION FOR PARTICIPANTS

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

PRINCIPLE TRIAL: TEXT MESSAGE INFORMATION FOR PARTICIPANTS (SHORT VERSION 1)

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

PRINCIPLE TRIAL: TEXT MESSAGE INFORMATION FOR PARTICIPANTS (SHORT VERSION 2)

This is a message from Dr XX at XX Medical Practice regarding a clinical trial exploring treatment for the COVID-19 virus. Please click <https://www.phctrials.ox.ac.uk/principle-trial/how-to-join> to find out more. Please call the Trial Team if you have any questions: 0800 138 0880

PRINCIPLE TRIAL: TEXT MESSAGE INFORMATION FOR PARTICIPANTS (SHORT VERSION 3)

This is a message from Dr XX at XX Medical Practice regarding a clinical trial exploring treatment for the COVID-19 virus. Please click <https://www.phctrials.ox.ac.uk/principle-trial/how-to-join> to find out more.



Website Trial Advert

Join a COVID-19 clinical trial

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

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

Help the fight against COVID-19

 **Do you have suspected or confirmed COVID-19?**

(Symptoms may include new cough, high temperature, loss/change in smell/taste)

**Are you aged 65 and above?
Or aged 50 to 64 with any of these illnesses?**



High blood pressure and/
or heart disease



Known diabetes



Asthma or lung disease



Stroke or
neurological
problems



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



Liver disease

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

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

To find out more or register for the study, please visit:

www.principletrial.org

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



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NIHR National Institute
for Health Research



UK Research
and Innovation

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



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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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 alter the COVID-19 disease course by reducing the need for hospital admission. 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 at altering the disease course by reducing the need for hospital admission. Our trial aims to evaluate potential treatments as they are identified. To be able to do this, we aim to test one or more suitable, potential treatments for COVID-19, as soon as they become available.

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

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

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

Aim

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

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

Can I take part?

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

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

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

OR

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

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

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

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

- heart disease or a diagnosis of high blood pressure
- asthma or lung disease
- known diabetes
- liver disease
- stroke or neurological problem

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

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

Do I have to take part?

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



What will happen to me if I take part?

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

Informed Consent

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

Initial Questionnaire

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



Letting Your GP Know

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

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

Randomisation

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

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



Swab

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

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

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



Blood test

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

Trial Treatment

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

Follow-Up

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



Flowchart—What Will I Need to Do?

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

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

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

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

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

Follow-up

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

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

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

Optional Follow-up

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

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

What happens if I am admitted to Hospital?

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

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

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

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

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



What are the possible benefits of taking part?

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

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

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



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

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

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

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

Expenses and Payments

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

What if there are any problems?

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

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

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

What will happen to my data?

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

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

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

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

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

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

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

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

What if relevant new information becomes available during the trial?

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

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

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

What will happen to the results of the trial?

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

Who is organising and funding the research?

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

Who has reviewed the trial?

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

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

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

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

Trial Address:

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

Trial Team:

Tel. 0800 138 0880

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

Appendix 3— Doxycycline

Drug Information

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

Side-effects

The common side effects are:

- * swelling
- * diarrhoea
- * headache
- * Henoch-Schönlein purpura
- * nausea/vomiting
- * hypersensitivity
- * chest pains
- * rash
- * difficulty breathing
- * low blood pressure
- * swelling of lower legs or hand
- * abnormally rapid heart rate

Participant Pictorial Information Sheet

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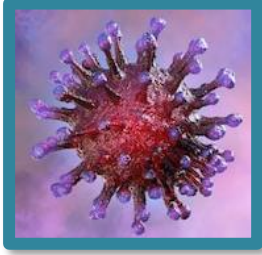
PRINCIPLE Trial

Platform Randomised trial of Interventions against COVID-19 In older people
Pictorial Participant Information Booklet v2.1, 2nd July 2020,

EudraCT number: 2020-001209-22

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

What is the trial about?

