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

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

Chief Investigator: Professor Chris Butler
Tel: +44 (0)1865 289670
Email: christopher.butler@phc.ox.ac.uk
Address: Primary Care Clinical Trials Unit
Gibson Building, 1st Floor, Radcliffe Observatory Quarter, Woodstock Road, Oxford. OX2 6GG

Date: 04 January 2021
REC Substantial Amendment 11
IRAS ID: 281958

Dear REC committee members,

Subject: REC Substantial Amendment 11 for PRINCIPLE Trial in relation to COVID-19

Many thanks for your response to our previous submission of SA 11 to Platform Randomised trial of INterventions against COVID-19 In older people (PRINCIPLE).

We have clarified in the protocol that residents who, in addition to their lack of capacity, have a quality of life which can reasonably be seen as not acceptable to them will not be recruited and clarified in the personal legal letter that the impact an individual's participation may have on their quality of life should be considered.

We can confirm that the hydroxychloroquine arm of the trial was discontinued on 22 May 2020, but that the relevant Intervention Specific Appendix remains part of the protocol, but with the note that this arm is discontinued.

Yours sincerely,

Professor Christopher Butler
Chief Investigator of the Principle Trial

Table 1: List of documentation submitted to REC

Document	Version	Date
Protocol *(tracked changes & clean)*	6.3	30.12.2020
Legal Representative Letter	1.1	30.12.2020

Sharon Tonner

From: berkshire.rec@hra.nhs.uk <noreply@harp.org.uk>
Sent: 17 December 2020 14:41
To: Christopher Butler
Cc: CTRG Sponsorship Correspondence; Sharon Tonner
Subject: IRAS 281958. Substantial Amendment valid for REC review

Dear Professor Butler,

Study title: Platform Randomised trial of INterventions against COVID-19 In older peoPLE
REC reference: 20/SC/0158
IRAS project ID: 281958
Amendment number: SA 11
Amendment date: 30 November 2020

Thank you for submitting the above amendment, which was received on 14th December 2020. I can confirm that this is a valid notice of a substantial amendment and will be reviewed by the Sub Committee at its next meeting.

Documents received

The documents to be reviewed are as follows:

Document	*Version*	*Date*
Completed Amendment Tool [Amendment Tool]	1	30 November 2020
Cover Letter [Rec SA11 Cover Letter]	1	10 December 2020
Letter from sponsor [Sponsor Confirmation]	1	09 December 2020
Letters of invitation to participant [Legal Rep Letter]	1	30 November 2020
Other [IRAS_Form_12122020]		12 December 2020
Participant consent form [Consent Form Clean]	2.2	26 November 2020
Participant consent form [Consent Form Tracked]	2.2	26 November 2020
Participant information sheet (PIS) [PIS Appendices Clean]	1.4	02 December 2020
Participant information sheet (PIS) [PIS Appendices Tracked]	1.4	02 December 2020
Participant information sheet (PIS) [PIS Clean]	3.4	26 November 2020
Participant information sheet (PIS) [PIS Tracked]	3.4	26 November 2020
Research protocol or project proposal [Protocol Clean]	6.2	26 November 2020
Research protocol or project proposal [Protocol Tracked]	6.2	26 November 2020

Notification of the Committee's decision

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

Kind regards

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

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Health Research Authority

South Central - Berkshire Research Ethics Committee

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

05 January 2021

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

Dear Professor Butler

Study title:	**Platform Randomised trial of INterventions against COVID-19 In older peoPLE**
REC reference:	**20/SC/0158**
Protocol number:	**PRINCIPLE**
EudraCT number:	**2020-001209-22**
Amendment number:	**SA 11**
Amendment date:	**30 November 2020**
IRAS project ID:	**281958**

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

Ethical opinion

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

Approved documents

The documents reviewed and approved at the meeting were:

Document	*Version*	*Date*
Completed Amendment Tool [Amendment Tool]	1	30 November 2020
Cover Letter [Rec SA11 Cover Letter]	1	10 December 2020
Cover Letter [04.01.21 REC SA11 cover letter]		04 January 2021
Letter from sponsor [Sponsor Confirmation]	1	09 December 2020
Other [IRAS_Form_12122020]		12 December 2020
Other [PRINCIPLE Legal Rep Letter v1.1 30.12.2020_clean]	1.1	30 December 2020
Other [PRINCIPLE Legal Rep Letter v1.1 30.12.2020_tracked]	1.1	30 December 2020
Participant consent form [Consent Form Clean]	2.2	26 November 2020

Participant consent form [Consent Form Tracked]	2.2	26 November 2020
Participant information sheet (PIS) [PIS Appendices Clean]	1.4	02 December 2020
Participant information sheet (PIS) [PIS Appendices Tracked]	1.4	02 December 2020
Participant information sheet (PIS) [PIS Clean]	3.4	26 November 2020
Participant information sheet (PIS) [PIS Tracked]	3.4	26 November 2020
Research protocol or project proposal [PRINCIPLE Protocol v6.3 30.12.2020_tracked]	6.3	30 December 2020
Research protocol or project proposal [PRINCIPLE Protocol v6.3 30.12.2020_clean]	6.3	30 December 2020

Membership of the Committee

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

Working with NHS Care Organisations

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

Amendments related to COVID-19

We will update your research summary for the above study on the research summaries section of our website. During this public health emergency, it is vital that everyone can promptly identify all relevant research related to COVID-19 that is taking place globally. If you have not already done so, please register your study on a public registry as soon as possible and provide the HRA with the registration detail, which will be posted alongside other information relating to your project.

Statement of compliance

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

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

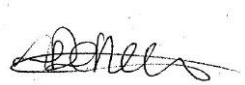
The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

HRA Learning

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

IRAS Project ID - 281958:	**Please quote this number on all correspondence**

Yours sincerely
PP



Mr David Carpenter
Chair

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

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

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

South Central - Berkshire Research Ethics Committee

Attendance at Sub-Committee of the REC meeting on 21 December 2020

Committee Members:

Name	*Profession*	*Present*	*Notes*
Mr David Carpenter (Chair)	Retired Social Scientist	Yes	
Dr Sarah Forster	Respiratory Registrar	Yes	Specialist Referee
Dr Mike Proven (Vice Chair)	University Research Governance Officer	Yes	

Also in attendance:

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

Sharon Tonner

From: berkshire.rec@hra.nhs.uk <noreply@harp.org.uk>
Sent: 05 January 2021 16:10
To: Christopher Butler; CTRG Sponsorship Correspondence
Cc: gram.nrspcc@nhs.scot; research.amendments@hscni.net; research-permissions@wales.nhs.uk; Sharon Tonner
Subject: IRAS PROJECT ID 281958, REC Reference 20/SC/0158 Confirmation of favourable opinion for substantial amendment
Attachments: IRAS 281958 SL32_Favourable_opinion_of_a_substantial_amendment-1.pdf

Follow Up Flag: Follow up
Flag Status: Flagged

Dear Professor Butler

IRAS project ID:	281958
REC reference:	20/SC/0158
Short Study title:	PRINCIPLE
Date complete amendment submission received:	14 December 2020
Amendment No./ Sponsor Ref:	SA 11
Amendment Date:	30 November 2020
Amendment Type:	**Substantial**
Outcome of HRA Assessment	**This email also constitutes HRA and HCRW Approval for the amendment, and you should not expect anything further.**

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

HRA and HCRW Approval Status

As detailed above, **this email also constitutes HRA and HCRW Approval for the amendment**. No separate confirmation of HRA and HCRW Approval will be issued.

User Feedback

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

If you require further information, please contact me.

Kind regards

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

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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

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

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

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

CONSENT FORM

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

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

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

		YES	NO
1	I confirm I have read and understood the information sheet version number ____-_____dated __ __ / __ __ __ / __ __ __ __ for the above study. I have had the opportunity to ask questions and had these answered satisfactorily.		
2	I understand my participation is voluntary and that I am free to withdraw at any time, without giving any reason, and without my medical care or legal rights being affected.		
3	I understand that if I chose to withdraw data already collected will continue to be used.		
4	I understand that I will be randomised to receive either: standard care plus a trial treatment or standard care, and that I will not be able to choose which I will receive.		
5	I understand that relevant sections of my GP and Hospital medical notes and data collected during the study may be looked at by members of the research team and individuals from University of Oxford, both during and for up to 10 years after the scheduled follow-up period. It may also be reviewed by relevant people from regulatory authorities and from the NHS Trust(s). I give permission for these individuals to have access to my records		
6	I understand that members of the research team may view my Summary Care Record (SCR) to check my medication, allergies, adverse reactions and additional information to make sure that it is safe for me to take trial medication. I give permission for these individuals to access my SCR for this purpose.		
7	I consent to being contacted by the research team for the purposes of trial follow up (up to 12 months) and I understand that this will require me to provide my contact details to the research team.		
8	I consent to my GP and/or Care Home being informed of my participation within the study.		
9	I agree to take part in the study		

	ADDITIONAL (optional, not required for study participation)	**YES**	**NO**
1	*I agree to provide the research team with the contact details of my Trial Partner. I confirm my Trial partner is aware of their role and willing to answer questions.*		
2	*I am happy to be contacted by the research team to be invited to a telephone interview at the end of the study.* *(Taking part in the interview is optional and will not affect your study participation. If you agree to be contacted, the research team will contact you with details of the interview in approximately 28 days. You can then decide whether you want to take part or not.)*		
3	I consent to allow the study team to access my sample results which are part of the RCGP RSC and PHE surveillance programme, the trial team to inform my GP of the results if required		

If you are the participant completing the consent form, please provide your signature below

Participant Signature:

First Name:_____ Last Name:_____

Date: __ __ / __ __ / __ __ __ __

If the participant has provided verbal consent, but they are unable to complete the consent form due to lack of online access, too unwell, too frail or consent is completed via the telephone (the participant must have capacity), please provide:

1. Name of the participant

First Name:_____ Last Name:_____

Date: __ __ / __ __ / __ __ __ __

2. Signature of person completing the form

First Name:_____ Last Name:_____

Role: Study Partner/Trial Team Member/Health Care Professional

Date: __ __ / __ __ / __ __ __ __

If participant lacks capacity to give consent:

I have read the information (or had it read to me) and had an opportunity to ask questions.

Participant:

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

I believe that if they were able to, the patient would wish to take part in this study.

……	…….	……../……../……
PRINTED name of Legal Representative	Signature	Today's date

……
Relationship to participant

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

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

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

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

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

LEGAL REPRESENTATIVE LETTER

Dear [Name of Legal Representative]

We are contacting you as the legal representative of [patient's name]. A legal representative is someone who has a personal relationship with the patient, such as a family member, friend or family doctor who does not have a conflict of interest, who can make decisions about medical care, or taking part in medical research, when a person no longer has capacity to make the decision themselves.

We are inviting people who are experiencing symptoms of Covid-19 to consent to join [{a study comparing possible treatments and [patient's name] may be eligible to join. Please find enclosed the participant information leaflet, this is the information we would provide to [patient's name] if they were able to consent for themselves.

We are asking you to consider if, taking into account any thoughts and/or wishes [patient's name]expressed, including any advance care directive or contemporaneous expressions of will they may make, if you believe [patient's name] would wish to join this study. Please also consider the impact taking part may have on their quality of life, for example, they may have to take additional medications, and if you feel this would be acceptable to them.

If you do not want to make this decision on their behalf then you do not have to and this will not affect [patient's name] care in anyway.

If you are happy to take this decision and believe that [patient's name] would wish to take part we will ask you to sign a consent form on their behalf. We will also let you know what arm of the trial they have been randomised to join and if you change your mind at any stage you can withdraw [patient's name] and this will not affect their care in anyway.

Please feel welcome to discuss the study with [patient's name] health care team, friends and/or family before making a final decision if you wish to. You can also contact the study team at principle@phc.ox.ac.uk or by calling 0800 138 0880 to discuss the study further.

Many thanks for considering [patient's name]'s participation in this study. If you are happy to proceed we would be grateful if you could sign below.

Best Wishes

I confirm that I am happy to act as the legal representative of [patient's name] for the purpose of consenting to take part in PRINCIPLE.

Name:

Relationship to patient:

Signature:

Date:

Please return this form to [Insert local details]

Appendix 1 — 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

Appendix 2

Inhaled Corticosteroid - Budesonide

Drug Information

Budesonide is a widely used inhaled corticosteroid used to treat asthma symptoms, but is not currently used to treat infections like COVID-19.

Side-effects

* The common side effects are:
* cough immediately after inhaling
* mouth and throat pain
* hoarse voice
* oral candidiasis (thrush).

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

PARTICIPANT INFORMATION LEAFLET

We are inviting people who are experiencing symptoms of Covid-19 to consent to join this study comparing possible treatments.

This leaflet has information about the trial, including aims, risks and benefits of taking part.

What is the purpose of the trial?

COVID-19

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

So far, there are no treatments that have been proven in clinical trials to be effective in treating COVID-19 infection. Most of the infections are being managed in the community and it is essential that we identify treatments that help to reduce the progression of the disease and therefore the need for hospital admission.

The Trial

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

We 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 common side-effects of these widely used medications.

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

or a high 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.**

You **also** need to be **aged 65 and over**

OR aged 50 to 64, where one of the following applies:

- weakened immune system due to a serious illness or medication (e.g. chemotherapy)
- heart disease or high blood pressure
- asthma or lung disease
- known diabetes
- liver disease
- stroke or neurological problem
- self-reported obesity or recorded body mass index ≥35 kg/m2

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.

We are contacting people who have recently tested positive for COVID-19 and your information has been provided to us by NHS Digital in these unique pandemic circumstances. You have the right to opt out of any future communications from PRINCIPLE should you wish to do so. If you do not wish to receive further communication from the trial team, please let us know next time we contact you. PRINCIPLE will not retain your data should you choose not to take part. Please see the General Notice under the Health Service Control of Patient Information Regulations 2002 for more information (LINK). We will make a maximum of three attempts to contact you about the trial.

What will happen to me if I take part?

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 at the end of the document.

Informed Consent

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

You will then 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.

Randomisation

The final part of the process will tell you whether you will receive standard care or standard care plus a trial treatment. 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. If we find that you cannot participate, we will let you know by email or phone.

Trial Treatment

If you are randomised to the standard care plus trial treatment group, arrangements will be made for the medication to be delivered to you. You will also receive instructions on how to take it and for how long and you will be asked to confirm receipt of the medication 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 online questions relating to your symptoms and how well you feel every day for up to 28 days after you start the trial. 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. We may contact you (email, text message or telephone call) once a month for up to 12 months after you enrol into the trial to collect information about ongoing symptoms, hospital visits and your well-being. Samples you have given or go on to give for COVID-19 in your standard care may also be used for national infection surveillance, if this is the case we would like to access the results from any samples (including testing swabs and convalescent blood samples) held in your GP record or by PHE. In addition, we will collect information from your GP records and data held by central NHS bodies (such as NHS Digital) for long-term follow-up for up to 10 years, to help us better understand the long-term effects of COVID-19 and the trial treatments.

Supporting other COVID-19 trials

Our main aim is to find effective treatments for COVID-19 in the community and we are working in collaboration with other academic organisations to achieve this. You may receive information about other treatment trials from the PRINCIPLE trial platform.

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.

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.

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.

Some people find having their blood taken causes slight discomfort and occasionally bruising.

What are the possible benefits of taking part?

We do not know if the treatments being tested will have additional benefits. Your study treatment may or may not help you personally, but this study should help future patients.

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.

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

Expenses and Payments

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

What if there are any problems?

If you have any questions about this trial, please contact the Trial Team (See Page 12for 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 ctrg@admin.ox.ac.uk.

What will happen to my data?

All information about you and your health will be kept private. The only people allowed to look at the information will be the doctors running the trial, the trial team and the regulatory authorities who check that the study is being carried out correctly. A privacy notice is on the study website www.principletrial.org.

As part of the trial enrolment process we may need to view your Summary Care Records (SCR) (https://digital.nhs.uk/services/summary-care-records-scr/summary-care-records-scr-information-for-patients) to check your medication, allergies, adverse reactions and 'Additional Information' to make sure that it is safe for you to take trial medication. A SCR is an electronic record of important patient information, created from GP medical records. SCR 'Additional

Information' includes information recorded in your GP record about your significant illnesses and health problems, operations and vaccinations you have had in the past, how you would like to be treated (such as where you would prefer to receive care), what support you might need and who should be contacted for more information about you. SCRs can be seen and used by authorised staff in other areas of the health and care system involved in your direct care.

We will ask for your consent to view your SCR. The SCR will not be retained by the trial team. If your SCR is unavailable or you do not consent for us to access it, you can still take part in the trial as we will obtain this information from your GP.

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 at the end of the document)

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.

Trial Team:
Tel. 0800 138 0880

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

Trial Title: Platform Randomised trial of INterventions against COVID-19 In older peoPLE
Internal Reference Number / Short title: PRINCIPLE
Ethics Ref: 20/SC/0158
IRAS Project ID: 281958
EudraCT Number: 2020-001209-22
Date and Version No: 30th December 2020 version 6.3

Chief Investigator and trial leader: Professor Chris Butler, Department of Primary Care Health Sciences University of Oxford

Co-Principal Investigator and Co-trial lead: Prof Richard Hobbs, Department of Primary Care Health Sciences University of Oxford

Co-Principal Investigators: Prof Simon de Lusignan, RCGP Research Surveillance Centre, University of Oxford

Prof Gail Hayward, Department of Primary Care Health Sciences University of Oxford

Investigators: Dr Ly-Mee Yu, Primary Care Clinical Trials Unit, Department of Primary Care Health Sciences, University of Oxford

Dr Emma Ogburn, Primary Care Clinical Trials Unit, Department of Primary Care Health Sciences, University of Oxford

Dr Oliver Van Hecke, Department of Primary Care Health Sciences, University of Oxford

Ms Julie Allen, Primary Care Clinical Trials Unit, Department of Primary Care Health Sciences, University of Oxford

Dr Emily Bongard, Primary Care Clinical Trials Unit, Department of Primary Care Health Sciences, University of Oxford

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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.

See *supplementary material B* for **Key Trial Contacts**.

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

Background: There is an urgent need to identify effective treatments for SARS-CoV-2 infection, that reduce the need for hospital admission and reduce the time to recovery. We have established an open, adaptive, platform trial to evaluate treatments suitable for use in the community for treating COVID-like-illness that might prevent hospitalisation and/or death and help people recover sooner.

Eligibility and randomisation: This protocol describes a randomised trial for people in the community aged 65 and over, or 50 and over with comorbidity, with possible (in accordance with the United Kingdom's Chief Medical Officer's syndromic case definition) or confirmed SARS-CoV-2 infection. Participants are randomised to receive either usual care or a trial treatment (see appendices for details of all trial arms). Participants can take part in the study if they are eligible to be randomised to at least one intervention arm as well as the Usual Care arm.

Platform trial: A "platform trial" is a trial in which multiple treatments for the same disease are tested simultaneously. New interventions can be added or replace existing ones during the course of the trial in accordance with pre-specified criteria.