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

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	3. At the moment, we do not have treatments for COVID-19 that we know definitely work to help recovery and prevent hospitalisation.
	4. The aim of this trial is to test possible treatments for COVID-19 in older adults. We hope to find treatments that help people recover quicker.

Who can take part?

	Anybody aged 65 years or over. AND Anybody aged 50 to 64 years with: • Weakened immune system (e.g. taking chemotherapy) • Heart disease • Lung disease • Known diabetes • Liver disease • Stroke or neurological problem WITH
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		A new continuous cough or fever or a change in taste/smell OR You have had a positive test for SARS-Co-V2 infection which was taken fewer than 15 days ago, AND are unwell with symptoms of COVID-19. <i>These symptoms may include, but are not limited to, shortness of breath, general feeling of being unwell, muscle pain, diarrhoea, vomiting, fever and cough, and you must have had them for fewer than 15 days. If you are starting to feel better, this study isn't for you.</i>
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Professor Christopher Butler IRAS Project no. 281958 REC Reference no.:20/SC/058

What will happen if I take part?

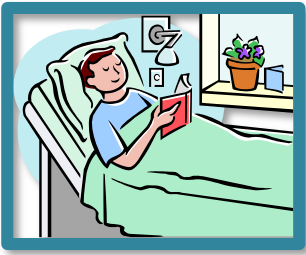
	6.	If you develop a fever or a new continuous cough or change in taste/smell, OR if you have a positive test for SARS-Co-V2 infection with symptoms in the past 14 days, please visit our trial website (see end of this leaflet).
	7.	We will ask you to fill in a short form online, to check that you can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

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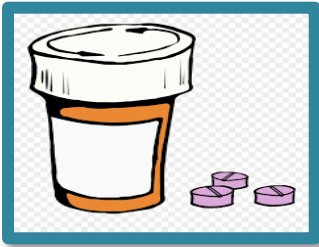
	8.	Your care will not be affected, whether or not you do take part in the trial.
	9.	If you are suitable to take part in the trial, you will be asked to fill in a consent form online, and to answer a few questions about yourself and your symptoms.
	10.	We will ask you to add details of a 'trial partner'.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

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

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

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

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

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What will happen to my information?

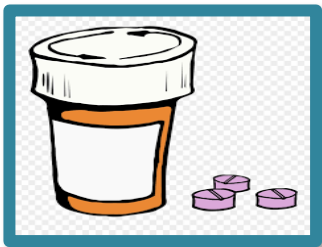
	18.	We will use the information you give us to find out which treatments work. We may also look at your general practice and hospital medical records for further information about you and your illness.
	19.	Any information that we collect about you will be kept safe. Your name will not go on any reports,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

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Pictorial Participant Information Booklet v2.1, 2nd July2020,

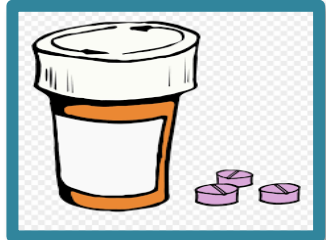
EudraCT number:2020-001209-22

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

What are the disadvantages of taking part?

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

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

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Will I be reimbursed for taking part?

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

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

What if there is a problem?

	26.	If you have a concern about any aspect of this trial at any time, you can contact the trial team or the University of Oxford Clinical Trials and Research Governance (CTRG) office (Contact details below).
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Professor Christopher Butler IRAS Project no. 281958 REC Reference no.:20/SC/058

Trial contact details

	27. Trial team: principle@phc.ox.ac.uk 0800 138 0880 Trial Website: www.principletrial.org CTRG: ctrig@admin.ox.ac.uk 01865 616480
	28. Thank you for taking the time to think about taking part in this trial.

Thank you!

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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 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: Wording on PRINCIPLE enrolment website to sign-post to the Imperial study

We would like to invite you to take part in an independent study run by a team at Imperial College. The study is for people with COVID-19 and research nurses would visit you at home to swab test your cohabitants for COVID-19 to determine household spread and take blood samples to measure immune responses. If you live in London and your symptoms have been present for less than 11 days, please email robert.varro@nhs.net for further information.



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HEALTH SCIENCES

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Clinical Trials Unit



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

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

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

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



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

You cannot take Hydroxychloroquine if you are taking any of the following medication: penicillamine, amiodarone, ciclosporin, digoxin: the following antimicrobials; azithromycin, clarithromycin, erythromycin, ciprofloxacin, levofloxacin, moxifloxacin, ketoconazole, itraconazole, or mefloquine: the following antidepressants; amitriptyline, citalopram, desipramine, escitalopram, imipramine, doxepin, fluoxetine, wellbutrin, venlafaxine; The following antipsychotic or mood stabilizers; haloperidol, droperidol, lithium, quetiapine, thioridazine, ziprasidone: Methadone: Sumatriptan, zolmitriptan. If you are taking any of the above medications, please do not take the trial medication and speak to your GP.

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

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

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

Doxycycline Capsules BP 100mg

Summary of Product Characteristics Updated 19-Dec-2019 | Accord-UK Ltd

1. Name of the medicinal product

DOXYCYCLINE CAPSULES BP 100mg

2. Qualitative and quantitative composition

Each capsule contains Doxycycline hyclate equivalent to 100mg of Doxycycline base.

For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Green hard gelatin capsules printed "C" and "DW" in black.

4. Clinical particulars

4.1 Therapeutic indications

Doxycycline has been found clinically effective in the treatment of a variety of infections caused by susceptible strains of Gram-positive and Gram-negative bacteria and certain other micro-organisms.

Respiratory tract infections: Pneumonia and other lower respiratory tract infections due to susceptible strains of *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Klebsiella pneumoniae* and other organisms. *Mycoplasma pneumoniae* pneumonia. Treatment of chronic bronchitis, sinusitis.

Urinary tract infections: caused by susceptible strains of *Klebsiella* species, *Enterobacter* species, *Escherichia coli*, *Streptococcus faecalis* and other organisms.

Sexually transmitted diseases: Infections due to *Chlamydia trachomatis* including uncomplicated urethral, endocervical or rectal infections. Non-gonococcal, urethritis caused by *Ureaplasma urealyticum* (T-mycoplasma). Doxycycline Capsules are also indicated in chancroid, granuloma inguinale and lymphogranuloma venereum. Doxycycline is an alternative drug in the treatment of gonorrhoea and syphilis.

Skin infections: Acne vulgaris when antibiotic therapy is considered necessary.

Since doxycycline is a member of the tetracycline series of antibiotics, it may be expected to be useful in the treatment of infections which respond to other tetracyclines, such as:

Ophthalmic infections: Due to susceptible strains of gonococci, staphylococci and *Haemophilus influenzae*. Trachoma, although the infectious agent, as judged by immunofluorescence, is not always eliminated. Inclusion conjunctivitis may be treated with oral Doxycycline alone or in combination with topical agents.

Rickettsial infections: Rocky Mountain spotted fever, typhus group, Q fever and *Coxiella endocarditis* and tick fevers.

Other infections: Psittacosis, brucellosis (in combination with streptomycin), cholera, bubonic plague, louse and tick-borne relapsing fever, tularaemia glanders, melioidosis, chloroquine-resistant falciparum malaria and acute intestinal amoebiasis (as an adjunct to amoebicides).

Doxycycline is an alternative drug in the treatment of leptospirosis, gas gangrene and tetanus.

Doxycycline Capsules are indicated for prophylaxis in the following conditions: Scrub typhus, travellers diarrhoea (enterotoxigenic *Escherichia coli*), leptospirosis and malaria. Prophylaxis of malaria should be used in accordance to current guidelines, as resistance is an ever changing problem.