Response adaptive randomisation: The initial randomisation ratio is fixed 1:1 for a comparison between two trial arms, but the trial has the capability for these proportions to be altered according to participants' responses to interventions. 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 may replace the usual care arm as the new standard of care. In the context of the COVID-19 pandemic, the trial may continue as long as the pandemic persists.

Outcomes: The trial has co-primary endpoints: 1) Time taken to self-reported recovery; and 2) hospitalisation and/or death. The main objective of the trial is to assess the effectiveness of the interventions in reducing time to recovery and in reducing the incidence of hospitalisation and/or death.

Key secondary outcomes include: Hospital assessment without admission; Oxygen administration; Intensive Care Unit admission; Mechanical ventilation (components of the WHO Clinical Progression Ordinal Scale); Duration of hospital admission; Duration of severe symptoms; Sustained recovery; Contacts with the health services; Consumption of antibiotics; Effects in those with a positive test for COVID-19 infection; WHO Well-being Index.

See *supplementary material C* for details of objectives and outcome measures.

Efficient study design: All enrolment (screening, informed consent, eligibility review and baseline data) and follow-up procedures (daily diary, hospitalisations and deaths) can be performed and captured online on the trial website or by telephone with a member of the trial team. Randomisation is online and automatic following eligibility confirmation. Participant packs and medications are sent from the central study team directly to the participant.

Data to be recorded: We will capture demographic features including ethnicity and care home residency at baseline. In the online daily diary (completed for 28 days)/ during telephone calls, participants or their Study Partners will rate the severity of symptoms, record contacts with the health services (including hospital admission), record medication use, and new infections in the household. The WHO-5 Wellbeing Index, a five-question instrument, will assess wellbeing at baseline and on days 14 and 28. Follow-up beyond 28 days after randomisation will be accessing electronic medical records and by participant questionnaire for information relevant to the longer term consequences of COVID-19.

Numbers to be randomised: The trial will continue until either superiority or futility is claimed for each intervention. We estimate that approximately 400 participants per arm (800 participants total if only a single intervention vs. Usual Care) will be required to provide 90% power for detecting an approximate difference of 2 days in median recovery time. 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 50% reduction in the relative risk of hospitalisation and/or death.

To enquire about the trial, contact the PRINCIPLE Trial Team:

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

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

Tel: 0800 1385451
Website: www.principletrial.org

TABLE OF CONTENTS

1. BACKGROUND and RATIONALE

We urgently need to know whether potential interventions for COVID-19-like-illness that are suitable for use in the community might help affected individuals recover more quickly and reduce the risk of hospitalisation and/or death. PRINCIPLE is a platform trial designed to efficiently evaluate potential treatments for people with COVID-19-like-illness, and who may be at higher risk of poorer outcomes. Eligible participants are those who meet the UK Chief Medical Officer's definition of COVID-19 illness, who are being managed in the community, and who are aged 50 and over with certain comorbidities, and those aged 65 and over (1-4).

The platform trial has the flexibility to allow additional interventions to be added in, or to replace existing interventions according to pre-specified criteria. If at any point a treatment is deemed superior to the usual care arm, the superior treatment may replace the usual care arm as the new standard of care. All approved intervention arms are outlined in Intervention Specific Appendices (ISAs).

The trial has co-primary endpoints: 1) Time taken to self-reported recovery; and 2) Hospitalisation and/or death. The main objective of the trial is to assess the effectiveness of the respective interventions in reducing time to recovery and in reducing the incidence of hospitalisation and/or death.

The primary analysis will be by "intention to treat", with secondary "intention to treat infected" analyses based on identified aetiology. Clinical data, and information from swab and blood tests, where available, will be used to classify participants according to aetiology.

2. TRIAL DESIGN AND PROCEDURES

PRINCIPLE is an open, prospective, individually randomised, platform, response adaptive, controlled clinical trial in community care.

2.1 Participant Identification

2.1.1 Trial Participants

The trial aims to include participants aged 50 and over with certain comorbidities, and those aged 65 and over with confirmed or possible COVID-19 who meet the case definition for COVID-19, and who are well enough to remain in the community. This definition 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*

The study is for people who have ongoing symptoms.

2.1.2 Inclusion Criteria

- Participant, or their legal representative, 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-Co-V2 infection with symptoms of COVID-19 must be within the last 14 days.
- Age criteria: Patients aged ≥65, or Patients aged ≥50-64 years and meeting at least one of the following criteria:
- 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;
- Self-report obesity or body mass index ≥35 kg/m^2

2.1.3 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.
- Previous randomisation to an arm of the PRINCIPLE trial

Additional exclusions specific to each intervention arm are listed in the ISAs. For participation, participants must be eligible to be randomised to at least one intervention arm as well as the Usual Care arm.

2.2 Trial procedures

2.2.1 Recruitment

Recruitment is possible through a variety of mechanisms:

2.2.2 Face to face

Attending clinicians, including research nurses or other health care professionals, at general medical practices, paramedic services, hospital emergency departments, clinical care hubs, Hospital at Home facilities, care of the elderly services, pharmacies, social care services, residential and nursing homes, or any health and social care facility, can facilitate recruitment into the trial. They can do this by discussing the study with potentially eligible participants, guiding them through informed consent procedures, collection of baseline data, completion of screening questions, collecting information for eligibility assessment, and randomising the participant. If required and appropriate, licensed prescribers may prescribe the medication appropriate to the group to which the participant is randomised. Alternatively, health care professionals may revert to the PC-CTU to complete the activity, including eligibility confirmation and issue of study medication and materials.

2.2.3 Remote recruitment

i) All Health, health related, and Social Care professionals will be able to give information verbally or via a trial text, email, poster, social media post, adverts, media release, leaflet or letter, to potential study participants and their study partners. They may also direct patients to the online study information and the study website.

ii) Potential participants may present directly to the study team via the website or by the study telephone contact. The study team can provide information about joining the trial and guide them through the consent and enrolment process.

iii) A General Practice may be contacted by a potential participant or the practice may contact patients, by text (or by letter), who may match the trial eligibility criteria, through running searches of their database. They will then direct patients to the trial enrolment website or seek verbal consent to be contacted by the trial team.

iv) NHS Digital will provide the PRINCIPLE trial with a daily list of contact details from the COVID-19 testing Pillar 2 data, for patients receiving a positive test result for SARS-Co-V2 infection, via a secure transfer system. NHS digital will apply an age filter to ensure only the details of those within the age range of the trial are passed on to PRINCIPLE. The trial team will make a limited number (maximum of 3) of attempts to telephone, text or email these patients to provide them with information about the trial, to invite them to consider taking part, and to enrol them if they provide full informed consent and are deemed eligible at screening.

Patient details will be provided in accordance with section 251 under the General Notice under the Health Service Control of Patient Information Regulations 2002, which applies only in England and Wales, providing 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.

For all recruitment models:

- Study Partner: at screening the potential participant will be asked to provide contact details for a Study Partner, to assist in completing trial procedures and to provide information on their behalf where necessary, but this is not a requirement for trial participation. However, it is strongly encouraged that participants who may be frailer and/or lack capacity to consent make use of a study partner to facilitate their participation. In addition to family member or friend, the study partner may also be a carer or other suitable person.
- Participants may be asked if they wish to enrol in additional studies that do not conflict with the main PRINCIPLE trial. Those who do not screen as eligible for PRINCIPLE may be alerted to the possibility of participating in other approved trials.

2.3 Screening

An online screening, eligibility and consent procedure is used. If online access is not possible, a member of the trial team collects this information during a telephone call. A trial free-phone number enables participants to contact the trial team for further information and study participation support. Participants are screened after they have read the PIS by completing an online eligibility questionnaire.

2.4 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 to them. Remote, paperless online/telephone consent is required, and appropriate during the pandemic. Participants will be able to download their consent form, or it may be printed by the central study team and delivered to participants with their study materials if they so prefer.

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 known side-effects and risks involved in taking part. It will be clear that the participant is free to withdraw from the study at any time. A summary, pictorial PIS is available which can be read by those feeling very unwell, lack capacity or have low reading comprehension skills. Adequate time will be given to the participant to consider the information and to ask any questions about the trial before deciding whether to participate. After consent, the participant will enter online baseline information, including their address, contact details and those of a Study Partner.

Population groups such as care home residents have been amongst those hardest hit by the pandemic and therefore stand to benefit the most from any effective treatments. However, some care home residents lack capacity to consent to research themselves. If the recruiting clinician deems a care home resident lacks capacity to consent then a personal or professional legal representative (England and Wales only) will be asked to provide consent for those lacking capacity to consent for themselves. A personal legal representative is defined as a person not connected with the conduct of the trial who is suitable to act as the legal representative by virtue of their relationship with the adult. A professional legal representative may be a doctor responsible for the medical treatment of the adult if they are independent of the study, or a person nominated by the healthcare provider. In all instances, a personal legal representative will be sought first and a professional legal representative sought only if a personal legal representative cannot be identified. A professional legal representative will be sought in order not to deny access to research to older adults who may not have personal legal representatives. Only residents of care homes who lack capacity to consent will be recruited, adults who lack capacity to consent will not be recruited from the wider community. Residents who, in addition to their lack of capacity, have a quality of life which can reasonably be seen as not acceptable to them will not be recruited

The legal representative will be provided with information about the trial and made aware of the following:

- They are being asked to give consent on behalf of the incapacitated adult,
- They are free to decide whether they wish to make this decision or not, and
- They are being asked to consider what the adult would want, and to set aside their own personal views when making this decision.

2.5 Eligibility Assessment

Eligibility of those who have provided appropriate consent 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, and who has appropriate access to the participant's summary care record or relevant medical information. If a participant's summary care record cannot be accessed centrally, the clinician/delegate will contact the participant's primary care medical practice for information relevant to confirming eligibility. 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.

2.6 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, to one of the arms they are eligible for (at least two arms), automatically by Sortition. Full details of response adaptive randomisation are described in section 5.2.

The participant, legal representative if applicable, trial team and participant's GP will be notified electronically of the treatment allocation. If the participant does not have an email address, they will be notified by telephone. 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.

2.7 Blinding and code-breaking

PRINCIPLE is an open-label trial. The participant, legal representative if applicable and the recruiting clinician will know the participant's allocation. Therefore, no unblinding or code breaking is required. 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 and Monitoring Committee will have access to the unblinded interim results.

2.8 Baseline Assessments

Once randomised, study medication (if so randomised), and a participant pack will be sent to participants, from their general practice, study team, Public Health England (PHE) or other approved central service (or collected from a general practice or pharmacy). Participants may be offered a swab test as part of standard care. 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 other viral aetiologies. While the aim is to have a swab result for all patients, where swabs are unavailable, patients may still participate and be included in the primary intention to treat analysis only.

2.9 Subsequent Visits

There is no requirement for participants to have a face-to-face visit as part of trial participation. All subsequent measurements consist of self-completed questionnaires online or through telephone calls, and primary care and/or hospital record searches. We will ascertain relevant data from primary care and/or hospital medical records about length of hospital stay, oxygen therapy, and ICU admission and ventilation, if applicable.

Participants will be sent a link to their online diary, which they will be asked to complete for 28 days. They will be asked to rate the severity of symptoms, record contacts with the health services (including hospital admission), record medication use and new infections in the household. It is becoming increasingly apparent the COVID-19 infection may have a considerable negative impact on well-being (14) and so the five questions of WHO-5, validated for measuring wellbeing over time, will be presented at baseline and on days 14 and 28. We will not ask for WHO-5 questions to be completed for participants who lack capacity. We will capture ethnicity and care home residency at baseline and day 28 (if missed at baseline).

All participants receive a call from the trial team on day 2/3 to confirm that they have received a participant pack, and trial medication (if randomised to a trial medication), and to explain 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* completed their diary for at least 2 consecutive days prior to the call. No more than six contact attempts will be made at each of these follow-up points.

We will seek consent from participants to contact them on a monthly basis for up to 12 months after enrolment (via email, text message or phone call) to collect information about any ongoing symptoms, hospitalisations and well-being. We will re-consent those already enrolled in the trial.

In addition to the swab being undertaken as part of the national RCGP RSC surveillance programme with PHE, trial participants will also be asked to consent to the trial team accessing a blood sample result. The study team will obtain the result from RCGP RSC/PHE.

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. This will be used as confirmation and a back-up for information obtained directly from study participants and other data sources outlined above. If obtaining data is not possible using this route, the GP surgery will be contacted to request a limited notes review. Participant records will be accessed up to twelve months following enrolment to ascertain follow up data from enrolment to day 28. Data will be collected as close to real time as possible; RCGP RSC, EMIS and NHS Digital and other sources of routinely collected data will be utilised if required To investigate the impact of trial interventions on the longer-term effects of COVID-19, we will use these data collection methods to follow-up participants, for up to 10 years.

2.10 Qualitative Sub-study

A qualitative sub-study will be nested within the trial, to 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. Healthcare professionals will also be asked about their experiences of taking part in the trial. See *supplementary material E* for further details. Participants who lack capacity will not be invited to participate in the qualitative sub study.

2.11 Early Discontinuation/Withdrawal of Participants

Each participant, or their legal representative on the participant's behalf, has the right to withdraw from the study at any time. For those that lack capacity, expression of dissent in any form will be taken as an indication they do not wish to be included and they will be withdrawn. 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.

2.12 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.

3 TRIAL INTERVENTIONS

IMP information can be found in the relevant ISAs.

In general, re-packaging and issuing of medication can be completed by: the patient's registered GP surgery or treatment and assessment facility; an accredited licensed central facility; an online, community or hospital pharmacy, and The Primary Care Clinical Trials Unit (as approved by the MHRA). Distribution of trial packs to participants will be tracked via courier or call/text message. Clinicians can prescribe trial medications that can be issued in the community and pharmacies can issue medication to the patient by community pharmacy services 'on-line pharmacy' services, NHS volunteers, or it can be collected from the pharmacy by the participant or someone on their behalf.

To record presence of symptoms and severity, as well as adherence to trial treatment, participants will receive a daily email asking them to complete an online diary where they will record their symptoms and medicines use. If incomplete, the trial team will contact the participant and/or their Study Partner to obtain the data. A risk-adapted approach will be used for drug accountability. Accountability logs will be kept by PC-CTU when they ship drug.

4 SAFETY REPORTING

All symptoms, medication side-effects and SAEs will be collected from participant daily diaries, calls to participants/Study Partners, medical records, notes reviews and RCGP data downloads. SAE information will be analysed as part of the interim and whole trial analysis and will be reviewed at each Data Safety & Monitoring Committee meeting.

4.1 Procedures for Reporting Adverse Events and Serious Adverse Events

The severity of events will be assessed by participants in daily diaries on the following scale: minor problem/moderate problem/major problem. Serious Adverse Events (SAE), but not Adverse events (AE), will be assessed for causality and expectedness in the trial. A participant may voluntarily withdraw from treatment due to what he or she perceives as an intolerable AE.

Hospitalisation and/or death due to confirmed or possible SARS-Cov-2 infection is a primary outcome, we will collect this data using a risk-adapted approach and will not report such SAEs. 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 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. 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.

See Appendix C for definitions of adverse events

4.1.1. 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.

4.1.2. 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.

4.1.3 Expectedness and Causality

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.

Assessment of Causality

The relationship of each serious 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 SAEs labelled possibly, probably or definitely will be considered as related to the IMP.

4.2 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.

4.3 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.

5 STATISTICS

5.1 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.

5.2 Open Adaptive Platform Trial

PRINCIPLE is an open, adaptive, platform trial to evaluate emerging treatments for symptomatic COVID-19-like illness. 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 may replace the Usual Care arm as the new standard of care. Because the process of dropping and adding treatments may be on-going for an indefinite period of time, platform trials may be better conceived of as a process rather than a singular clinical trial. In the context of the COVID-19 pandemic, the trial may continue as long as the pandemic persists.

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

5.2.1 Co-Primary Endpoints & Analyses

There are two co-primary endpoints. The first co-primary endpoint is time to recovery from possible COVID-19 infection within 28 days from randomization, where time to recovery is defined as the first instance that a participant reports feeling recovered. The second co-primary endpoint is hospital admission or death related to possible or confirmed COVID-19 within 28 days from randomization. Unless otherwise specified in the ISAs, the co-primary outcomes will be evaluated using a "gate-keeping" strategy. For a given treatment, the hypothesis for the time to recovery endpoint will be evaluated first, and if the recovery null hypothesis is rejected, the hypothesis for the second co-primary endpoint of hospitalization/death will be evaluated. This gate-keeping strategy preserves the overall Type I error of the primary endpoints without additional adjustments for multiple hypotheses. In addition, the gate-keeping structure reflects the clinical belief that an intervention is unlikely to demonstrate benefit on the hospitalization/death endpoint without first demonstrating benefit on the time to recovery endpoint.

The primary outcome of time to recovery is defined as the first instance that a participant reports feeling recovered. The corresponding primary analysis for this outcome is a Bayesian piecewise exponential model, with time to recovery regressed on treatment and stratification covariates (age, comorbidity). Let θ_j denote the log hazards ratio comparing the hazards of recovery for participants in treatment group *j* versus participants in the Usual Care arm. A corresponding Bayesian posterior distribution will be derived for the estimated log hazards ratio. The first co-primary analysis for intervention *j* will test the following hypothesis:

$$H_{10}: \theta_j \leq 0$$
$$H_{11}: \theta_j > 0$$

If the Bayesian posterior probability of superiority (a log hazards ratio greater than 0 corresponding to quicker recovery) 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 with respect to time to recovery. 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.

The second co-primary endpoint is hospital admission or death due to possible SARS-CoV-2 infection. The corresponding analysis will be a Bayesian generalised linear model of hospitalisation/death regressed on treatment and stratification covariates (age, comorbidity). Let δ_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. If the first co-primary endpoint hypothesis (for time to recovery) is rejected for intervention *j*, the second co-primary hypothesis for intervention *j* be tested:

$$H_{20}: \delta_j \leq 0$$
$$H_{21}: \delta_j > 0$$

If the Bayesian posterior probability of superiority on hospitalization/death 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 with respect to hospitalization/death. The exact threshold of the superiority decision criterion (e.g. 0.99) will be determined *a priori* via simulation to control the one-sided Type I error of the study at approximately 0.025, and will be specified in the M-SAP.

5.2.2 Adaptive Design

The pre-specified design will allow adaptations to the trial based on the observed co-primary endpoint 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 pre-specified criteria for decisions regarding futility or effectiveness of interventions and/or replacing interventions in the trial.

5.2.3 Interim Analyses

Precise timing of the first interim analysis and frequency of subsequent interim analyses will be specified in the Adaptive Design Report, based on both simulations and logistical considerations. At each interim analysis, all enrolled intervention arms will be evaluated for success and futility on both co-primary endpoints using the Bayesian primary analyses. These interim analyses will maintain the gate-keeping sequential order by first evaluating the hypothesis for time to recovery, and if the recovery endpoint null hypothesis is rejected, subsequently evaluating the hypothesis for hospitalisation and/or death. If the Bayesian posterior probability of superiority of a given intervention versus Usual Care is sufficiently large for a given endpoint (e.g. ≥ 0.99) within the gate-keeping structure, superiority will be declared versus Usual Care with respect to that endpoint.