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

4.2 Posology and method of administration

Posology

Adults and children aged 12 years to less than 18 years

The usual dose of Doxycycline Capsules for the treatment of acute infections in adults and children aged 12 years to less than 18 years is 200mg on the first day (as a single dose or divided doses), followed by a maintenance dose of 100mg/day. In the management of more severe infections, 200mg daily should be given throughout treatment.

Children aged 8 years to less than 12 years. (Section 4.4)

The use of doxycycline for the treatment of acute infections in children aged 8 years to less than 12 years should be carefully justified in situations where other drugs are not available, are not likely to be effective or are contraindicated.

In such circumstance, the doses for the treatment of acute infections are:

- For children 45 kg or less- Initial dose: 4.4 mg/kg (in single or 2 divided doses) with maintenance dose: 2.2 mg/kg (in single or 2 divided doses). In the management of more severe infections, up to 4.4 mg/kg should be given throughout treatment.
- For children, over 45 kg - Dose administered for adults should be used.

Children aged from birth to less than 8 years.

Doxycycline should not be used in children aged younger than 8 years due to the risk of teeth discolouration. (Section 4.4 and 4.8)

Dosage recommendations in specific infections:

Acne vulgaris: 50mg daily with food or fluid for 6-12 weeks.

Sexually transmitted diseases: 100mg twice daily for 7 days is recommended in the following infections: uncomplicated gonococcal infections (except anorectal infections in men); uncomplicated urethral, endocervical or rectal infection caused by Chlamydia trachomatis; non-gonococcal urethritis caused by Ureaplasma urealyticum.

Acute epididymo-orchitis caused by Chlamydia trachomatis or Neisseria gonorrhoeae: 100mg twice daily for 10 days.

Primary and secondary syphilis: Non-pregnant penicillin-allergic patients who have primary or secondary syphilis can be treated with the following regimen: doxycycline 200 mg orally twice daily for two weeks, as an alternative to penicillin therapy.

Louse-borne and tick-borne relapsing fevers: A single dose of 100mg or 200mg according to severity.

Treatment of chloroquine-resistant falciparum malaria: 200mg daily for at least 7 days. Due to the potential severity of the infection, a rapid-acting schizonticide such as quinine should always be given in conjunction with doxycycline; quinine dosage recommendations vary in different areas.

Prophylaxis of malaria: 100mg daily in adults and children over the age of 12 years. Prophylaxis can begin 1-2 days before travel to malarial areas. It should be continued daily during travel in the malarial areas and for 4 weeks after the traveller leaves the malarial area. For current advice on geographical resistance patterns and appropriate chemoprophylaxis, current guidelines or the Malaria Reference Laboratory should be consulted, details of which can be found in the British National Formulary (BNF).

For the prevention of scrub typhus: 200mg as a single dose.

For the prevention of travellers' diarrhoea in adults: 200mg on the first day of travel (administered as a single dose or as 100mg every 12 hours) followed by 100mg daily throughout the stay in the area. Data on the use of the drug prophylactically are not available beyond 21 days.

For the prevention of leptospirosis: 200mg once each week throughout the stay in the area and 200mg at the completion of the trip. Data on the use of the drug prophylactically are not available beyond 21 days.

Use in the elderly: Doxycycline may be prescribed in the elderly in the usual dosages with no special precautions. No dosage adjustment is necessary in the presence of renal impairment.

Use in patients with impaired hepatic function: See section 4.4.

Use in patients with renal impairment: Studies to date have indicated that administration of Doxycycline at the usual recommended doses does not lead to accumulation of the antibiotic in patients with renal impairment see section 4.4.

Rocky Mountain spotted fever

Adults: 100 mg every 12 hours.

Children: weighing less than 45 kg: 2.2 mg/kg body weight given twice a day. Children weighing 45 kg or more should receive the adult dose (see section 4.4 paediatric population).

Patients should be treated for at least 3 days after the fever subsides and until there is evidence of clinical improvement. Minimum course of treatment is 5-7 days.

Method of administration

The capsules should be swallowed with plenty of fluid in either the resting or standing position and well before going to bed for the night to reduce the likelihood of oesophageal irritation and ulceration.

If gastric irritation occurs, it is recommended that Doxycycline Capsules be given with food or milk. Studies indicate that the absorption of doxycycline is not notably influenced by simultaneous ingestion of food or milk.

Exceeding the recommended dosage may result in an increased incidence of side effects. Therapy should be continued for at least 24 to 48 hours after symptoms and fever have subsided.

When used in streptococcal infections, therapy should be continued for 10 days to prevent the development of rheumatic fever or glomerulonephritis.

4.3 Contraindications

- **Hypersensitivity** to the active substance, any of the tetracyclines or to any of the excipients listed in section 6.1.
- **Pregnancy:** Doxycycline is contra-indicated in pregnancy. It appears that the risks associated with the use of tetracyclines during pregnancy are predominantly due to effects on teeth and skeletal development. (See section 4.4 regarding use during tooth development).
- **Nursing mothers:** Tetracyclines are excreted into milk and are therefore contra-indicated in nursing mothers. (See section 4.4 regarding use during tooth development).

4.4 Special warnings and precautions for use

Paediatric population

The use of drugs of the tetracycline class during tooth development (last half of pregnancy; infancy and childhood to the age of 8 years) may cause permanent discolouration of the teeth (yellow-grey-brown). This adverse reaction is more common during long-term use of the drugs but has been observed following repeated short-term courses. Enamel hypoplasia has also been reported. Use doxycycline in paediatric patients aged younger than 8 years only when the potential benefits are expected to outweigh the risks in severe or life-threatening conditions (e.g. Rocky Mountain spotted fever), only when there are no adequate alternative therapies.

Although the risk of permanent teeth staining is rare in children aged 8 years to less than 12 years, the use of doxycycline should be carefully justified in situations where other drugs are not available, are not likely to be effective or are contraindicated.

Use in patients with impaired hepatic function: Doxycycline should be administered with caution to patients with hepatic impairment or those receiving potentially hepatotoxic drugs. Abnormal hepatic function has been reported rarely and has been caused by both the oral and parenteral administration of tetracyclines, including doxycycline.

Use in patients with renal impairment: Excretion of doxycycline by the kidney is about 40%/72 hours in individuals with normal renal function. This percentage excretion may fall to a range as low as 1-5%/72 hours in individuals with severe renal insufficiency (creatinine clearance below 10ml/min). Studies have shown no significant difference in the serum half-life of doxycycline in individuals with normal and severely impaired renal function. Haemodialysis does not alter the serum half-life of doxycycline. The anti-anabolic action of the tetracyclines may cause an increase in blood urea. Studies to date indicate that this anti-anabolic effect does not occur with the use of doxycycline in patients with impaired renal function.

Serious skin reactions: Serious skin reactions, such as exfoliative dermatitis, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, and drug reaction with eosinophilia and systemic symptoms (DRESS) have been reported in patients receiving doxycycline (see section 4.8). If serious skin reactions occur, doxycycline should be discontinued immediately and appropriate therapy should be instituted.

Photosensitivity: Photosensitivity manifested by an exaggerated sunburn reaction has been observed in some individuals taking tetracyclines, including doxycycline. Patients likely to be exposed to direct sunlight or ultraviolet light should be advised that this reaction can occur with tetracycline drugs and treatment should be discontinued at the first evidence of skin erythema.

Photoonycholysis has also been reported in patients receiving doxycycline (see section 4.8).