If the Bayesian posterior probability of a clinically meaningful treatment effect is sufficiently small (e.g. < 0.01) for the first co-primary endpoint (time to recovery), the intervention arm may be dropped from the study for futility. If there are no other intervention arms available, the trial may be suspended; otherwise accrual continues to the remaining treatment arms. The exact futility thresholds will be pre-specified in the Adaptive Design Report and determined via simulation.

5.2.4 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 experimental 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.

5.2.5 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 each intervention, or until the pandemic expires in the population. We estimate that approximately 400 participants per arm (800 participants total if only a single intervention vs. Usual Care) will be required to provide 90% power for detecting a hazard ratio of 1.3 (approximate difference of 2 days in median recovery time). This calculation is based on the assumption of an exponential distribution for time to recovery with a median of 9 days in the Usual Care arm, with some adjustments for missing data and 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 hazard ratio is 1.5 (3 day benefit in median time to recovery), on average only 150 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.

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 50% reduction in the relative risk of hospitalisation and/or death. This calculation is based on the assumption of an underlying 5% combined hospitalisation and/or death rate in the Usual Care arm, with an intervention lowering the hospitalisation and/or death rate to 2.5%, with some adjustments for the multiple interim analyses. We expect fewer participants to be required to detect a 50% reduction if the event rate in the Usual Care arm is greater than 5%.

5.2.6 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 Usual Care 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. Complete details of the simulations will be provided in the Adaptive Design Report.

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

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

5.3 Primary Analysis Population

The primary analysis population is defined as all randomised 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.

5.4 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.

5.5 Qualitative sub-study analysis

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

6 DATA MANAGEMENT

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

6.1 Source Data

Source documents are where data are first recorded. 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/Study 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.

6.2 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.

6.3 Data Recording and Record Keeping

A CTU data manager will oversee the receiving, entering, cleaning, querying, analysing and storing all data that accrues from the study by designated persons. 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 authorised 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. The software used for the trial is described in *supplementary material D*.

7 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.

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 and will meet regularly throughout the course of the trial.

7.1 Risk assessment and Monitoring

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. 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.

7.2 Trial committees

The responsibilities of each group are as follows:

- Data Monitoring and Safety Committee (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.
- Trial Steering Committee (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.
- Trial Management Group (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.

8 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.

9 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.

10 ETHICAL AND REGULATORY CONSIDERATIONS

10.1 Declaration of Helsinki

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

10.2 Guidelines for Good Clinical Practice

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

10.3 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.

10.4 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.

Participants who lack capacity to consent for themselves will only be recruited after consultation with their legal representative. Any sign of dissent in any form from the participant who lacks consent will be taken as an indication they do not wish to be involved and they will be withdrawn. Only residents of care homes who lack capacity to consent will be recruited, adults who lack capacity to consent will not be recruited from the wider community.

10.5 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.

10.6 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.

10.7 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.

10.8 Expenses and Benefits

All participants will be reimbursed with a £20 voucher, to cover the payment of a prescription, should they incur this as a result of study participation, and a token of recognition of giving their time and contribution to the study. The vast majority of participants will not have to pay a prescription change, should a prescription be issued as a result of trial participation. Most people with the co-morbidities outlines and in the age-range required for eligibility, are not required to pay for prescriptions. Participants who complete a telephone interview as part of the qualitative sub-study will be reimbursed with a (second) £20 voucher for their time to participate.

11 FINANCE AND INSURANCE

11.1 Funding

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

11.2 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.

11.3 Contractual arrangements

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

12 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.

13 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.

14 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	**Participant contacts**							
	Visit timing Day 0	**Day 0**	**Day 0**	**Day 0**	**Daily Day 1-28 incl**	**Day 28-12 months (monthly contact)**	**Day 29-12mths**	**Up to 10 years**
	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**	**Contacted by study team if consent provided**	**Retrospective data collection by study team**	**By data extraction from clinical records**
Informed consent	X	X	X	X	X			
Demographics	X	X	X				X	
Medical history	X	X	X	X			X	
Swab as part of the RCGP RSC/PHE national surveillance programme	When available, preferably by self-swabbing at study entry							
Concomitant medications		X					X	
Eligibility assessment	X	X						

Randomisation				X				
Dispensing of trial drugs				X	X			
Questionnaire					X	X		
WHO 5 Well Being Index	X				Day 14 and day 28	X		
Telephone interview (for subset of patient participants)					X			
Compliance					X			
Adverse event assessments					X*		X	
Optional SARS-CoV-2 blood test as part of the RCGP RSC/PHE national surveillance programme							X	
Evidence of sequalae and health care utilisation						X		X

* Patient reported AEs will not be assessed by a clinician. The only exception is AEs collected from the hydroxychloroquine group. Participants in this group, will receive a telephone call on day 7 from the trial team to collect any information about cardiovascular Adverse Events (please see hydroxychloroquine appendix). Such events will be assessed by a clinician.

23 APPENDIX B: AMENDMENT HISTORY

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made
1 (SA1)	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 (SA2)	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 (SA3)	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 (SA4)	*2.1*		*No changes to the protocol*	
5 (SA5)	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

				Usual Care arm; ICF may be sent to participants.
6 (SA6)	4.0		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.
7 (NS1)	4.0		*No changes to the protocol*	
8 (SA7)	5.0		Chris Butler; Emma Ogburn; Ben Saville; Ly-Mee Yu; Hannah Swayze	Including a second primary outcome, time to recovery, change to sample size estimation, new eligibility criteria: obesity, formatting changes, blood test process.
9 (SA8)	5.0		*No changes to the protocol*	
10 (SA9)	5.0		*No changes to the protocol*	
11 (NS2)	5.0		*No changes to the protocol*	
12 (SA10)	6.0		Chris Butler; Emma Ogburn; Hannah Swayze	Addition of inhaled corticosteroid treatment arm, enrolment to additional trials, long-term follow-up, access to NHS Digital Pillar 2 test data, removal of investigators, additional trial contact with participants for up to 12 months, changes to objectives/outcomes/ time-points, removal of sampling from study
13 (NS3)	6.1		Sharon Tonner	Removal of patient already taking a treatment arm medication as an exclusion
14 (NS4)	6.1		*No changes to the protocol*	
15 (SA11)	6.2		Sharon Tonner, Hannah Swayze	Inclusion of patients who lack capacity to consent, discontinuation of azithromycin arm

Lists details of all protocol amendments 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 and that can be used in the community. Clinicians managing possible 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 (DISCONTINUED)

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 EC_{90} 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 tri***al. 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 that 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 sate, "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 COPVID-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:

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.

For hydroxychloroquine, GP practices can order a supply of trial medication from Public Health England using the existing ImmForm process. 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.

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 (DISCONTINUED)

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 administrated 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.

26 APPENDIX G: USUAL CARE PLUS INHALED CORTICOSTEROID (ICS) ARM

1. Background and rationale

a. Evidence for potential benefits of inhaled corticosteroids in COVID-19 illness

Inhaled corticosteroids (ICS) are a commonly prescribed class of medication throughout the world. They are reasonably cheap and have been used widely for the last 60 years. The inhaled action and type2 pneumocyte target of COVID make ICS a potential therapeutic agent in COVID-19[1]. They have been shown to be very effective in improving asthma and COPD care over the long term, where the recommendation is that most, if not all, patients with asthma should be prescribed an inhaled corticosteroid[2,3] and up to 90% of patients with COPD in the UK are prescribed ICS[4]. The rationale of ICS is to reduce the inflammatory process that underlies exacerbations, which can be triggered by viruses in asthma and COPD. Systemic corticosteroids have been found to be effective at reducing mortality amongst hospitalised patients with COVID-19 [46, 47], but it is not known whether pre-hospital treatment with ICS is also beneficial.

Further evidence is as described below:

Evidence from the ARDS literature

ICS in patients at risk of acute respiratory distress syndrome (ARDS) have been shown to improve physiology and reduce inflammatory markers[5]. In patients admitted to hospital at risk of ARDS or acute lung injury, there was an almost 50% reduction of ARDS in patients that were using ICS pre-admission, even controlling for covariates such as age, gender and chronic respiratory disease[6]. Moreover, this ICS effect can also be seen to improve pulmonary physiology[7].

Potential mechanism of efficacy

Recently published *in vitro* data suggest a role for ICS inhibition of coronavirus replication in infected epithelial cells[8], whilst there is an indication that there is accelerated hyperinflammation at the onset of SARS-CoV-2 infection[9], which potentially can be modified by anti-inflammatory therapy. This suggests a plausible mechanism for ICS efficacy against COVID-19 in which ICS has a dual role: firstly, toning down the inflammatory “runaway train” (ARDS-like) response affecting a minority of COVID-19 patients; and secondly, inhibiting viral replication. It has long been known that the ICS effect on epithelial cells is as a direct consequence of gene transcription[10], and investigation of gene expression of ACE2 and TMPRSS2 in the sputum of asthmatic patients has very recently demonstrated lower expression of these key receptors in the presence of ICS[11]. Furthermore, ICS attenuates expression of the ACE2 receptor in human and murine in vitro and in vivo models[12]. This is of relevance as the SARS-CoV-2 mechanism of action is upon direct action of the ACE2 receptor, a receptor highly expressed on epithelial cells in the oral mucosa and type 2 alveolar cells and the serine protease TMPRSS2 for SARS-CoV-2 spike protein priming[13,14]. Furthermore, there is experimental evidence that inhaled corticosteroids inhibit coronavirus replication in vitro[15,16]. SARS-CoV-2 binds to cells via the angiotensin converting enzyme 2 (ACE2) receptor. ACE2 is highly expressed on epithelial cells in the oral mucosa and type 2 alveolar epithelial cells. The use of inhaled corticosteroids as a therapy suggests it would target the cells of interest. Furthermore, the primary action of the inhaled steroids is on the type 2 pneumocytes where viral replication is going to be at its most, where we know that ACE2 receptor expression is high.

2. Changes to outcome measures

The addition of this arm will not require any changes to outcome measures.

3. Eligibility criteria specifically related to ICS

Inclusion criteria: No changes

Exclusion criteria:

- A known allergy to inhaled corticosteroids
- Any known contraindication to inhaled corticosteroids (as per SmPC, *patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine. Lactose, the excipient in the product, contains small amounts of milk proteins and can therefore cause allergic reactions*).
- Patient currently prescribed inhaled or systemic corticosteroids
- Unable to administer inhaler

4. Detail of intervention

Participants randomised to the usual care plus ICS arm will receive usual clinical care as per NHS guidelines, plus inhaled corticosteroids for 14 days. We will use the IMP distribution methods described in the protocol to deliver IMP to participants.

a. Investigational Medicinal Product (IMP) description

The IMP is the inhaled corticosteroid budesonide (dose 400mcg, Pulmicort turbohaler®). Inhaled budesonide comes in a polyethylene container consisting of a white cover screwed onto a brown bottom plate. Inside this is the inhaler with its main parts: a mouthpiece, a dosing mechanism and a substance store. The device will have 50 actuations of 400mcg/actuation. This product has marketing authorisation in the UK (PL 17901/0164) and is manufactured by AstraZeneca UK Ltd, 600 Capability Green, Luton, LU1 3LU, UK. This IMP will be taken as 2 puffs twice a day for 14 days.

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

iii. Precautions

Budesonide is a commonly prescribed inhaled steroid with an established safety profile.

iv. Concomitant medications

Largely, there is no restriction to concomitant medications using inhaled budesonide. The SmPC states that concomitant treatment with ketoconazole, HIV protease inhibitors or other

potent CYP3A inhibitors may increase systemic budesonide levels, but that this is of little clinical significance for a short term treatment of 2 weeks, which is the duration of IMP use in the trial.

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 and/or potential side effects from IMP include:

- Cough immediately after inhaling
- Mouth and throat pain
- Hoarse voice
- Oral candidiasis (thrush)

These are all reversible upon ceasing IMP

27. Supplementary Material

A. 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

B. Key Trial Contacts

Chief Investigator	Professor Chris Butler Nuffield Department of Primary Care Health Sciences Gibson Building Radcliffe Observatory Quarter Woodstock Road Oxford OX2 6GG christopher.butler@phc.ox.ac.uk
Sponsor	Joint Research Office 1st floor, Boundary Brook House Churchill Drive, Headington Oxford OX3 7GB ctrg@admin.ox.ac.uk Tel: +44 (0)1865572224 Fax: +44 (0)1865572228
Funder(s)	UKRI/NIHR
Clinical Trials Unit	Primary Care Clinical Trials Unit, Nuffield Department of Primary Care Health Sciences Radcliffe Observatory Quarter Woodstock Road Oxford OX2 6GG principle@phc.ox.ac.uk 01865 289296
Statistician	Ben Saville, Berry Consultants, Austin, Texas, USA, And Department of Biostatistics, Vanderbilt University School of Medicine, Nashville, Tennessee, USA. Dr Ly-Mee Yu Primary Care Clinical Trials Unit, Nuffield Department of Primary Care Health Sciences Radcliffe Observatory Quarter Woodstock Road Oxford OX2 6GG
Committees	**DMSC Chair:** Prof. Deborah Ashby Chair in Medical Statistics and Clinical Trials Director of the School of Public Health Imperial College London Faculty of Medicine, School of Public Health, 153 Medical School St Mary's Campus Imperial College London deborah.ashby@imperial.ac.uk

	(0)20 7594 8704 **DMSC Members:** Prof Simon Gates Cancer Research Clinical Trials Unit (CRCTU) Institute of Cancer and Genomic Sciences University of Birmingham Edgbaston Birmingham B15 2TT S.Gates@bham.ac.uk Prof Gordon Taylor College House, University of Exeter, St Luke's Campus, Heavitree Road, Exeter, EX1 2LU, UK g.j.taylor@exeter.ac.uk Prof Nick Francis Primary Care and Population Science, University of Southampton, Southampton, UK. Nick.Francis@soton.ac.uk
	TSC Chair Prof Paul Little, Primary Care and Population Science, University of Southampton, Southampton, UK. P.Little@soton.ac.uk **TSC Members** Prof Philip Hannaford, NHS Professor of Primary Care University of Aberdeen, Aberdeen, UK p.hannaford@abdn.ac.uk Prof Matt Sydes, Professor of Clinical Trials & Methodology, MRC Clinical Trials Unit, University College of London, London, UK m.sydes@ucl.ac.uk *PPI representatives* Ms Carol Green Mr Tim Mustill

C. Objectives and Outcome Measures

	Objectives	Outcome Measures	Timepoint (s)
Primary	To assess the effectiveness of trial treatments in reducing 1) Time to recovery, 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, and 2) Hospitalisation and/or death.	1) Time to recovery, defined as the first instance that a participant reports feeling recovered from possible COVID-19, and 2) Hospitalisation and/or death	Within 28 days of randomisation Patient report, Study Partner report, medical records, Daily online symptom scores
Secondary	To explore whether trial treatment reduces 1) Patient-reported illness severity 2) Duration of severe symptoms and symptom recurrence 3) Contacts with the health services 4) Consumption of antibiotics 5) Hospital assessment without admission 6) Oxygen administration 7) Intensive Care Unit admission 8) Mechanical ventilation 9) Duration of hospital admission 10) Negative effects on well being 11) New infections in household 12) To determine if effects are specific	1-2. Patient reports daily and monthly (after 28 days) symptoms. 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 5-9. Patient report/carer report/medical record in primary and secondary care 9 10. WHO-5 Well Being Index 11. Reports of new infections in the household (from daily questionnaire)	Daily online symptom scores. Telephone call or text on days 2, 7, 14 and 28 and once a month for 12 months 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. Medical notes review for up to 10 years. 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

	to those with a positive test for SARS-CoV-2	12. Swab test results will indicate an "Intention to Treat Infected" group within the overall cohort for sub analysis. Blood test results on recovery (optional) for evidence of historic COVID-19	and/or convalescent blood test result for evidence of historic COVID-19 WHO 5 Well Being Index at baseline, day 14, and day 28 and monthly for up to 12 months, either via online diary or telephone
Qualitative sub-study	1. To explore patients' experiences of consulting, being tested and taking (trial) medication for possible 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.		

D. Adverse Events

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"

E. Data Recording and Record Keeping

The data will be entered into the 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 form a trial's clinical data. Sentry can also act as a central participant portal to manage online eligibility, eConsent and ePRO - acting as an intermediary between the participant and the clinical databases. Sentry is accessed via a secure HTTPS connection and all stored sensitive data is encrypted at rest to AES-256 standards. Participant and Trial Partner data will be kept and stored securely for as long as it's required by the study and reviewed on annual basis.

F. Qualitative Sub-study

With consent, participants will be contacted for a telephone interview within three months after they complete their day 28 follow up. The researcher will provide study information over the telephone and the Interview Patient PIS, and ICF will be available on the study website and emailed to participants if requested.

Once a practice has completed patient recruitment and one of their patients has been interviewed, we may ask 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.

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. 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.

Data Collection:
Each interview will be audio-recorded with the participant's permission. Recordings will allow verbatim transcription of interviews. Transcription will be completed by an independent transcription company. 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.

Sharon Tonner

From: Elaine Chick
Sent: 09 December 2020 14:33
To: Sharon Tonner; Hannah Swayze
Cc: oxfordjro@mail.studyline.uk.com
Subject: FW: PRINCIPLE Trial - substantial Amendment 11
Attachments: 281958_SA 11_.pdf

Dear Sharon

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 (ctrg@admin.ox.ac.uk).

Please send a copy of the approval letter(s) to the CTRG generic email address (ctrg@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

Elaine Chick

Deputy Head | Clinical Trials and Research Governance (CTRG)
Research Services, University of Oxford
Joint Research Office
Boundary Brook House, Churchill Drive Oxford OX3 7GB

Please note I usually work Monday-Thursday only

☎ 01865 616481
✉ elaine.chick@admin.ox.ac.uk
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/ctrg
PID14903-A016-SP001-AC001

Welcome to the Integrated Research Application System

IRAS Project Filter

The integrated dataset required for your project will be created from the answers you give to the following questions. The system will generate only those questions and sections which (a) apply to your study type and (b) are required by the bodies reviewing your study. Please ensure you answer all the questions before proceeding with your applications.

Please complete the questions in order. If you change the response to a question, please select 'Save' and review all the questions as your change may have affected subsequent questions.

Please enter a short title for this project (maximum 70 characters)
PRINCIPLE

1. Is your project research?

(●) Yes ( ) No

2. Select one category from the list below:

(●) Clinical trial of an investigational medicinal product

( ) Clinical investigation or other study of a medical device

( ) Combined trial of an investigational medicinal product and an investigational medical device

( ) Other clinical trial to study a novel intervention or randomised clinical trial to compare interventions in clinical practice

( ) Basic science study involving procedures with human participants

( ) Study administering questionnaires/interviews for quantitative analysis, or using mixed quantitative/qualitative methodology

( ) Study involving qualitative methods only

( ) Study limited to working with human tissue samples (or other human biological samples) and data (specific project only)

( ) Study limited to working with data (specific project only)

( ) Research tissue bank

( ) Research database

If your work does not fit any of these categories, select the option below:

( ) Other study

2a. Is this a commercially sponsored Phase 1 or Phase 1/2a trial involving healthy volunteers?