Benign intracranial hypertension: Bulging fontanelles in infants have been reported in individuals receiving tetracyclines. Benign intracranial hypertension (pseudotumor cerebri) has been associated with the use of tetracyclines including doxycycline. Benign intracranial hypertension (pseudotumor cerebri) is usually transient, however cases of permanent visual loss secondary to benign intracranial hypertension (pseudotumor cerebri) have been reported with tetracyclines including doxycycline. If visual disturbance occurs during treatment, prompt ophthalmologic evaluation is warranted. Since intracranial pressure can remain elevated for weeks after drug cessation patients should be monitored until they stabilize. Concomitant use of isotretinoin or other systemic retinoids and doxycycline should be avoided because isotretinoin is also known to cause benign intracranial hypertension (pseudotumor cerebri). (See section 4.5).

Microbiological overgrowth: The use of antibiotics may occasionally result in over-growth of non-susceptible organisms, including *Candida*. If a resistant organism appears, the antibiotic should be discontinued and appropriate therapy instituted.

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including doxycycline, and has ranged in severity from mild to life-threatening. It is important to consider this diagnosis in patients who present with diarrhoea subsequent to the administration of antibacterial agents.

Clostridium difficile associated diarrhoea (CDAD) has been reported with use of nearly all antibiotics, including doxycycline, and has ranged 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 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 treatment.

Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.

Oesophagitis: instances of oesophagitis and oesophageal ulcerations have been reported in patients receiving capsule and tablet forms of drugs in the tetracycline class, including doxycycline. Most of these patients took medications immediately before going to bed or with inadequate amounts of fluid.

Porphyria: There have been rare reports of porphyria in patients receiving tetracyclines.

Venereal disease: When treating venereal diseases, where co-existent syphilis is suspected, proper diagnostic procedures, including dark-field examinations, should be utilised. In all such cases monthly serological tests should be made for at least four months.

Beta-haemolytic streptococci infections: Infections due to Group A beta-haemolytic Streptococci should be treated for at least 10 days.

Myasthenia gravis: Due to a potential for weak neuromuscular blockade, care should be taken in administering tetracyclines to patients with myasthenia gravis.

Systemic lupus erythematosus: Tetracyclines can cause exacerbation of systemic lupus erythematosus (SLE).

Methoxyflurane: Caution is advised in administering tetracyclines with methoxyflurane (see section 4.5).

Jarisch-Herxheimer reaction: Some patients with spirochete infections may experience a Jarisch-Herxheimer reaction shortly after doxycycline treatment is started. Patients should be reassured that this is a usually self-limiting consequence of antibiotic treatment of spirochete infections.

4.5 Interaction with other medicinal products and other forms of interaction

The absorption of doxycycline may be impaired by concurrently administered antacids containing aluminium, calcium, magnesium or other drugs containing these cations; oral zinc, iron salts or bismuth preparations. Dosages should be maximally separated.

Since bacteriostatic drugs may interfere with the bactericidal action of penicillin, it is advisable to avoid giving doxycycline in conjunction with penicillin.

There have been reports of prolonged prothrombin time in patients taking warfarin and doxycycline. Tetracyclines depress plasma prothrombin activity and reduced doses of concomitant anticoagulants may be necessary.

The serum half-life of doxycycline may be shortened when patients are concurrently receiving barbiturates, carbamazepine or phenytoin. An increase in the daily dosage of Doxycycline should be considered.

Alcohol may decrease the half-life of doxycycline.

A few cases of pregnancy or breakthrough bleeding have been attributed to the concurrent use of tetracycline antibiotics with oral contraceptives.

Doxycycline may increase the plasma concentration of ciclosporin. Co-administration should only be undertaken with appropriate monitoring.

The concurrent use of tetracyclines and methoxyflurane has been reported to result in fatal renal toxicity. See section 4.4.

Concomitant use of isotretinoin or other systemic retinoids and doxycycline should be avoided. Each of these agents used alone has been associated with benign intracranial hypertension (pseudotumor cerebri). (See section 4.4).

Laboratory test interactions

False elevations of urinary catecholamine levels may occur due to interference with the fluorescence test.