( ) Yes (●) No

2b. Will the study involve the use of any medical device without a CE Mark, or a CE marked device which has been modified or will be used outside its intended purposes?

( ) Yes (●) No

2c. Please answer the following question:

Is this trial subject to advice from the Expert Advisory Group on Clinical Trials and the Commission on Human Medicine prior to authorisation from MHRA? ○ Yes ◉ No

2d. Please answer the following question:

Is this a trial of a gene therapy medicinal product? ○ Yes ◉ No

2e. Please answer the following question(s):

a) Does the study involve the use of any ionising radiation? ○ Yes ◉ No

b) Will you be taking new human tissue samples (or other human biological samples)? ◉ Yes ○ No

c) Will you be using existing human tissue samples (or other human biological samples)? ○ Yes ◉ No

3. In which countries of the UK will the research sites be located?*(Tick all that apply)*

- ☑ England
- ☑ Scotland
- ☑ Wales
- ☑ Northern Ireland

3a. In which country of the UK will the lead NHS R&D office be located:

- ◉ England
- ○ Scotland
- ○ Wales
- ○ Northern Ireland
- ○ This study does not involve the NHS

4. Which applications do you require?

- ☑ IRAS Form
- ☑ Medicines and Healthcare products Regulatory Agency (MHRA) – Medicines
- ☐ Confidentiality Advisory Group (CAG)
- ☐ Her Majesty's Prison and Probation Service (HMPPS)

5. Will any research sites in this study be NHS organisations?

◉ Yes ○ No

5a. Are all the research costs and infrastructure costs (funding for the support and facilities needed to carry out research e.g. NHS Support costs) for this study provided by a NIHR Biomedical Research Centre, NIHR Collaboration for Leadership in Health Research and Care (CLAHRC), NIHR Patient Safety Translational Research Centre or Medtech and In Vitro Diagnostic Cooperative in all study sites?

Please see information button for further details.

○ Yes ◉ No

Please see information button for further details.

5b. Do you wish to make an application for the study to be considered for NIHR Clinical Research Network (CRN) Support and inclusion in the NIHR Clinical Research Network Portfolio?

Please see information button for further details.

(●) Yes ( ) No

The NIHR Clinical Research Network (CRN) provides researchers with the practical support they need to make clinical studies happen in the NHS in England e.g. by providing access to the people and facilities needed to carry out research "on the ground".

If you select yes to this question, information from your IRAS submission will automatically be shared with the NIHR CRN. ***Submission of a Portfolio Application Form (PAF) is no longer required.***

6. Do you plan to include any participants who are children?

( ) Yes (●) No

7. Do you plan at any stage of the project to undertake intrusive research involving adults lacking capacity to consent for themselves?

(●) Yes ( ) No

Answer Yes if you plan to recruit living participants aged 16 or over who lack capacity, or to retain them in the study following loss of capacity. Intrusive research means any research with the living requiring consent in law. This includes use of identifiable tissue samples or personal information, except where application is being made to the Confidentiality Advisory Group to set aside the common law duty of confidentiality in England and Wales. Please consult the guidance notes for further information on the legal frameworks for research involving adults lacking capacity in the UK.

8. Do you plan to include any participants who are prisoners or young offenders in the custody of HM Prison Service or who are offenders supervised by the probation service in England or Wales?

( ) Yes (●) No

9. Is the study or any part of it being undertaken as an educational project?

( ) Yes (●) No

10. Will this research be financially supported by the United States Department of Health and Human Services or any of its divisions, agencies or programs?

( ) Yes (●) No

11. Will identifiable patient data be accessed outside the care team without prior consent at any stage of the project (including identification of potential participants)?

( ) Yes (●) No

Integrated Research Application System
Application Form for Clinical trial of an investigational medicinal product

IRAS Form (project information)

Please refer to the E-Submission and Checklist tabs for instructions on submitting this application.

The Chief Investigator should complete this form. Guidance on the questions is available wherever you see this symbol displayed. We recommend reading the guidance first. The complete guidance and a glossary are available by selecting Help.

Please define any terms or acronyms that might not be familar to lay reviewers of the application.

Short title and version number: (maximum 70 characters - this will be inserted as header on all forms)
PRINCIPLE

Please complete these details after you have booked the REC application for review.

REC Name:
South Central - Berkshire

REC Reference Number:
TBC

Submission date:
23/03/2020

PART A: Core study information

1. ADMINISTRATIVE DETAILS

A1. Full title of the research:

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

A3-2. National coordinating investigator (for a multicentre trial) **or principal investigator** (for a single centre trial)

- (●) National coordinating investigator
- ( ) Principal investigator

Given name	Christopher
Family name	Butler
Qualification (MD...)	Professor
ORCID ID	
Institution name	University of Oxford
Institution department name	Department of Primary Care Health Sciences
Street address	Radcliffe Observatory Quarter, Woodstock Road
Town/city	Oxford
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Work Telephone	0000
* Personal Telephone/Mobile	01865 289670
Fax	0000

** This information is optional. It will not be placed in the public domain or disclosed to any other third party without prior consent.*
A copy of a current CV (maximum 2 pages of A4) for the Chief Investigator must be submitted with the application.

A4. Who is the contact on behalf of the sponsor for all correspondence relating to applications for this project?
This contact will receive copies of all correspondence from REC and HRA/R&D reviewers that is sent to the CI.

Title	Forename/Initials	Surname
N/A	N/A	CTRG

Address	University of Oxford, Joint Research Office
	1st floor, Boundary Brook House, Churchill Drive, Headington
	Oxford
Post Code	OX3 7GB
E-mail	ctrg@admin.ox.ac.uk
Telephone	000000000
Fax	000000000

A5-1. Research reference numbers. *Please give any relevant references for your study:*

Applicant's/organisation's own reference number, e.g. R & D (if available):	PRINCIPLE
Sponsor's/protocol number:	PRINCIPLE
Protocol Version:	0.12
Protocol Date:	23/03/2020
Funder's reference number (enter the reference number or state not applicable):	PRINCIPLE
Project website:	000000

Registry reference number(s):
The UK Policy Framework for Health and Social Care Research sets out the principle of making information about research publicly available. Furthermore: Article 19 of the World Medical Association Declaration of Helsinki adopted in 2008 states that "every clinical trial must be registered on a publicly accessible database before recruitment of the first subject"; and the International Committee of Medical Journal Editors (ICMJE) will consider a clinical trial for publication only if it has been registered in an appropriate registry. Please see guidance for more information.

International Standard Randomised Controlled Trial Number (ISRCTN):	ISRCTN86534580
ClinicalTrials.gov Identifier (NCT number):	
European Clinical Trials Database (EudraCT) number:	2020-001209-22

Additional reference number(s):

Ref.Number Description	Reference Number

A5-2. Is this application linked to a previous study or another current application?

○ Yes ◉ No

Please give brief details and reference numbers.

2. OVERVIEW OF THE RESEARCH

To provide all the information required by review bodies and research information systems, we ask a number of specific questions. This section invites you to give an overview using language comprehensible to lay reviewers and members of the public. Please read the guidance notes for advice on this section.

A6-1. Summary of the study. *Please provide a brief summary of the research (maximum 300 words) using language easily understood by lay reviewers and members of the public. Where the research is reviewed by a REC within the UK Health Departments' Research Ethics Service, this summary will be published on the Health Research Authority (HRA) website following the ethical review. Please refer to the question specific guidance for this question.*

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

We propose establishing a platform randomised controlled trial in primary care that can be rapidly deployed to evaluate low risk interventions for high risk people. In the first instance this platform will evaluate a drug called hydroxychloroquine. This is a drug that is already available within the NHS but that has not been subject to randomised controlled trials for this indication in Europe or in community healthcare settings with the aim of reducing the need for hospital assessment. Using a simple, streamlined open trial design, with procedures embedded in existing health service structures and capabilities, our trial aims to give a rapid answer about the effectiveness of trial treatments in modifying the disease course. The goal is to prevent disease progression such that affected individuals will recover sooner, but critically, avoid the need for hospital assessment and admission. The platform trial will be flexible in that it will operate under a master protocol that will allow the addition of further interventions into the trial while it is in progress, should such suitable interventions become available.

The trial will be implemented in the first instance by the Royal College of General Practitioners (RCGP) Research and Surveillance Centre (RSC) general practices.

A6-2. Summary of main issues. *Please summarise the main ethical, legal, or management issues arising from your study and say how you have addressed them.*

Not all studies raise significant issues. Some studies may have straightforward ethical or other issues that can be identified and managed routinely. Others may present significant issues requiring further consideration by a REC, HRA, or other review body (as appropriate to the issue). Studies that present a minimal risk to participants may raise complex organisational or legal issues. You should try to consider all the types of issues that the different reviewers may need to consider.

Purpose and design:

This will be an open, prospective, individually randomised, platform, controlled clinical trial in community care. In the first instance, PRINCIPLE will be a two-arm trial comparing standard care to standard care plus hydroxychloroquine.

It will be implemented in the first instance in practices that are already part of the RCGP RSC Network. Currently over 500 practices are part of this network, with 100 already offering a sentinel viral swabbing service which we plan to scale up.

There is a major demand for COVID-19 treatments and this study will investigate trial treatments in older at risk adults. For rapid recruitment we will text potentially eligible participants to invite them to enrol if they have COVID-19 symptoms.

Consent
To ensure that we enrol patients as quickly as they start to experience COVID-19 symptoms we are using e-consent. We will ensure that participants fully understand the study by giving them access to the PIS on the website before completing the consent form. They will be able to view the PIS at any time and will be provided with the trial team phone number to call if they have any questions. The intervention is a well established and understood medication

with no contraindications to use and well characterised side effects, which has been outlined fully in the PIS. For those that lack capacity to consent, a personal or professional legal representative will be asked to provide consent on their behalf.

Inclusion and exclusion criteria
We are recruiting patients aged ≥65 with or without comorbidity, and patients aged ≥50 years with comorbidities, presenting in the community within 7 days since onset of symptoms, with a new continuous cough and/or high temperature and registered with a participating general practice. We are excluding any patients who may not be suitable to receive the trial medication. To ensure that ineligible patients are not recruited, a registered GP or nurse will always confirm eligibility prior to study entry.

Risk
This is a low risk study as all medications that we are using will have a wellestablished safety profile. 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.

Confidentiality
We will be contacting the participants as pa rt of the follow-up process and therefore we will need to collect the participant contact details. These will be stored securely at the Primary Care Clinical Trial Unit. This information will be collected but kept separate from the main dataset which will contain no personal identifiers other than the trial ID, sex and date of birth in order to help with monitoring the data. The personal contact information will be stored in a paper form or electronically on password protected computers or in a locked filing cabinet in a restricted access building. The information will be pseudo-anonymised as soon as it is no longer required and only authorised staff will have access to it.

NHS digital data requires secure transfer of identifiable data to NHS digital.

3. PURPOSE AND DESIGN OF THE RESEARCH

A7. Select the appropriate methodology description for this research. *Please tick all that apply*:

- ☐ Case series/ case note review
- ☐ Case control
- ☐ Cohort observation
- ☐ Controlled trial without randomisation
- ☐ Cross-sectional study
- ☐ Database analysis
- ☐ Epidemiology
- ☐ Feasibility/ pilot study
- ☐ Laboratory study
- ☐ Metanalysis
- ☐ Qualitative research
- ☐ Questionnaire, interview or observation study
- ☑ Randomised controlled trial
- ☐ Other (please specify)

A8. Type of medicinal trial:

- ☐ Clinical trial of an unlicensed investigational medicinal product
- ☑ Clinical trial of a licensed medicinal product in new conditions of use (different from those in the SmPC, i.e. new target population, new dosage schemes, new administration route, etc.)
- ☐ Clinical trial of a licensed medicinal product used according to the SmPC
- ☐ Other (please specify)

A9. Phase of medicinal trial: *(Tick one category only)*

Human pharmacology (Phase I)	○ Yes	◉ No
Therapeutic exploratory trial (Phase II)	○ Yes	◉ No
Therapeutic confirmatory trial (Phase III)	◉ Yes	○ No
Therapeutic use trial (Phase IV)	○ Yes	◉ No

A10. What is the principal research question/objective? *Please put this in language comprehensible to a lay person.*

To assess the effectiveness of trial treatments in reducing the need for hospital admission or death for patients aged ≥50 years with serious comorbidity, and aged ≥65 with or without comorbidity and suspected COVID-19 infection during time of prevalent COVID-19 infections.

A11. What are the secondary research questions/objectives if applicable? *Please put this in language comprehensible to a lay person.*

To explore whether trial treatment reduces
1) Duration of severe symptoms
2) Time taken to resumption of usual daily activities
3) Contacts with the health services
4) Consumption of antibiotics
5) Hospital assessment not leading to admission
6) Oxygen administration
7) Intensive Care Unit admission
8) Mechanical ventilation
9) To determine if effects are specific to those with the infections syndrome but who test positive for COVID-19
10) Duration of hospital admission

A12. What is the scientific justification for the research? *Please put this in language comprehensible to a lay person.*

Europe is now the centre of the COVID-19 epidemic caused by the highly infectious SARS-COV2 virus. Currently in the UK (18.03.20), 103 patients have died of COVID-19 and 2626 of those tested have been positive. There are no specific interventions against COVID-19 that have been proven, in rigorous trials, to alter the disease course by reducing the need for hospital assessment and admission.

A candidate intervention, a drug called hydroxychloroquine, has become available following early evaluation in some studies in China. This drug may work through limiting viral replication. Hydroxychloroquine is already available within the NHS on prescription for other indications, and has a generally benign safety profile. Chloroquine is available to buy in the UK over the counter. We urgently need to know whether this drug might modify the course of COVID-19 infections, particularly amongst those who are at higher risk of complications. At the present time, those are higher risk appear to be people aged 50 and over with comorbidity and those aged 65 and over.

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

We urgently need to know whether hydroxychloroquine or other potential treatments might benefit patients and enhance the sustainability of NHS care during this crisis.

A13. Please summarise your design and methodology. *It should be clear exactly what will happen to the research participant, how many times and in what order. Please complete this section in language comprehensible to the lay person. Do not simply reproduce or refer to the protocol. Further guidance is available in the guidance notes.*

Design:
This will be an open, prospective, individually randomised, platform, controlled clinical trial in community care. In the first instance, PRINCIPLE will be a two-arm trial comparing standard care to standard care plus hydroxychloroquine.

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

Study intervention:
Hydroxychloroquine 200 mg twice a day for 7 days. Further interventions may be added and all necessary approvals being obtained.

Trial Procedures:
Patients reporting COVID-19 symptoms to a clinically qualified person (GP, 111) or the study team or through responding to a text link to the trial website, will be recruited. They will be asked to complete the online; screening, contact details, informed consent and baseline forms.

Once consent has been obtained and eligibility confirmed by a clinically qualified person, patients will be randomised using Sortition online. A form and sampling kit will be generated and sent to the patient's home for self-sampling. All participants, whether in the intervention or control group, will be asked to provide a self-swab. Once they take the swab, they will put it in the secure container and double bag, and post it to the PHE laboratory supporting the study.

For those randomised to receive trial treatment, an NHS prescription will be issued or it will be sent by the trial team, and the patient or their family will be told how the drug can be obtained, either through collection at a pharmacy, or by home delivery.

Patient follow-up will be primarily online for 28 days, where they will be asked to complete questions about the presence and severity of symptoms each day. The practice network that will be implementing the trial, the Royal College of General Practitioners Research and Surveillance Network, has the capacity to extract patient information from the clinical records twice a week. This more or less real-time ascertainment of Primary Care will enhance data capture from patients themselves their families or from the hospital records about oxygen use, intensive care high dependency and intensive care admission and ventilation.

A14-1. In which aspects of the research process have you actively involved, or will you involve, patients, service users, and/or their carers, or members of the public?

- ☐ Design of the research
- ☐ Management of the research
- ☐ Undertaking the research
- ☐ Analysis of results
- ☐ Dissemination of findings
- ☑ None of the above

Give details of involvement, or if none please justify the absence of involvement.
We have prepared the study Protocol in a very short time-frame given the urgency of the COVID-19 pandemic and the need for treatment and therefore it has not been possible to involve patients, service users or members of the public at this stage.

4. RISKS AND ETHICAL ISSUES

RESEARCH PARTICIPANTS

A15. What is the sample group or cohort to be studied in this research?

Select all that apply:

- [ ] Blood
- [ ] Cancer
- [ ] Cardiovascular
- [ ] Congenital Disorders
- [ ] Dementias and Neurodegenerative Diseases
- [ ] Diabetes
- [ ] Ear
- [ ] Eye
- [ ] Generic Health Relevance
- [x] Infection
- [ ] Inflammatory and Immune System
- [ ] Injuries and Accidents
- [ ] Mental Health
- [ ] Metabolic and Endocrine
- [ ] Musculoskeletal
- [ ] Neurological
- [ ] Oral and Gastrointestinal
- [ ] Paediatrics
- [ ] Renal and Urogenital
- [ ] Reproductive Health and Childbirth
- [ ] Respiratory
- [ ] Skin
- [ ] Stroke

Gender:	Male and female participants
Lower age limit: 50	Years
Upper age limit:	Years

A17-1. Please list the principal inclusion criteria (list the most important, max 5000 characters).

• Participant, or their legal representative, is willing and able to give informed consent for participation in the study.

• Participant, or their legal representative, is willing to comply with all trial procedures

• Onset of symptoms of possible COVID-19 in the community (continuous cough and/or high temperature) within 7 days of inclusion

• Patients aged ≥50-64 years with any of the following listed comorbidities:

- known weakened immune system due to a serious illness or medication (e.g. chemotherapy)
- known heart disease
- known asthma or lung disease
- known diabetes not treated with insulin
- known mild hepatic impairment
- known stroke or neurological problem

OR

• Patients aged ≥65 with or without comorbidity

A17-2. Please list the principal exclusion criteria (list the most important, max 5000 characters).

- Pregnancy
- Breastfeeding
- Known severe hepatic impairment
- Known severe renal impairment
- Known acute porphyrias
- 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
- Known retinal disease
- Judgement of the recruiting clinician deems ineligibile

RESEARCH PROCEDURES, RISKS AND BENEFITS

A18. Give details of all non-clinical intervention(s) or procedure(s) that will be received by participants as part of the research protocol. *These include seeking consent, interviews, non-clinical observations and use of questionnaires.*

Please complete the columns for each intervention/procedure as follows:

1. Total number of interventions/procedures to be received by each participant as part of the research protocol.
2. If this intervention/procedure would be routinely given to participants as part of their care outside the research, how many of the total would be routine?
3. Average time taken per intervention/procedure (minutes, hours or days)
4. Details of who will conduct the intervention/procedure, and where it will take place.

Intervention or procedure	1	2	3	4
Informed Consent	2	N/A	20	Participant or their legal representative (automated online system) on day 0 and GCP trained study team member on day 1 (over the phone)
Eligibility and Baseline assessment (demographics, medical history and concomitant medication)	1	N/A	20	Participant (automated online system)
Eligibility assessment	1	N/A	6	Responsible clinician
Randomisation	1	N/A	5	Clinician/Automated online system
Dispensing of trial drug	1	1	5	Clinician online/phone
Daily diary	28	N/A	5	Completed by participant for 28 days
Follow-up telephone calls	3	N/A	5	GCP trained study team member. Telephone call or text day 7, 14 and 28 if data not being received online
Daily email/text message reminder for 28 days	28	N/A	2	Sent to participants from study team

A19. Give details of any clinical intervention(s) or procedure(s) to be received by participants as part of the research protocol. *These include uses of medicinal products or devices, other medical treatments or assessments, mental health interventions, imaging investigations and taking samples of human biological material. Include procedures which might be received as routine clinical care outside of the research.*

Please complete the columns for each intervention/procedure as follows:

1. Total number of interventions/procedures to be received by each participant as part of the research protocol.
2. If this intervention/procedure would be routinely given to participants as part of their care outside the research, how many of the total would be routine?
3. Average time taken per intervention/procedure (minutes, hours or days).

4. Details of who will conduct the intervention/procedure, and where it will take place.

Intervention or procedure	1	2	3	4
Usual Care	N/A	N/A	N/A	Participant will continue with usual care.
Hydroxychloroquine	14	0	1	Participant will self-administer hydroxychloroquine 200 mg twice a day for 7 days. Further interventions may be added during the course of the trial, subject to suitable interventions becoming available and ethics and other necessary approvals
Swab	1	0	5	Swab by GP or self-swab, put in the secure container and double bag, and post it to the PHE laboratory supporting the study

A20. Will you withhold an intervention or procedure, which would normally be considered a part of routine care?

○ Yes ◉ No

A21. How long do you expect each participant to be in the study in total?

28 days

A22. What are the potential risks and burdens for research participants and how will you minimise them?

For all studies, describe any potential adverse effects, pain, discomfort, distress, intrusion, inconvenience or changes to lifestyle. Only describe risks or burdens that could occur as a result of participation in the research. Say what steps would be taken to minimise risks and burdens as far as possible.

The trial is an adaptive trial and will use low risk interventions for high risk people. There is a potential risk for using hydroxychloroquine or other treatments for the first time in participants likely to be infected with COVID-19. However, the drug is licensed with a good safety profile. We will record SAEs and have a DMSC in place to review ongoing safety events to reduce the risk to the participants.

Hydroxychloroquine is known to cause certain side-effects. 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: 1 = mild, 2 = moderate, 3 = severe. 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.

The trial diaries will be completed by the trial participants daily and may be a burden on the participant, but is essential to the trial. We have made the diaries as streamlined and easy to complete as possible and only participants that have the time and ability to complete the diary will be able to join the trial.

A23. Will interviews/ questionnaires or group discussions include topics that might be sensitive, embarrassing or upsetting, or is it possible that criminal or other disclosures requiring action could occur during the study?

◉ Yes ○ No

If Yes, please give details of procedures in place to deal with these issues:

If the participant is hospitalised or very ill, we may ask a trial partner about the hospitalisation of their relative/spouse/friend with the participant's prior permission.

A24. What is the potential for benefit to research participants?

Hydroxychloroquine and other potential treatments may benefit patients with COVID-19 and enhance the sustainability of NHS care during the current crisis.

A25. What arrangements are being made for continued provision of the intervention for participants, if appropriate, once the research has finished? *May apply to any clinical intervention, including a drug, medical device, mental health intervention, complementary therapy, physiotherapy, dietary manipulation, lifestyle change, etc.*

This is a 7 day treatment in the first instance, therefore there will be no provision of the IMP beyond the trial period.

A26. What are the potential risks for the researchers themselves? *(if any)*

There are no face to face visits and so there is no risk to the researchers.

RECRUITMENT AND INFORMED CONSENT

In this section we ask you to describe the recruitment procedures for the study. Please give separate details for different study groups where appropriate.

A27-1. How will potential participants, records or samples be identified? Who will carry this out and what resources will be used?*For example, identification may involve a disease register, computerised search of GP records, or review of medical records. Indicate whether this will be done by the direct healthcare team or by researchers acting under arrangements with the responsible care organisation(s).*

Patients ≥50 years with comorbidity, and patients aged ≥65 with or without comorbidity presenting in the community within 7 days since onset of symptoms, with a new continuous cough - this means coughing a lot more than an hour, or 3 or more coughing episodes in 24 hours (if you usually have a cough, it may be worse than usual) and/or high temperature - this means you feel hot to touch on your chest or back (you do not need to take your temperature), during a time of prevalent COVID-19 infections and registered with a participating general practice.

Recruitment will happen in a variety of ways due to the changing pandemic environment, including but not an exhaustive list:

1. People who are concerned about COVID-19 continue to contact their general practices in large numbers. In the first instance, we will ask participating general practices to record whether a person phoning about COVID-19 is potentially eligible for the study. The practice will then ask the person if they are interested in finding out about potential trial participation. If they are, information will be provided verbally and online either by the GP surgery or their contact details passed to the trial team who will provide such information.

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

3. The study team will receive contact due to word of mouth and media exposure (including but not limited to calls, and emails) from potential participants and will give them the trial information.

4. Any agencies from national bodies, such as NHS 111, who receive COVID-19 calls will provide trial information.

A27-2. Will the identification of potential participants involve reviewing or screening the identifiable personal information of patients, service users or any other person?

(●) Yes ( ) No

Please give details below:
Patient primary and secondary care medical records will be reviewed by their GPs for potentially eligible participants.

A27-3. Describe what measures will be taken to ensure there is no breach of any duty of confidentiality owed to

patients, service users or any other person in the process of identifying potential participants.*Indicate what steps have been or will be taken to inform patients and service users of the potential use of their records for this purpose. Describe the arrangements to ensure that the wishes of patients and service users regarding access to their records are respected. Please consult the guidance notes on this topic.*

Information in the PIS will clearly explain who has access to patient data and how the data will be stored, as well as the duration. Patients will consent to providing these data.

For patients calling their GP regarding COVID-19 symptoms and who are willing to take part in the trial, the practice will seek verbal consent from the patient to securely transfer their contact details to the trial team.

For patients enrolling online, the study team will only have access to identifiable personal information when the participant has willingly entered the information into the trial website.

A27-4. Will researchers or individuals other than the direct care team have access to identifiable personal information of any potential participants?

(●) Yes ( ) No

A27-5. Has prior consent been obtained or will it be obtained for access to identifiable personal information?

(●) Yes ( ) No

If Yes, please give details below.

Patients will consent to the following two points:

I understand that relevant sections of my GP and Hospital medical notes and data collected during the study may be looked at by individuals from University of Oxford. It may also be reviewed by relevant people from regulatory authorities and from the NHS Trust(s). I give permission for these individuals to have access to my records.

I consent to being contacted by the research team for the purposes of trial follow up and I understand that this will require me to provide my details to the research team.

A28. Will any participants be recruited by publicity through posters, leaflets, adverts or websites?

( ) Yes (●) No

A29. How and by whom will potential participants first be approached?

Any potential participants identified through their medical records will be invited to the trial. They will be given (text, phone, letter) a link to an online system where they will be able to view a participant information sheet, study team contact details, eligibility form, consent form and baseline questionnaire. Participants will be able to call a study telephone number if they are interested in taking part in the study or wish to discuss any further questions about the research.

Patients will also be approached by their GP practice/111 when the patient contacts these services to report COVID-19 symptoms.

A30-1. Will you obtain informed consent from or on behalf of research participants?

(●) Yes ( ) No

If you will be obtaining consent from adult participants, please give details of who will take consent and how it will be done, with details of any steps to provide information (a written information sheet, videos, or interactive material). Arrangements for adults unable to consent for themselves should be described separately in Part B Section 6, and for children in Part B Section 7.

If you plan to seek informed consent from vulnerable groups, say how you will ensure that consent is voluntary and fully informed.

All volunteers, or their legal representative, will be required to provide informed consent before any study specific procedures are performed. They will be provided with a trial team phone number to call and ask any questions. The information sheet will be made available to the participant via the website.

Through the trial website the participant will be fully informed of all aspects of the trial, the potential risks and their obligations. The following general principles will be emphasised:
- Participation in the study is entirely voluntary
- Declining to participate involves no penalty or loss of medical benefits
- The volunteer may withdraw from the study at any time without having to give a reason and without prejudice to their ongoing health care
- The volunteer is free to ask questions at any time to allow him or her to understand the purpose of the study and the procedures involved
- The study involves research of an investigational medicine

The aims of the study will be explained. The participant will be given the opportunity to ask about details of the trial. If they do decide to participate, they will provide e-consent. The participant, GP and trial team will have access to the completed electronic consent form, which can be download and printed/stored at any time.

If you are not obtaining consent, please explain why not.

Please enclose a copy of the information sheet(s) and consent form(s).

A30-2. Will you record informed consent (or advice from consultees) in writing?

○ Yes ◉ No

If No, how will it be recorded?

Electronic consent will be provided due to the rapid nature and urgency of the trial.

A31. How long will you allow potential participants to decide whether or not to take part?

Participants can respond to the text invite at any stage during the COVID-19 infections phase, as long as their symptoms are within 7 days of the symptoms starting.

A32. Will you recruit any participants who are involved in current research or have recently been involved in any research prior to recruitment?

○ Yes
○ No
◉ Not Known

If Yes, please give details and justify their inclusion. If Not Known, what steps will you take to find out?

A33-1. What arrangements have been made for persons who might not adequately understand verbal explanations or written information given in English, or who have special communication needs?*(e.g. translation, use of interpreters)*

Translation, use of interpreters will be used if available.

A33-2. What arrangements will you make to comply with the principles of the Welsh Language Act in the provision of information to participants in Wales?

A34. What arrangements will you make to ensure participants receive any information that becomes available during the course of the research that may be relevant to their continued participation?

The research team will inform all participants and their general practitioners if information relevant to continued participation becomes available during the trial.

CONFIDENTIALITY

In this section, personal data means any data relating to a participant who could potentially be identified. It includes pseudonymised data capable of being linked to a participant through a unique code number.

Storage and use of personal data during the study

A36. Will you be undertaking any of the following activities at any stage (including in the identification of potential participants)? *(Tick as appropriate)*

- [x] Access to medical records by those outside the direct healthcare team
- [ ] Access to social care records by those outside the direct social care team
- [x] Electronic transfer by magnetic or optical media, email or computer networks
- [x] Sharing of personal data with other organisations
- [ ] Export of personal data outside the EEA
- [x] Use of personal addresses, postcodes, faxes, emails or telephone numbers
- [ ] Publication of direct quotations from respondents
- [ ] Publication of data that might allow identification of individuals
- [ ] Use of audio/visual recording devices
- [x] Storage of personal data on any of the following:
  - [x] Manual files (includes paper or film)
  - [x] NHS computers
  - [ ] Social Care Service computers
  - [ ] Home or other personal computers
  - [x] University computers
  - [ ] Private company computers
  - [ ] Laptop computers

Further details:
The participants' contact details will be stored on the dedicated study website to allow participants to be contacted for follow-up as part of the study.

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

A37. Please describe the physical security arrangements for storage of personal data during the study?

Electronic forms containing contact details will be stored on secure computers in a secure database. Any paper based trial and personal data will be stored in locked cabinets in a room with access restricted only to authorised personnel in a secure building which requires electronic tags to enter. The Case Report Forms and diaries will not include these details but will include a unique participant identification number for each participant. A separate electronic file will be securely stored providing linkage between the unique participant identification numbers and the contact details. In compliance with the Data Protection Act and GDPR, data will be pseudo-anonymised as soon as it is practical to do so.

A38. How will you ensure the confidentiality of personal data?*Please provide a general statement of the policy and procedures for ensuring confidentiality, e.g. anonymisation or pseudonymisation of data.*

A unique participant ID for each individual will be assigned as each individual enters the study. All clinical data will be referred using this ID and stored separately from any identifiable contact details. All research staff associated with the study will be trained on the Data Protection Policy regarding privacy and security according to PC-CTU SOPs. Only the Sponsor representatives, Investigators, the DMSC, the REC and the MHRA will have access to the records.

A40. Who will have access to participants' personal data during the study? *Where access is by individuals outside the direct care team, please justify and say whether consent will be sought.*

Consent will be sought for the storage of and access to the Case Report Forms and contact details of participants by the trial team. This is required in order for the trial team to orchestrate the collection of outcome data. Telephone contact is required as part of the study procedures. The only individuals with access to the participant contact details will be delegated members of the trial team. This personal data will only be shared to the wider trial team in the event of an SAE and the need for urgent follow up. Pseudo-anonymised trial data will be accessible by the wider trial team for review and analysis, also to specifically delegated monitors for monitoring and audit of the trial to ensure we are complying with regulations. Personal data to be used for data linkage to routine collected data will be accessed by a delegated member of the trial team and once data linkage has been completed the personal information used to perform the data linkage will be destroyed.

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

Storage and use of data after the end of the study

A41. Where will the data generated by the study be analysed and by whom?

The data analysis will be performed by Berry Consultancy with support fron statisticians at the University of Oxford. The company is based in the USA, however no identifiable data will be given to them during this process.

A42. Who will have control of and act as the custodian for the data generated by the study?

	Title	Forename/Initials	Surname
	Prof	Christopher	Butler
Post	Chief Investigator		
Qualifications	MBChB, Dip Child Health, MRCGP, MD, FRCGP, HonFFPH		
Work Address	University of Oxford		
	Nuffield Department of Primary Care Health Sciences, Radcliffe Observatory Quarter, Woodstock Road		
	Oxford		
Post Code	OX2 6GG		
Work Email	Christopher.butler@phc.ox.ac.uk		
Work Telephone	01865 289363		
Fax			

A43. How long will personal data be stored or accessed after the study has ended?

- ○ Less than 3 months
- ○ 3 – 6 months
- ◉ 6 – 12 months
- ○ 12 months – 3 years

○ Over 3 years

A44. For how long will you store research data generated by the study?

Years: 20
Months: 0

A45. Please give details of the long term arrangements for storage of research data after the study has ended. *Say where data will be stored, who will have access and the arrangements to ensure security.*

Research documents with personal information, such as consent forms, will be held securely at the University of Oxford for 20 years after the end of the study.

INCENTIVES AND PAYMENTS

A46. Will research participants receive any payments, reimbursement of expenses or any other benefits or incentives for taking part in this research?

◉ Yes ○ No

If Yes, please give details. For monetary payments, indicate how much and on what basis this has been determined.
All participants will be reimbursed with a £20 voucher, to covers the payment of a prescription, should they incur tis as a result of study participation, and a token of recognition of giving their time and contribution to the study. The vast majority of participant's will not have to pay a prescription change, should a prescription be issued as a result of trial participation. Most people with the co-morbidities outlines and in the age range required for eligibility, are not required to pay for prescriptions.

A47. Will individual researchers receive any personal payment over and above normal salary, or any other benefits or incentives, for taking part in this research?

○ Yes ◉ No

A48. Does the Chief Investigator or any other investigator/collaborator have any direct personal involvement (e.g. financial, share holding, personal relationship etc.) in the organisations sponsoring or funding the research that may give rise to a possible conflict of interest?

○ Yes ◉ No

NOTIFICATION OF OTHER PROFESSIONALS

A49-1. Will you inform the participants' General Practitioners (and/or any other health or care professional responsible for their care) that they are taking part in the study?

◉ Yes ○ No

If Yes, please enclose a copy of the information sheet/letter for the GP/health professional with a version number and date.

A49-2. Will you seek permission from the research participants to inform their GP or other health/ care professional?

◉ Yes ○ No

It should be made clear in the participant's information sheet if the GP/health professional will be informed.

PUBLICATION AND DISSEMINATION

A50. Will the research be registered on a public database?

The UK Policy Framework for Health and Social Care Research sets out the principle of making information about research publicly available. Furthermore: Article 19 of the World Medical Association Declaration of Helsinki adopted in 2008 states that "every clinical trial must be registered on a publicly accessible database before recruitment of the first subject"; and the International Committee of Medical Journal Editors (ICMJE) will consider a clinical trial for publication only if it has been registered in an appropriate registry. Please see guidance for more information.

◉ Yes ○ No

Please give details, or justify if not registering the research.
The trial is registered with ISRCTN.

Please ensure that you have entered registry reference number(s) in question A5-1.

A51. How do you intend to report and disseminate the results of the study? *Tick as appropriate:*

- ☑ Peer reviewed scientific journals
- ☑ Internal report
- ☐ Conference presentation
- ☑ Publication on website
- ☑ Other publication
- ☑ Submission to regulatory authorities
- ☐ Access to raw data and right to publish freely by all investigators in study or by Independent Steering Committee on behalf of all investigators
- ☐ No plans to report or disseminate the results
- ☐ Other (please specify)

A52. If you will be using identifiable personal data, how will you ensure that anonymity will be maintained when publishing the results?

No personal data will be published and the study team will ensure that the participants' anonymity is maintained. Participants paperwork will only be identifiable through the an ID number, there will be no personal details present on any CRFs or diaries. ID numbers will be linked to the participant through a document that is only accessible by the study team and stored on a secure server within the University of Oxford.

A53. Will you inform participants of the results?

◉ Yes ○ No

Please give details of how you will inform participants or justify if not doing so.
We will provide a summary of the study findings to all participants via the study website.

5. Scientific and Statistical Review

A54. How has the scientific quality of the research been assessed? *Tick as appropriate:*

- ☐ Independent external review
- ☐ Review within a company

- [x] Review within a multi−centre research group
- [x] Review within the Chief Investigator's institution or host organisation
- [x] Review within the research team
- [ ] Review by educational supervisor
- [ ] Other

Justify and describe the review process and outcome. If the review has been undertaken but not seen by the researcher, give details of the body which has undertaken the review:
This study has been reviewed by expert members: members of the CTU senior management team, the study team, the sponsor, PHE.

For all studies except non-doctoral student research, please enclose a copy of any available scientific critique reports, together with any related correspondence.

For non-doctoral student research, please enclose a copy of the assessment from your educational supervisor/ institution.

A56. How have the statistical aspects of the research been reviewed?*Tick as appropriate:*

- [ ] Review by independent statistician commissioned by funder or sponsor
- [x] Other review by independent statistician
- [ ] Review by company statistician
- [ ] Review by a statistician within the Chief Investigator's institution
- [x] Review by a statistician within the research team or multi−centre group
- [ ] Review by educational supervisor
- [ ] Other review by individual with relevant statistical expertise
- [ ] No review necessary as only frequencies and associations will be assessed – details of statistical input not required

In all cases please give details below of the individual responsible for reviewing the statistical aspects. If advice has been provided in confidence, give details of the department and institution concerned.