4.6 Fertility, pregnancy and lactation

See section 4.3.

4.7 Effects on ability to drive and use machines

The effect of doxycycline on the ability to drive or operate heavy machinery has not been studied. There is no evidence to suggest that doxycycline may affect these abilities.

4.8 Undesirable effects

The following adverse reactions have been observed in patients receiving tetracyclines, including doxycycline.

	Common	Uncommon	Rare	Not known
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System Organ Class	≥1/100 to <1/10	≥1/1000 to <1/100	≥1/10,000 to <1/1000	Cannot be estimated from the available data.
Infections and infestations		Vaginal infection	Candida Infection	
Blood and lymphatic system disorders			Haemolytic anaemia, neutropenia, thrombocytopenia, eosinophilia	
Immune system disorders	Hypersensitivity (including anaphylactic shock, anaphylactic reaction, anaphylactoid reaction, angioedema, exacerbation of systemic lupus erythematosus, pericarditis, serum sickness, Henoch-Schonlein purpura, hypotension, dyspnoea, tachycardia, peripheral oedema and urticaria)		Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), Jarisch-Herxheimer reaction ^b (see section 4.4)	
Endocrine disorders			Brown-black microscopic discolouration of thyroid glands	
Metabolism and nutrition disorders			Porphyria, decreased appetite	
Nervous system disorders	Headache		Anxiety, benign intracranial hypertension (pseudotumor cerebri) *, fontanelle bulging	
Ear and labyrinth disorders			Tinnitus	
Vascular disorders			Flushing	
Gastrointestinal disorders	Nausea/vomiting	Dyspepsia (Heartburn/gastritis)	Pancreatitis, pseudomembranous colitis, <i>Clostridium difficile</i> colitis, oesophageal ulcer, oesophagitis, enterocolitis, inflammatory lesions (with monilial overgrowth) in the anogenital region, dysphagia, abdominal pain, diarrhoea, glossitis, stomatitis	tooth discolouration ^a
Hepatobiliary disorders			Hepatic failure, hepatitis, hepatotoxicity, jaundice, hepatic function abnormal	

Skin and subcutaneous tissue disorders	Photosensitivity reaction, rash including maculopapular and erythematous rashes		Toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme, dermatitis exfoliative, photoonycholysis, <u>skin hyperpigmentation^c</u>	
Musculoskeletal, connective tissue and bone disorders			Arthralgia, myalgia	
Renal and urinary disorders			Blood urea increased	

* Symptoms included blurring of vision, scotomata and diplopia. Permanent visual loss has been reported.

^a Reversible and superficial discolouration of permanent teeth has been reported with the use of doxycycline but frequency cannot be estimated from available data.

^b in the setting of spirochete infections treated with doxycycline.

^c with chronic use of doxycycline.

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

4.9 Overdose

Acute overdosage with antibiotics is rare. In the event of overdosage discontinue medication. Gastric lavage plus appropriate supportive treatment is indicated.

Dialysis does not alter serum half-life and thus would not be of benefit in treating cases of overdosage.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: tetracyclines,

ATC code: J01AA02

Doxycycline is primarily bacteriostatic and is believed to exert its antimicrobial effect by the inhibition of protein synthesis. Doxycycline is active against a wide range of Gram-positive and Gram-negative bacteria and certain other micro-organisms.

5.2 Pharmacokinetic properties

Tetracyclines are readily absorbed and are bound to plasma proteins in varying degrees. They are concentrated by the liver in the bile and excreted in the urine and faeces at high concentrations and in a biologically active form. Doxycycline is virtually completely absorbed after oral administration. Studies reported to date indicate that the absorption of doxycycline, unlike certain other tetracyclines, is not notably influenced by the ingestion of food or milk.

Following a 200 mg dose, normal adult volunteers averaged peak serum levels of 2.6 micrograms/ml of doxycycline at 2 hours decreasing to 1.45 micrograms/ml at 24 hours. Doxycycline has a high degree of lipid solubility and a low affinity for calcium. It is highly stable in normal human serum. Doxycycline will not degrade into an epianhydro form.

5.3 Preclinical safety data

Not applicable.

6. Pharmaceutical particulars

6.1 List of excipients

Also contains:

Gelatin

Magnesium stearate

Shellac glaze
Sodium lauryl sulfate
Starch
Quinoline Yellow (E104)
Erythrosine (E127)
Patent Blue V (E131)
Titanium Dioxide (E171)
Iron oxide black (E172)
Propylene glycol

6.2 Incompatibilities

None known.

6.3 Shelf life

PVC Blister packs

Five years.

All other containers

Four years.

6.4 Special precautions for storage

Store below 25°C in a dry place.

6.5 Nature and contents of container

The product containers are rigid injection moulded polypropylene or injection blow-moulded polyethylene containers with polyfoam wad or polyethylene ullage filler and snap-on polyethylene lids; in case any supply difficulties should arise the alternative is amber glass containers with screw caps and polyfoam wad or cotton wool.

The product may also be supplied in blister packs in cartons:

a) Carton: Printed carton manufactured from white folding box board.

b) Blister pack: (i) 250µm white rigid PVC. (ii) Surface printed 20µm hard temper aluminium foil with 5-7g/M² PVC and PVdC compatible heat seal lacquer on the reverse side.

Pack sizes: 7s, 8s, 10s, 14s, 16s, 28s, 30s, 50s, 56s, 60s, 84s, 90s, 100s, 112s, 120s, 168s, 180s

6.6 Special precautions for disposal and other handling

Not applicable.

Administrative Data

7. Marketing authorisation holder

Accord-UK Ltd
(Trading style: Accord)
Whiddon Valley
Barnstaple
Devon
EX32 8NS

8. Marketing authorisation number(s)

PL 0142/0407

9. Date of first authorisation/renewal of the authorisation

02.04.97, 02.04.03

10. Date of revision of the text

12/12/2019

Company Contact Details

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NUFFIELD DEPARTMENT OF
PRIMARY CARE
HEALTH SCIENCES

Primary Care
Clinical Trials Unit



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

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

The medication you have been given is called **Doxycycline**. You need to take your trial medication for **7 days**. You have been given 100mg capsules and should take TWO capsules on the first day (as a single dose or in divided doses with a twelve hour interval) followed by **ONE** capsule a day for 6 days.

Capsules should be swallowed whole with plenty of fluid, while sitting or standing. Capsules should be taken during meals. Please avoid exposure to sunlight or sun lamps.

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

The common side effects of this medication include: **swelling, diarrhoea, headache, Henoch-Schönlein purpura, nausea, hypersensitivity, chest pains, rash, vomiting, difficulty breathing, low blood pressure, swelling of lower legs or hand, abnormally rapid heart rate.**

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

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

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 **Doxycycline** if you are taking any of the following medications: **ciclosporin, retinoids (acitretin, alitretinoin, isotretinoin, tretinoin), methotrexate, ergotamine, methoxyflurane, lithium**. 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. Avoid exposure to sunlight or sun lamps.

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.

Study Title	PRINCIPLE
EudraCT No	2020-001209-22
Version Number, Date	v1.0 02.07.20

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;	Doxycycline (100mg) capsules The capsules 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;	
Kit/Pack 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)	Doxycycline 100mg capsules. Take 200mg on the first day (as a single dose or in divided doses with a twelve hour interval) followed by 100mg a day for 6 days (7 day course in total). The capsules are for oral administration. Special instructions: Capsules should be swallowed whole with plenty of fluid, while sitting or standing, well before going to bed. Capsules should be taken during meals. Due to the risk of photosensitivity, avoid exposure to sunlight or sun lamps.
“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	7 days Expiry date: month/year

month/year format and in a manner that avoids any ambiguity	Shelf life is 5 years.
“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