	Title	Forename/Initials	Surname
	Prof	Ly-Mee	Yu
Department	Primary Care Clinical Trials Unit, Nuffield Department of Primary Care Health Sciences		
Institution	University of Oxford		
Work Address	Primary Care Clinical Trials Unit,		
	Nuffield Department of Primary Care Health Sciences,		
	Radcliffe Observatory Quarter, Woodstock Road		
Post Code	OX2 6GG		
Telephone	+44 (0)1865 617199		
Fax			
Mobile			
E-mail	ly-mee.yu@phc.ox.ac.uk		

Please enclose a copy of any available comments or reports from a statistician.

A57. What is the primary outcome measure for the study?

Hospital admission or mortality related to suspected COVID-19.

A58. What are the secondary outcome measures?*(if any)*

To explore whether trial treatment reduces the following:

1. Duration of severe symptoms
2. Time taken to resumption of usual daily activities

Measured by daily online symptoms score and the day the patient reports they returned to usual activities.

3. Contacts with health services

Reported by patients and captured by reports of patients‘ medical records where the practice is a member of RSC.

4. Consumption of antibiotics

Measured using bi-weekly reports from participants primary care medical records.

5. Hospital assessment not leading to admission
6. Oxygen administration
7. Intensive Care Unit admission
8. Mechanical ventilation

All measured using patient report/carer report/medical record in primary care and hospital care. HES/ONS data linkage after 28 days where patients have been assessed in hospital.

9. To determine if effects are specific to those with the infections syndrome but who test positive for COVID-19.

Swab results for COVID-19 will indicate an “Intention to Treat Infected” group within the overall cohort for sub analysis (Swab result available once processed from GP record and from PHE laboratory).

10. Duration of hospital admission

Measured using patient report/carer report/medical record in primary care and hospital care. HES/ONS data linkage after 28 days where patients have been assessed in hospital.

A59. What is the sample size for the research? *How many participants/samples/data records do you plan to study in total? If there is more than one group, please give further details below.*

Total UK sample size:	3000
Total international sample size (including UK):	3000
Total in European Economic Area:	3000

Further details:
Total: 3000 (i.e. 1500 per arm)

A60. How was the sample size decided upon? *If a formal sample size calculation was used, indicate how this was done, giving sufficient information to justify and reproduce the calculation.*

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.

A61. Will participants be allocated to groups at random?

◉ Yes ○ No

If yes, please give details of the intended method of randomisation:
Consenting participants who have satisfied all the eligibility criteria will be individually randomised using a fully validated web-based randomisation system called Sortition. At the baseline assessment, the recruiter will enter the participant's baseline data into the online system, which will then enable the randomisation to take place. The randomisation process will take only a few moments via the online system and will not delay trial participation

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

A62. Please describe the methods of analysis (statistical or other appropriate methods, e.g. for qualitative research) by which the data will be evaluated to meet the study objectives.

The primary endpoint is hospital admission or death as a result of COVID-19 infection. The primary analysis will be a Bayesian generalised linear model of the primary outcome regressed on treatment and stratification covariates (age, comorbidity).

The first interim analysis will occur when first 100 randomised participants have completed 28 days of follow-up, and subsequent weekly interim analyses. At each interim analysis, all enrolled intervention arms will be evaluated for success or futility using the Bayesian primary analysis.

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

6. MANAGEMENT OF THE RESEARCH

A63. Other key investigators/collaborators. *Please include all grant co−applicants, protocol co−authors and other key members of the Chief Investigator's team, including non-doctoral student researchers.*

	Title	Forename/Initials	Surname
	Dr	James	Ray
Post	Oxford University Hospitals Emergency Medicine Consultant, NHS England lead for Urgent and Emergency Care for Thames Valley and London		
Qualifications			
Employer			
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Post Code	OX3 9DU		
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Mobile			
Work Email	james.ray@nhs.net		

	Title	Forename/Initials	Surname
	Prof	Richard	Hobbs
Post	Nuffield Professor of Primary Care Health Sciences		
Qualifications	CBE, FMedSci, FRCGP, FRCP (London), FESC, FRCP (Edin), MA (Ox)		
Employer	University of Oxford		
Work Address	Department of Primary Care Health Sciences Radcliffe Observatory Quarter		
Post Code	OX2 6GG		
Telephone			
Fax			
Mobile			
Work Email	richard.hobbs@phc.ox.ac.uk		

	Title	Forename/Initials	Surname
	Professor	Simon	de Lusignan
Post	Professor of Primary Care and Clinical Informatics		
Qualifications			
Employer	University of Oxford		
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Work Email	simon.delusignan@phc.ox.ac.uk		

	Title	Forename/Initials	Surname
	Associate Professor	Gail	Hayward
Post	Associate Professor		
Qualifications	MBBChir, D.Phil, MRCP, DRCOG, MRCGP		
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	Title	Forename/Initials	Surname
	Dr	Oliver	van Hecke
Post	NIHR Academic Clinical Lecturer		
Qualifications	MBChB (Pret) DMJ (Clin) MRCGP FRACGP DPhil		
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Title	Forename/Initials	Surname
Professor	Martin	Llewellyn

Post	Professor in Infectious Diseases
Qualifications	BSc, FRCP, DTMH, PhD)
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Title	Forename/Initials	Surname
Prof	Ly-Mee	Yu

Post	Associate Professor and Deputy Director Academic (Primary Care Clinical Trials Unit)
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Title	Forename/Initials	Surname
Dr	Emma	Ogburn

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	Title	Forename/Initials	Surname
	Ms	Julie	Allen
Post	Senior Trial Manager		
Qualifications			
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	Title	Forename/Initials	Surname
	Dr	Emily	Bongard
Post	Senior Trial Manager		
Qualifications	BSc (Hons), MSc, PhD		
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Work Email	emily.bongard@phc.ox.ac.uk		

	Title	Forename/Initials	Surname
	Dr	Hannah	Swayze
Post	Senior Trial Manager		
Qualifications	BSc, PhD		
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	Title	Forename/Initials	Surname
	Professor	Maria	Zambon
Post	Director of Reference Microbiology		
Qualifications			
Employer	National Infection Service, Public Health England		
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Title	Forename/Initials	Surname
Dr	Ben	Saville

Post	Statistical Scientist
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Title	Forename/Initials	Surname
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Qualifications	
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Title	Forename/Initials	Surname
	Gayatri	Amirthalingam

Post	Consultant Epidemiologist
Qualifications	
Employer	National Infection Service, Public Health England
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Mobile	
Work Email	Gayatri.Amirthalingam@phe.gov.uk

Title	Forename/Initials	Surname
Dr	Jamie	Lopez Bernal

Post	Consultant Epidemiologist
Qualifications	
Employer	National Infection Service, Public Health England
Work Address	Public Information Access Office, Wellington House 133-155 Waterloo Road London
Post Code	SE1 8UG
Telephone	020 7654 8000
Fax	
Mobile	
Work Email	Jamie.LopezBernal@phe.gov.uk

A64. Details of research sponsor(s)

A64-1. Sponsor

SP1

Status:
- ○ NHS or HSC care organisation
- ◉ Academic
- ○ Pharmaceutical industry
- ○ Medical device industry
- ○ Local Authority
- ○ Other social care provider (including voluntary sector or private organisation)
- ○ Other

Commercial status: Non-Commercial

If Other, please specify:

Contact person

Name of organisation	University of Oxford / Clinical Trials and Research Governance
Given name	N/A
Family name	CTRG
Address	Joint Research Office, 1st floor, Boundary Brook House, Churchill Drive, Headington
Town/city	Oxford
Post code	OX3 7GB
Country	United Kingdom
Telephone	0000
Fax	0000
E-mail	ctrg@admin.ox.ac.uk

Legal representative in the European Economic Area for the purpose of this trial
A legal representative must be appointed for a clinical trial of an investigational medicinal product if the sponsor is not established within the European Economic Area (EEA) (see article 19 of Directive 2001/20/EC). If this applies, please enclose evidence that the legal representative is established within the EEA and has accepted the role of legal representative.

Legal representative

Contact person

Name of organisation
Given name
Family name
Address
Town/city
Post code
Country
Telephone
Fax
E-mail

A65. Has external funding for the research been secured?

Please tick at least one check box.

- [x] Funding secured from one or more funders
- [ ] External funding application to one or more funders in progress
- [ ] No application for external funding will be made

What type of research project is this?

- (•) Standalone project
- ( ) Project that is part of a programme grant
- ( ) Project that is part of a Centre grant
- ( ) Project that is part of a fellowship/ personal award/ research training award
- ( ) Other

Other – please state:

Please give details of funding applications.

Organisation	Dept. of Health and Social Care
Address	39 Victoria Street London
Post Code	SW1H 0EU
Telephone	0207 210 4850
Fax	
Mobile	
Email	

Funding Application Status: (•) Secured ( ) In progress

Amount: £1.9 million

Duration
Years: 2
Months: 0

If applicable, please specify the programme/ funding stream:

What is the funding stream/ programme for this research project?

The trial will continue until the last data capture of all participants and no further suitable interventions are available and/or COVID 19 is no longer prevalent

A66. Has responsibility for any specific research activities or procedures been delegated to a subcontractor (other than a co-sponsor listed in A64-1) ? *Please give details of subcontractors if applicable.*

○ Yes ◉ No

A67. Has this or a similar application been previously rejected by a Research Ethics Committee in the UK or another country?

○ Yes ◉ No

Please provide a copy of the unfavourable opinion letter(s). You should explain in your answer to question A6-2 how the reasons for the unfavourable opinion have been addressed in this application.

A68-1. Give details of the lead NHS R&D contact for this research:

Title	Forename/Initials	Surname
Mrs	Vicki	Clatworthy

Organisation	NIHR Clinical Research Network: Thames valley and South Midlands
Address	TVCN Offices Block-8 Nuffield Orthopaedic Centre
	Windmill Road, Headington
	Oxford
Post Code	OX3 7HE
Work Email	vicki.clatworthy@oxfordhealth.nhs.uk
Telephone	07900 407260
Fax	
Mobile	

Details can be obtained from the NHS R&D Forum website: http://www.rdforum.nhs.uk

A68-2. Select Local Clinical Research Network for NHS Organisation identified in A68-1:

Thames Valley and South Midlands

For more information, please refer to the question specific guidance.

A69-1. How long do you expect the study to last in the UK?

Planned start date: 25/03/2020

Planned end date: 25/03/2022
Total duration:
Years: 2 Months: 0 Days: 1

A69-2. How long do you expect the study to last in all countries?

Planned start date: 25/03/2020
Planned end date:
Total duration:
Years: 2 Months: 0 Days: 1

A70. Definition of the end of trial, and justification in the case where it is not the last visit of the last subject undergoing the trial (1)

Last data capture of last participant, when no further suitable interventions are available and/or COVID 19 is no longer prevalent.

A71-1. Is this study?

- ○ Single centre
- ◉ Multicentre

A71-2. Where will the research take place? *(Tick as appropriate)*

- ☑ England
- ☑ Scotland
- ☑ Wales
- ☑ Northern Ireland
- ☐ Other countries in European Economic Area

Total UK sites in study 300

Does this trial involve countries outside the EU?
○ Yes ◉ No

A72. Which organisations in the UK will host the research?*Please indicate the type of organisation by ticking the box and give approximate numbers if known:*

- ☐ NHS organisations in England
- ☐ NHS organisations in Wales
- ☐ NHS organisations in Scotland
- ☐ HSC organisations in Northern Ireland
- ☑ GP practices in England 300
- ☐ GP practices in Wales
- ☐ GP practices in Scotland
- ☐ GP practices in Northern Ireland
- ☐ Joint health and social care agencies (eg community mental health teams)

☐ Local authorities
☐ Phase 1 trial units
☐ Prison establishments
☐ Probation areas
☐ Independent (private or voluntary sector) organisations
☐ Educational establishments
☐ Independent research units
☐ Other (give details)

Total UK sites in study: 300

A73-1. Will potential participants be identified through any organisations other than the research sites listed above?

○ Yes ◉ No

A74. What arrangements are in place for monitoring and auditing the conduct of the research?

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

A75-1. What arrangements will be made to review interim safety and efficacy data from the trial? Will a formal data monitoring committee or equivalent body be convened?

Trial committees:
A Data Monitoring Safety Committee (DMSC) will be formed. They will meet initially to agree the Protocol and periodically, at their request. They will receive interim data. A 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 the updates to the randomisation scheme occur in order to ensure that the process is working correctly and to review and monitor the accruing data to ensure the rights, safety and wellbeing of the trial participants. They will make recommendations about how the study is operating, any ethical or safety issues and any data being produced from other relevant studies that might impact the trial. This Committee will also take on the role of a Trial Steering Committee, and so act as a single oversight committee.

• TMG- is responsible for the day-to-day running of the trial, including monitoring all aspects of the trial and ensuring that the protocol is being adhered to. It will include Co-Investigators and will meet weekly in the first instance.

If a formal DMC is to be convened, please forward details of the membership and standard operating procedures to the Research Ethics Committee when available. The REC should also be notified of DMC recommendations and receive summary reports of interim analyses.

A75-2. What are the criteria for electively stopping the trial or other research prematurely?

After interim analysis if there is enough data to satisfy primary outcome question, evaluation of that drug can be stopped and another drug added.

A76. Insurance/ indemnity to meet potential legal liabilities

***Note:** in this question to NHS indemnity schemes include equivalent schemes provided by Health and Social Care (HSC) in Northern Ireland*

A76-1. What arrangements will be made for insurance and/or indemnity to meet the potential legal liability of the sponsor(s) for harm to participants arising from the management of the research? *Please tick box(es) as applicable.*

Note: Where a NHS organisation has agreed to act as sponsor or co-sponsor, indemnity is provided through NHS schemes. Indicate if this applies (there is no need to provide documentary evidence). For all other sponsors, please describe the arrangements and provide evidence.

☐ NHS indemnity scheme will apply (NHS sponsors only)

☑ Other insurance or indemnity arrangements will apply (give details below)

The University has a specialist insurance policy in place – Newline Underwriting Management Ltd, at Lloyd's of London – that would operate in the event of any participant suffering harm as a result of their involvement in the research.

Please enclose a copy of relevant documents.

A76-2. What arrangements will be made for insurance and/ or indemnity to meet the potential legal liability of the sponsor(s) or employer(s) for harm to participants arising from the design of the research? *Please tick box(es) as applicable.*

Note: Where researchers with substantive NHS employment contracts have designed the research, indemnity is provided through NHS schemes. Indicate if this applies (there is no need to provide documentary evidence). For other protocol authors (e.g. company employees, university members), please describe the arrangements and provide evidence.

☐ NHS indemnity scheme will apply (protocol authors with NHS contracts only)

☑ Other insurance or indemnity arrangements will apply (give details below)

The University has a specialist insurance policy in place – Newline Underwriting Management Ltd, at Lloyd's of London – that would operate in the event of any participant suffering harm as a result of their involvement in the research.

Please enclose a copy of relevant documents.

A76-3. What arrangements will be made for insurance and/ or indemnity to meet the potential legal liability of investigators/collaborators arising from harm to participants in the conduct of the research?

Note: Where the participants are NHS patients, indemnity is provided through the NHS schemes or through professional indemnity. Indicate if this applies to the whole study (there is no need to provide documentary evidence). Where non-NHS sites are to be included in the research, including private practices, please describe the arrangements which will be made at these sites and provide evidence.

☑ NHS indemnity scheme or professional indemnity will apply (participants recruited at NHS sites only)

☑ Research includes non-NHS sites (give details of insurance/ indemnity arrangements for these sites below)

The University has a specialist insurance policy in place – Newline Underwriting Management Ltd, at Lloyd's of London – that would operate in the event of any participant suffering harm as a result of their involvement in the research.

Please enclose a copy of relevant documents.

A77. Has the sponsor(s) made arrangements for payment of compensation in the event of harm to the research participants where no legal liability arises?

○ Yes ◉ No

Please enclose a copy of relevant documents.

A78. Could the research lead to the development of a new product/process or the generation of intellectual property?

(●) Yes ( ) No ( ) Not sure

Part B Section 1: Investigational Medicinal Products

Information on each IMP.

Information on each 'bulk product' before trial-specific operations (blinding, trial specific packaging and labelling) should be provided in this section for each investigational medicinal product (IMP) being tested including each comparator, if applicable.
If the trial is performed with several products please create a separate set of the following questions for each product. If the product is a combination product please give separate information for each active substance.
Click on the first row and enter details of the product in the following screens. When you have completed the details, click on the navigate button or the "See All" link and return to this section to enter details of the next product. When you have completed details of all products please move to question 13 using the navigation screen.

Investigational medicinal products

PR1 Plaquenil-Hydroxychloroquine

PR3 Azithromycin

PR4 Doxycycline

PR5 Pulmicort Turbohaler 400

13. Indicate which of the following is described below then repeat as necessary for each:

This refers to the IMP number: **PR1**
Investigational medicinal product category:
Test IMP

14. STATUS OF THE IMP
If the IMP has a marketing authorisation in the Member State concerned by this application but the trade name and marketing authorisation holder are not fixed in the protocol, go to question 14-.2

14-1. Does the IMP to be used in the trial have a marketing authorisation?

◉ Yes ○ No ○ Not Answered

Trade name:
Plaquenil-Hydroxychloroquine
EV Product Code
Name of the MA holder:
Zentiva Pharma UK Limited
MA number (if MA granted by a Member State):
PL 17780/0748
Is the IMP modified in relation to its MA?

○ Yes ◉ No ○ Not Answered

Which country granted the MA?
UK - MHRA
Is this the Member State concerned with this application?

○ Yes ◉ No ○ Not Answered

14-2. Situations where an IMP to be used in the CT has a MA in the MS concerned, but the protocol allows that any brand of the IMP with a MA in that MS be administered to the trial subjects and it is not possible to clearly identify the IMP(s) in advance of the trial start

In the protocol, is treatment defined only by active substance?
◯ Yes ◉ No ◯ Not Answered

In the protocol, do treatment regimens allow different combinations of marketed products used according to local clinical practice at some or all investigator sites in the MS?
◯ Yes ◉ No ◯ Not Answered

The products to be administered as IMPs are defined as belonging to an ATC group
◯ Yes ◯ No ◉ Not Answered

Other :
◯ Yes ◯ No ◉ Not Answered

14-3. IMPD submitted:

Full IMPD
◯ Yes ◉ No ◯ Not Answered

Simplified IMPD
◯ Yes ◉ No ◯ Not Answered

Provide justification for using simplified dossier in the covering letter

Summary of product characteristics (SmPC) only
◉ Yes ◯ No ◯ Not Answered

14-4. Has the use of the IMP been previously authorised in a clinical trial conducted by the sponsor in the Community?

◯ Yes ◉ No ◯ Not Answered

14-5. Has the IMP been designated in this indication as an orphan drug in the Community?

◯ Yes ◉ No ◯ Not Answered

14-6. Has the IMP been the subject of scientific advice related to this clinical trial?

◯ Yes ◉ No ◯ Not Answered

Please indicate source of advice and provide a copy in the CTA request:

From the CHMP?
◯ Yes ◉ No ◯ Not Answered

CHMP = Committee for Medicinal Products for Human Use

From a MS competent authority?
◯ Yes ◉ No ◯ Not Answered

This is a sub-set of questions about each IMP. To return to the list of IMPs select "See all" at the top of the page or select "Navigate". To complete further questions about this IMP select "Next".

Description of IMP

15-1. Description of IMP

Product name where applicable	Plaquenil-Hydroxychloroquine
Product code where applicable	
ATC codes, if officially registered	P01B A02.
Pharmaceutical form (use standard terms)	Film-coated tablet
Is this a specific paediatric formulation?	◯ Yes ◉ No ◯ Not Answered
Maximum duration of treatment of a subject according to the protocol	7 days

Dose allowed

First dose for first-in-human clinical trial

Specify per day or total: ◯ per day ◯ total ◉ Not Answered

Specify total dose (number and unit)

Route of administration (relevant to the first dose):

Maximum dose allowed

Specify per day or total ◯ per day ◯ total ◉ Not Answered

Specify total dose (number and unit)

Route of administration (relevant to the maximum dose):

Routes of administration for this IMP

Oral use

This is a sub-set of questions about each IMP. To return to the list of IMPs select "See all" at the top of the page or select "Navigate". To complete further questions about this IMP select "Next".

15-2. Active substances

Complete all fields that currently apply to this Active Substance in this Product. If you have IMPs with different concentrations of the Active Substance complete a new Sub-section D for each.

Active Substance 1

Name of active substance (INN or proposed INN if available):	Hydroxychloroquine Sulfate 200 mg
CAS number:	
Current sponsor code:	
Other descriptive name:	
Full Molecular formula	

Chemical/biological description of the Active Substance	Antimalarial agents like chloroquine and hydroxychloroquine have several pharmacological actions which may be involved in their therapeutic effect in the treatment of rheumatic disease, but the role of each is not known. These include interaction with sulphydryl groups, interference with enzyme activity (including phospholipase, NADH-cytochrome C reductase, cholinesterase, proteases and hydrolases), DNA binding, stabilisation of lysosomal membranes, inhibition of prostaglandin formation, inhibition of polymorphonuclear cell chemotaxis and phagocytosis, possible interference with interleukin 1 production from monocytes and inhibition of neutrophil superoxide release.

Strength

Concentration unit:	mg milligram(s)
Concentration type:	equal
Concentration number (only use both fields for range):	200

15-3. Type of IMP

Does the IMP contain an active substance:

Of chemical origin?	(●) Yes ( ) No ( ) Not Answered
Of biological / biotechnological origin?(other than Advanced Therapy IMP (ATIMP))	( ) Yes (●) No ( ) Not Answered

Is this a:

Advanced Therapy IMP (ATIMP) [1]	( ) Yes (●) No ( ) Not Answered
Combination product that includes a device, but does not involve an Advanced Therapy	( ) Yes (●) No ( ) Not Answered
Radiopharmaceutical medicinal product?	( ) Yes (●) No ( ) Not Answered
Immunological medicinal product (e.g. vaccine, allergen, immune serum)?	( ) Yes (●) No ( ) Not Answered
Plasma derived medicinal product?	( ) Yes (●) No ( ) Not Answered
Extractive medicinal product?	( ) Yes (●) No ( ) Not Answered
Recombinant medicinal product?	( ) Yes (●) No ( ) Not Answered
Medicinal product containing genetically modified organisms?	( ) Yes (●) No ( ) Not Answered
Herbal medicinal product?	( ) Yes (●) No ( ) Not Answered
Homeopathic medicinal product?	( ) Yes (●) No ( ) Not Answered
Another type of medicinal product?	( ) Yes (●) No ( ) Not Answered

Specify the mode of action for the active substance in this medicinal product
The mode of action should briefly describe the chemical, biochemical, immunological or biological means that the IMP uses to effect its pharmaceutical action. Antimalarial agents like chloroquine and hydroxychloroquine have several pharmacological actions which may be involved in their therapeutic effect in the treatment of rheumatic disease, but the role of each is not known. These include interaction with sulphydryl groups, interference with enzyme activity (including phospholipase, NADH-cytochrome C reductase, cholinesterase, proteases and hydrolases), DNA binding, stabilisation of lysosomal membranes, inhibition of prostaglandin formation, inhibit

Is it an IMP to be used in a first-in-human clinical trial? ( ) Yes (●) No ( ) Not Answered

(1,2,3,4,5) Complete sections D.4, D.5, D.6. and D.7, as applicable

(2,3) As defined in Annex 1 part IV of Directive 2001/83/EC as amended

(4) As defined in Article 2(1)(b) of Regulation 1394/2007/EC

(6) Guideline on strategies to identify and mitigate risks for first-in-human clinical trials with investigational medicinal products. EMEA/CHMP/SWP/28367/2007

13. Indicate which of the following is described below then repeat as necessary for each:

This refers to the IMP number: **PR3**
Investigational medicinal product category:

14. STATUS OF THE IMP
If the IMP has a marketing authorisation in the Member State concerned by this application but the trade name and marketing authorisation holder are not fixed in the protocol, go to question 14-.2

14-1. Does the IMP to be used in the trial have a marketing authorisation?

◉ Yes ○ No ○ Not Answered

Trade name:
Azithromycin
EV Product Code
Name of the MA holder:
Teva UK Limited
MA number (if MA granted by a Member State):
PL 00289/1570
Is the IMP modified in relation to its MA?
○ Yes ◉ No ○ Not Answered

Which country granted the MA?
UK - MHRA
Is this the Member State concerned with this application?
○ Yes ◉ No ○ Not Answered

14-2. Situations where an IMP to be used in the CT has a MA in the MS concerned, but the protocol allows that any brand of the IMP with a MA in that MS be administered to the trial subjects and it is not possible to clearly identify the IMP(s) in advance of the trial start

In the protocol, is treatment defined only by active substance?
○ Yes ◉ No ○ Not Answered

In the protocol, do treatment regimens allow different combinations of marketed products used according to local clinical practice at some or all investigator sites in the MS?
○ Yes ◉ No ○ Not Answered

The products to be administered as IMPs are defined as belonging to an ATC group
○ Yes ○ No ◉ Not Answered

Other :
○ Yes ○ No ◉ Not Answered

14-3. IMPD submitted:

Full IMPD
○ Yes ◉ No ○ Not Answered

Simplified IMPD
○ Yes ◉ No ○ Not Answered

Provide justification for using simplified dossier in the covering letter

Summary of product characteristics (SmPC) only
◉ Yes ○ No ○ Not Answered

14-4. Has the use of the IMP been previously authorised in a clinical trial conducted by the sponsor in the Community?

○ Yes ◉ No ○ Not Answered

14-5. Has the IMP been designated in this indication as an orphan drug in the Community?

○ Yes ○ No ◉ Not Answered

14-6. Has the IMP been the subject of scientific advice related to this clinical trial?

○ Yes ◉ No ○ Not Answered

Please indicate source of advice and provide a copy in the CTA request:

From the CHMP?
○ Yes ◉ No ○ Not Answered

CHMP = Committee for Medicinal Products for Human Use

From a MS competent authority?
○ Yes ◉ No ○ Not Answered

This is a sub-set of questions about each IMP. To return to the list of IMPs select "See all" at the top of the page or select "Navigate". To complete further questions about this IMP select "Next".

Description of IMP

15-1. Description of IMP

Product name where applicable	Azithromycin
Product code where applicable	
ATC codes, if officially registered	
Pharmaceutical form (use standard terms)	Film-coated tablet
Is this a specific paediatric formulation?	○ Yes ○ No ◉ Not Answered
Maximum duration of treatment of a subject according to the protocol	

Dose allowed

First dose for first-in-human clinical trial
Specify per day or total: ○ per day ○ total ◉ Not Answered

Specify total dose (number and unit)

Route of administration (relevant to the first dose):

Maximum dose allowed

Specify per day or total ◯ per day ◯ total ◉ Not Answered

Specify total dose (number and unit)

Route of administration (relevant to the maximum dose):

Routes of administration for this IMP

Oral use

This is a sub-set of questions about each IMP. To return to the list of IMPs select "See all" at the top of the page or select "Navigate". To complete further questions about this IMP select "Next".

15-2. Active substances

Complete all fields that currently apply to this Active Substance in this Product. If you have IMPs with different concentrations of the Active Substance complete a new Sub-section D for each.

Active Substance 1

Name of active substance (INN or proposed INN if available):	Azithromycin 250 mg or 500 mg
CAS number:	
Current sponsor code:	
Other descriptive name:	
Full Molecular formula	
Chemical/biological description of the Active Substance	sensitive to azithromycin (see sections 4.4 and 5.1): - acute bacterial sinusitis (adequately diagnosed) - acute bacterial otitis media (adequately diagnosed) - pharyngitis, tonsillitis - acute exacerbation of chronic bronchitis (adequately diagnosed) - mild to moderately severe community acquired pneumonia - skin and soft tissue infections - uncomplicated Chlamydia trachomatis urethritis and cervicitis Considerations should be given to official guidance on the appropriate use of antibacterial agents.

Strength

Concentration unit:	mg milligram(s)
Concentration type:	equal
Concentration number (only use both fields for range):	500

15-3. Type of IMP

Does the IMP contain an active substance:

Of chemical origin? ◉ Yes ◯ No ◯ Not Answered

Of biological / biotechnological origin?(other than Advanced Therapy IMP (ATIMP))	◯ Yes ◉ No ◯ Not Answered
Is this a:	
Advanced Therapy IMP (ATIMP) [1]	◯ Yes ◉ No ◯ Not Answered
Combination product that includes a device, but does not involve an Advanced Therapy	◯ Yes ◉ No ◯ Not Answered
Radiopharmaceutical medicinal product?	◯ Yes ◉ No ◯ Not Answered
Immunological medicinal product (e.g. vaccine, allergen, immune serum)?	◯ Yes ◉ No ◯ Not Answered
Plasma derived medicinal product?	◯ Yes ◉ No ◯ Not Answered
Extractive medicinal product?	◯ Yes ◉ No ◯ Not Answered
Recombinant medicinal product?	◯ Yes ◉ No ◯ Not Answered
Medicinal product containing genetically modified organisms?	◯ Yes ◉ No ◯ Not Answered
Herbal medicinal product?	◯ Yes ◉ No ◯ Not Answered
Homeopathic medicinal product?	◯ Yes ◉ No ◯ Not Answered
Another type of medicinal product?	◯ Yes ◉ No ◯ Not Answered
Specify the mode of action for the active substance in this medicinal product *The mode of action should briefly describe the chemical, biochemical, immunological or biological means that the IMP uses to effect its pharmaceutical action.*	
Is it an IMP to be used in a first-in-human clinical trial?	◯ Yes ◉ No ◯ Not Answered

[1,2,3,4,5] Complete sections D.4, D.5, D.6. and D.7, as applicable

[2,3] As defined in Annex 1 part IV of Directive 2001/83/EC as amended

[4] As defined in Article 2(1)(b) of Regulation 1394/2007/EC

[6] Guideline on strategies to identify and mitigate risks for first-in-human clinical trials with investigational medicinal products. EMEA/CHMP/SWP/28367/2007

13. Indicate which of the following is described below then repeat as necessary for each:

This refers to the IMP number: **PR4**
Investigational medicinal product category:
Test IMP

14. STATUS OF THE IMP
If the IMP has a marketing authorisation in the Member State concerned by this application but the trade name and marketing authorisation holder are not fixed in the protocol, go to question 14-.2

14-1. Does the IMP to be used in the trial have a marketing authorisation?

◉ Yes ○ No ○ Not Answered

Trade name:
Doxycycline
EV Product Code
Name of the MA holder:
Accord-UK Ltd
MA number (if MA granted by a Member State):
PL 0142/0407
Is the IMP modified in relation to its MA?
○ Yes ◉ No ○ Not Answered
Which country granted the MA?
UK - MHRA
Is this the Member State concerned with this application?
○ Yes ◉ No ○ Not Answered

14-2. Situations where an IMP to be used in the CT has a MA in the MS concerned, but the protocol allows that any brand of the IMP with a MA in that MS be administered to the trial subjects and it is not possible to clearly identify the IMP(s) in advance of the trial start

In the protocol, is treatment defined only by active substance?
○ Yes ◉ No ○ Not Answered

In the protocol, do treatment regimens allow different combinations of marketed products used according to local clinical practice at some or all investigator sites in the MS?
○ Yes ◉ No ○ Not Answered

The products to be administered as IMPs are defined as belonging to an ATC group
○ Yes ○ No ◉ Not Answered

Other :
○ Yes ○ No ◉ Not Answered

14-3. IMPD submitted:

Full IMPD
○ Yes ◉ No ○ Not Answered

Simplified IMPD
○ Yes ◉ No ○ Not Answered
Provide justification for using simplified dossier in the covering letter

Summary of product characteristics (SmPC) only

◉ Yes ○ No ○ Not Answered

14-4. Has the use of the IMP been previously authorised in a clinical trial conducted by the sponsor in the Community?

○ Yes ◉ No ○ Not Answered

14-5. Has the IMP been designated in this indication as an orphan drug in the Community?

○ Yes ○ No ◉ Not Answered

14-6. Has the IMP been the subject of scientific advice related to this clinical trial?

○ Yes ◉ No ○ Not Answered

Please indicate source of advice and provide a copy in the CTA request:

From the CHMP?

○ Yes ◉ No ○ Not Answered

CHMP = Committee for Medicinal Products for Human Use

From a MS competent authority?

○ Yes ◉ No ○ Not Answered

This is a sub-set of questions about each IMP. To return to the list of IMPs select "See all" at the top of the page or select "Navigate". To complete further questions about this IMP select "Next".

Description of IMP

15-1. Description of IMP

Product name where applicable	Doxycycline
Product code where applicable	
ATC codes, if officially registered	
Pharmaceutical form (use standard terms)	Capsule, hard
Is this a specific paediatric formulation?	○ Yes ○ No ◉ Not Answered
Maximum duration of treatment of a subject according to the protocol	

Dose allowed

First dose for first-in-human clinical trial

Specify per day or total: ○ per day ○ total ◉ Not Answered

Specify total dose (number and unit)

Route of administration (relevant to the first dose):

Maximum dose allowed

Specify per day or total ◯ per day ◯ total ◉ Not Answered

Specify total dose (number and unit)

Route of administration (relevant to the maximum dose):

Routes of administration for this IMP

Oral use

This is a sub-set of questions about each IMP. To return to the list of IMPs select "See all" at the top of the page or select "Navigate". To complete further questions about this IMP select "Next".

15-2. Active substances

Complete all fields that currently apply to this Active Substance in this Product. If you have IMPs with different concentrations of the Active Substance complete a new Sub-section D for each.

Active Substance 1

Name of active substance (INN or proposed INN if available):	Doxycycline hyclate equivalent to 100mg of Doxycycline base
CAS number:	
Current sponsor code:	
Other descriptive name:	
Full Molecular formula	
Chemical/biological description of the Active Substance	Therapeutic indications (see sections 4.1 of SmP - Respiratory tract infections - Urinary tract infections - Sexually transmitted diseases: - Skin infections - Ophthalmic infection - Rickettsial infections - Other infections

Strength

Concentration unit:	mg milligram(s)
Concentration type:	equal
Concentration number (only use both fields for range):	100

15-3. Type of IMP

Does the IMP contain an active substance:

Of chemical origin? ◉ Yes ◯ No ◯ Not Answered

Of biological / biotechnological origin?(other than Advanced Therapy IMP (ATIMP)) ◯ Yes ◉ No ◯ Not Answered

Is this a:

Advanced Therapy IMP (ATIMP) [1]	○ Yes ◉ No ○ Not Answered
Combination product that includes a device, but does not involve an Advanced Therapy	○ Yes ◉ No ○ Not Answered
Radiopharmaceutical medicinal product?	○ Yes ◉ No ○ Not Answered
Immunological medicinal product (e.g. vaccine, allergen, immune serum)?	○ Yes ◉ No ○ Not Answered
Plasma derived medicinal product?	○ Yes ◉ No ○ Not Answered
Extractive medicinal product?	○ Yes ◉ No ○ Not Answered
Recombinant medicinal product?	○ Yes ◉ No ○ Not Answered
Medicinal product containing genetically modified organisms?	○ Yes ◉ No ○ Not Answered
Herbal medicinal product?	○ Yes ◉ No ○ Not Answered
Homeopathic medicinal product?	○ Yes ◉ No ○ Not Answered
Another type of medicinal product?	○ Yes ◉ No ○ Not Answered

Specify the mode of action for the active substance in this medicinal product
The mode of action should briefly describe the chemical, biochemical, immunological or biological means that the IMP uses to effect its pharmaceutical action.

Is it an IMP to be used in a first-in-human clinical trial?	○ Yes ◉ No ○ Not Answered

[1,2,3,4,5] Complete sections D.4, D.5, D.6. and D.7, as applicable
[2,3] As defined in Annex 1 part IV of Directive 2001/83/EC as amended
[4] As defined in Article 2(1)(b) of Regulation 1394/2007/EC
[6] Guideline on strategies to identify and mitigate risks for first-in-human clinical trials with investigational medicinal products. EMEA/CHMP/SWP/28367/2007

13. Indicate which of the following is described below then repeat as necessary for each:

This refers to the IMP number: **PR5**
Investigational medicinal product category:
Test IMP

14. STATUS OF THE IMP
If the IMP has a marketing authorisation in the Member State concerned by this application but the trade name and marketing authorisation holder are not fixed in the protocol, go to question 14-.2

14-1. Does the IMP to be used in the trial have a marketing authorisation?

◉ Yes ○ No ○ Not Answered

Trade name:
Pulmicort Turbohaler 400
EV Product Code
Name of the MA holder:
AstraZeneca UK Ltd
MA number (if MA granted by a Member State):
PL 17901/0164
Is the IMP modified in relation to its MA?
○ Yes ◉ No ○ Not Answered

Which country granted the MA?
UK - MHRA
Is this the Member State concerned with this application?
○ Yes ◉ No ○ Not Answered

14-2. Situations where an IMP to be used in the CT has a MA in the MS concerned, but the protocol allows that any brand of the IMP with a MA in that MS be administered to the trial subjects and it is not possible to clearly identify the IMP(s) in advance of the trial start

In the protocol, is treatment defined only by active substance?
○ Yes ◉ No ○ Not Answered

In the protocol, do treatment regimens allow different combinations of marketed products used according to local clinical practice at some or all investigator sites in the MS?
○ Yes ◉ No ○ Not Answered

The products to be administered as IMPs are defined as belonging to an ATC group
○ Yes ○ No ◉ Not Answered

Other :
○ Yes ○ No ◉ Not Answered

14-3. IMPD submitted:

Full IMPD
○ Yes ◉ No ○ Not Answered

Simplified IMPD
○ Yes ◉ No ○ Not Answered
Provide justification for using simplified dossier in the covering letter

Summary of product characteristics (SmPC) only

◉ Yes ○ No ○ Not Answered

14-4. Has the use of the IMP been previously authorised in a clinical trial conducted by the sponsor in the Community?

○ Yes ◉ No ○ Not Answered

14-5. Has the IMP been designated in this indication as an orphan drug in the Community?

○ Yes ◉ No ○ Not Answered

14-6. Has the IMP been the subject of scientific advice related to this clinical trial?

○ Yes ◉ No ○ Not Answered

Please indicate source of advice and provide a copy in the CTA request:

From the CHMP?

○ Yes ◉ No ○ Not Answered

CHMP = Committee for Medicinal Products for Human Use

From a MS competent authority?

○ Yes ◉ No ○ Not Answered

This is a sub-set of questions about each IMP. To return to the list of IMPs select "See all" at the top of the page or select "Navigate". To complete further questions about this IMP select "Next".

Description of IMP

15-1. Description of IMP

Product name where applicable	Pulmicort Turbohaler 400
Product code where applicable	
ATC codes, if officially registered	R03B A02
Pharmaceutical form (use standard terms)	Inhalation powder
Is this a specific paediatric formulation?	○ Yes ◉ No ○ Not Answered
Maximum duration of treatment of a subject according to the protocol	14 days

Dose allowed

First dose for first-in-human clinical trial

Specify per day or total: ○ per day ○ total ◉ Not Answered

Specify total dose (number and unit)

Route of administration (relevant to the first dose):

Maximum dose allowed

Specify per day or total ◯ per day ◯ total ◉ Not Answered

Specify total dose (number and unit)

Route of administration (relevant to the maximum dose):

Routes of administration for this IMP

Inhalation use

This is a sub-set of questions about each IMP. To return to the list of IMPs select "See all" at the top of the page or select "Navigate". To complete further questions about this IMP select "Next".

15-2. Active substances

Complete all fields that currently apply to this Active Substance in this Product. If you have IMPs with different concentrations of the Active Substance complete a new Sub-section D for each.

Active Substance 1

Name of active substance (INN or proposed INN if available):	Budesonide 400 micrograms/actuation
CAS number:	
Current sponsor code:	
Other descriptive name:	
Full Molecular formula	
Chemical/biological description of the Active Substance	Budesonide is a glucocorticosteroid which possesses a high local anti-inflammatory action, with a lower incidence and severity of adverse effects than those seen with oral corticosteroids. Recommended in patients with bronchial asthma.

Strength

Concentration unit:	µg microgram(s)
Concentration type:	equal
Concentration number (only use both fields for range):	400

15-3. Type of IMP

Does the IMP contain an active substance:

Of chemical origin? ◉ Yes ◯ No ◯ Not Answered

Of biological / biotechnological origin?(other than Advanced Therapy IMP (ATIMP)) ◯ Yes ◉ No ◯ Not Answered

Is this a:

Advanced Therapy IMP (ATIMP) [1] ◯ Yes ◉ No ◯ Not Answered

Combination product that includes a device, but does not involve an Advanced Therapy	○ Yes ◉ No ○ Not Answered
Radiopharmaceutical medicinal product?	○ Yes ◉ No ○ Not Answered
Immunological medicinal product (e.g. vaccine, allergen, immune serum)?	○ Yes ◉ No ○ Not Answered
Plasma derived medicinal product?	○ Yes ◉ No ○ Not Answered
Extractive medicinal product?	○ Yes ◉ No ○ Not Answered
Recombinant medicinal product?	○ Yes ◉ No ○ Not Answered
Medicinal product containing genetically modified organisms?	○ Yes ◉ No ○ Not Answered
Herbal medicinal product?	○ Yes ◉ No ○ Not Answered
Homeopathic medicinal product?	○ Yes ◉ No ○ Not Answered
Another type of medicinal product?	○ Yes ◉ No ○ Not Answered

Specify the mode of action for the active substance in this medicinal product
The mode of action should briefly describe the chemical, biochemical, immunological or biological means that the IMP uses to effect its pharmaceutical action. Budesonide is a glucocorticosteroid which possesses a high local anti-inflammatory action, with a lower incidence and severity of adverse effects than those seen with oral corticosteroids.

Pharmacotherapeutic group: Other drugs for obstructive airway diseases, inhalants, glucocorticoids.

Is it an IMP to be used in a first-in-human clinical trial?	○ Yes ◉ No ○ Not Answered

(1,2,3,4,5) Complete sections D.4, D.5, D.6. and D.7, as applicable
(2,3) As defined in Annex 1 part IV of Directive 2001/83/EC as amended
(4) As defined in Article 2(1)(b) of Regulation 1394/2007/EC
(6) Guideline on strategies to identify and mitigate risks for first-in-human clinical trials with investigational medicinal products. EMEA/CHMP/SWP/28367/2007

Information on Placebo

13. Is there a placebo:

○ Yes ◉ No

Index of Sites where the qualified person certifies batch release

14. IMPs and placebos for which no responsible site needs to be identified:

This section is used to identify IMPs and placebos which:

- Have an MA in the EU **and**
- Are sourced from the EU market **and**
- Are used in the trial without modification (eg not overencapsulated) **and**
- The packaging and labeling is carried out for local use only as per article 9.2 of the Directive 2005/28/EC (GCP Directive).

If all the conditions above are met, then select below the IMPs and placebos to which this applies.

Finished IMP
PR3

Finished IMP
PR4

Finished IMP
PR5

This section is dedicated to finished IMPs, i.e. medicinal products randomised, packaged, labelled and certified for use in the clinical trial. In the case of multiple sites indicate the product certified by each site.

15. Identify who is responsible in the Community for the certification of the finished IMPs.
Where the product does not have a MA in the EU, but is supplied in bulk and final packaging and labelling for local use is carried out in accordance with article 9.2. of Directive 2005/28/EC (GCP Directive) then enter the site where the product was finally certified for release by the Qualified Person for use in the clinical trial.

RS1

Importer

Organisation Zentiva
Address Zentiva Pharma Limited
Town/city
Post code
Country United Kingdom

Give the manufacturing authorisation number
PL17780/0748

If no authorisation, give the reasons:

Select the relevant IMP(s) and Placebo(s) from the drop down lists.

IMP
PR1

RS3

Both

Organisation	FISHER CLINICAL SERVICES UK LIMITED
Address	LANGHURSTWOOD ROAD
Town/city	HORSHAM
Post code	RH12 4QD
Country	United Kingdom

Give the manufacturing authorisation number

MIA(IMP) Number: MIA(IMP) 18693

If no authorisation, give the reasons:

Select the relevant IMP(s) and Placebo(s) from the drop down lists.

IMP
PR1

IMP
PR3

IMP
PR4

IMP
PR5

RS4

Both

Organisation	Accord-UK Ltd
Address	Whiddon Valley, Barnstaple
Town/city	Devon
Post code	EX32 8NS
Country	United Kingdom

Give the manufacturing authorisation number

PL 0142/0407

If no authorisation, give the reasons:

Select the relevant IMP(s) and Placebo(s) from the drop down lists.

IMP
PR4

RS5

Both

Organisation	AstraZeneca UK Limited
Address	Horizon Place, 600 Capability Green
Town/city	Luton
Post code	LU1 3LU
Country	United Kingdom

Give the manufacturing authorisation number
PL 17901/0164

If no authorisation, give the reasons:

Select the relevant IMP(s) and Placebo(s) from the drop down lists.

IMP
PR5

RS6

Both

Organisation	Ringwood Pharmacy
Address	43A Southampton Road, Ringwood
Town/city	
Post code	BH24 1HE
Country	United Kingdom

Give the manufacturing authorisation number

If no authorisation, give the reasons:
GPhC Reg. Number: 9010477

Select the relevant IMP(s) and Placebo(s) from the drop down lists.

IMP
PR5

Part B: Section 5 – Use of newly obtained human tissue(or other human biological materials) for research purposes

1. What types of human tissue or other biological material will be included in the study?

Nasal/nasopharyngeal swab and blood sample

2. Who will collect the samples?

Unless a swab can be taken face-to-face in the course of usual care, this will be a self-swab process with the practice generating the required forms. Once the swab has been taken it will be put in the regulation contained packaging, double bagged, and posted to the PHE laboratory that is supporting the study using their existing, safe, compliant processes. The trial team will utilise PHE and their existing processes and documentation.

As part of the national RCGP RSC surveillance programme with PHE, trial participants will also be asked for a blood sample. A blood test kit will be sent directly to the participant, who will make arrangements with their GP for the blood test. Providing a blood sample is not a requirement of participation. Participants will be informed of their blood test result by their GP. The study team will obtain the result from RCGP RSC/PHE.

3. Who will the samples be removed from?

- [x] Living donors
- [ ] The deceased

4. Will informed consent be obtained from living donors for use of the samples? *Please tick as appropriate*

In this research?

(•) Yes ( ) No

In future research?

(•) Yes ( ) No ( ) Not applicable

6. Will any tissues or cells be used for human application or to carry out testing for human application in this research?

( ) Yes (•) No

8. Will the samples be stored: *[Tick as appropriate]*

In fully anonymised form? *(link to donor broken)*

( ) Yes (•) No

In linked anonymised form? *(linked to stored tissue but donor not identifiable to researchers)*

( ) Yes (•) No

In a form in which the donor could be identifiable to researchers?

(•) Yes ( ) No

If Yes, please justify.

The trial team do not intend to store the swab once tested, and it won't be stored for the purpose of this trial. The swab material will fall under PHE and not the trial remit, and PHE may retain the swab for up to 5 years.

Swabs and blood samples are outside of the trial remit, for PHE purposes adhering to their retention policy.

9. What types of test or analysis will be carried out on the samples?

PCR for SARS-COV2 at PHE laboratory according to their standard practice for COVID-19.

PHE currently recommended blood test for evidence of SARS-CoV-2 infection and other associated biomarkers.

10. Will the research involve the analysis or use of human DNA in the samples?

○ Yes ◉ No

11. Is it possible that the research could produce findings of clinical significance for donors or their relatives?

◉ Yes ○ No

12. If so, will arrangements be made to notify the individuals concerned?

◉ Yes ○ No ○ Not applicable

If No, please justify. If Yes, say what arrangements will be made and give details of the support or counselling service.

Participants will be informed of their COVID-19 swab/blood results by their GP.

13. Give details of where the samples will be stored, who will have access and the custodial arrangements.

The trial team do not intend to store the swab once tested, and it won't be stored for the purpose of this trial. The swab material will fall under PHE and not the trial remit, and PHE may retain the swab for up to 5 years.

Swabs and blood samples are outside of the trial remit, for PHE purposes adhering to their retention policy.

14. What will happen to the samples at the end of the research? *Please tick all that apply and give further details.*

☐ Transfer to research tissue bank

(If the bank is in England, Wales or Northern Ireland the institution will require a licence from the Human Tissue Authority to store relevant material for possible further research.)

☐ Storage by research team pending ethical approval for use in another project

(Unless the researcher's institution holds a storage licence from the Human Tissue Authority, or the tissue is stored in Scotland, or it is not relevant material, a further application for ethical review should be submitted before the end of this project.)

☐ Storage by research team as part of a new research tissue bank

(The institution will require a licence from the Human Tissue Authority if the bank will be storing relevant material in England, Wales or Northern Ireland. A separate application for ethical review of the tissue bank may also be submitted.)

☐ Storage by research team of biological material which is not "relevant material" for the purposes of the Human Tissue Act

☐ Disposal in accordance with the Human Tissue Authority's Code of Practice

☑ Other

☐ Not yet known

Please give further details of the proposed arrangements:

PHE may keep the swab specimen for up to 5 years. Swabs and blood samples are outside of the trial remit, for PHE purposes adhering to their retention policy.

Part B: Section 6 - Adults unable to consent for themselves

A. Clinical trials of investigational medicinal products

In this sub-section, an adult means a person aged 16 or over.

A1. What clinical condition(s) will the participants have? *The trial must relate directly to this condition.*

The trial recruits adults 50-64 with known co-morbidity or adults over 65 with or without known co-morbdity and with symptoms of COVID-19 or a positive COVID-19 test result while unwell with symptoms. Adults living in care homes have been heavily impacted by the COVID-19 pandemic and stand to benefit significantly from effective treatments. A signifcant number of adults in care home have conditions such as dementia which means they lack capacity to consent to research for themselves.

A2. Could the trial be carried out equally effectively if confined to adults capable of giving consent?

○ Yes ◉ No

A3. Who in the research team will decide whether or not the participants have the capacity to give consent? What training/experience will they have to enable them to reach this decision?

The recruiting clinician at the care home will be responsible for determining if particiapnts have capacity to consent or not. This will often be the clinicain responsible for the participants standard care and will know them well.

A4. What benefit is the administration of the investigational medicinal product expected to produce for these participants? *You may refer back to your answer to Question A24.*

Potential treatments may benefit patients with COVID-19 and enhance the sustainability of NHS care during the current crisis.

A5. Will the trial involve any foreseeable risk or burden for these participants, or interfere in any way with their freedom of action or privacy?

○ Yes ◉ No

A6. What arrangements will be made to identify and seek informed consent from a legal representative?

Participants who lack capacity will be recruited from care homes. Care homes will have details of their resident's next of kin etc. to be contacted. They will likely be contacting next of kin to inform them of the resident's illness/positive COVID test and can introduce consideration into joining the trial at same time.

A7. Is it possible that a participant requiring urgent treatment might need to be recruited into the trial before it is possible to identify and seek consent from a legal representative?

○ Yes ◉ No

If Yes, outline how decisions will be made on the inclusion of participants and what arrangements will be made to seek consent from the participant (if capacity has been recovered) or a legal representative as soon as practicable thereafter.

Participants will only be recruited once a personal, or professional, legal reprsentative has provided consent. Every effort will be made to identify a personal legal representative in the first instance.

A8. What arrangements will be made to continue to consult legal representatives during the course of the research where necessary?

Legal representatives will be informed of trial allocation. They may also act as study partners if they wish too.

A9. Will steps be taken to provide information about the trial to participants, according to their capacity of understanding, and to consider the wishes of participants capable of forming an opinion?

(●) Yes ( ) No

If Yes, give details.

A pictorial PIS is available for participants.

A10-1. What will be the criteria for withdrawal of participants?

Legal represenatives can withdraw the participant at any time. Dissent in any form from the partcipant will be taken as they do not wish to participate and they will be withdrawn.

PART C: Overview of research sites

Please enter details of the host organisations (Local Authority, NHS or other) in the UK that will be responsible for the research sites. *For further information please refer to guidance.*

Investigator identifier	Research site		Investigator Name	
IN1	◉ NHS/HSC Site ○ Non-NHS/HSC Site		Forename	Christopher
			Middle name	
			Family name	Butler
	Organisation name	NIHR CRN: Thames Valley and South Midlands	Email	chris.butler@phc.ox.ac.uk
			Qualification (MD...)	MBChB, Dip Child Health, MRCGP, MD, FRCGP, HonFFPH
	Address		Country	United Kingdom
	Post Code	OX3 9DU		
	Country	GBR		
IN2	◉ NHS/HSC Site ○ Non-NHS/HSC Site		Forename	Christopher
			Middle name	
			Family name	Butler
			Email	christopher.butler@phc.ox.ac.uk
	Organisation name	NIHR CRN:North East and North Cumbria	Qualification (MD...)	MBChB, Dip Child Health, MRCGP, MD, FRCGP, HonFFPH
			Country	United Kingdom
	Address			
	Post Code			
	Country			
IN3	◉ NHS/HSC Site ○ Non-NHS/HSC Site		Forename	Christopher
			Middle name	
			Family name	Butler
			Email	christopher.butler@phc.ox.ac.uk
	Organisation	NIHR CRN:North	Qualification (MD...)	MBChB, Dip Child Health, MRCGP, MD, FRCGP, HonFFPH

	name	West Coast	Country	United Kingdom
	Address			
	Post Code			
	Country			

IN4

- (●) NHS/HSC Site
- ( ) Non-NHS/HSC Site

		Forename	Christopher
		Middle name	
		Family name	Butler
		Email	christopher.butler@phc.ox.ac.uk
Organisation name	NIHR CRN:Yorkshire and Humber	Qualification (MD...)	MBChB, Dip Child Health, MRCGP, MD, FRCGP, HonFFPH
Address		Country	United Kingdom
Post Code			
Country			

IN5

- (●) NHS/HSC Site
- ( ) Non-NHS/HSC Site

		Forename	Christopher
		Middle name	
		Family name	Butler
		Email	christopher.butler@phc.ox.ac.uk
Organisation name	NIHR CRN:Greater Manchester	Qualification (MD...)	MBChB, Dip Child Health, MRCGP, MD, FRCGP, HonFFPH
Address		Country	United Kingdom
Post Code			
Country			

IN6

- (●) NHS/HSC Site
- ( ) Non-NHS/HSC Site

		Forename	Christopher
		Middle name	
		Family name	Butler
		Email	christopher.butler@phc.ox.ac.uk

	Organisation name	NIHR CRN:East Midlands	Qualification (MD...)	MBChB, Dip Child Health, MRCGP, MD, FRCGP, HonFFPH
	Address		Country	
	Post Code			
	Country			

IN7

- (●) NHS/HSC Site
- ( ) Non-NHS/HSC Site

		Forename	Christopher
		Middle name	
		Family name	Butler
		Email	christopher.butler@phc.ox.ac.uk
	Organisation name	NIHR CRN:West Midlands	Qualification (MD...)	MBChB, Dip Child Health, MRCGP, MD, FRCGP, HonFFPH
	Address		Country	United Kingdom
	Post Code			
	Country			

IN8

- (●) NHS/HSC Site
- ( ) Non-NHS/HSC Site

		Forename	Christopher
		Middle name	
		Family name	Butler
		Email	christopher.butler@phc.ox.ac.uk
	Organisation name	NIHR CRN:West of England	Qualification (MD...)	MBChB, Dip Child Health, MRCGP, MD, FRCGP, HonFFPH
	Address		Country	United Kingdom
	Post Code			
	Country			

IN9

- (●) NHS/HSC Site
- ( ) Non-NHS/HSC Site

		Forename	Christopher
		Middle name	
		Family name	Butler
		Email	christopher.butler@phc.ox.ac.uk
	Organisation	NIHR	Qualification	MBChB, Dip Child Health, MRCGP, MD, FRCGP,

	name	CRN:Eastern	(MD...)	HonFFPH
	Address		Country	
	Post Code			
	Country			

IN10

◉ NHS/HSC Site			Forename	Christopher
○ Non-NHS/HSC Site			Middle name	
			Family name	Butler
			Email	christopher.butler@phc.ox.ac.uk
	Organisation name	NIHR CRN:Kent, Surrey and Sussex	Qualification (MD...)	MBChB, Dip Child Health, MRCGP, MD, FRCGP, HonFFPH
	Address		Country	United Kingdom
	Post Code			
	Country			

IN11

◉ NHS/HSC Site			Forename	Christopher
○ Non-NHS/HSC Site			Middle name	
			Family name	Butler
			Email	christopher.butler@phc.ox.ac.uk
	Organisation name	Wessex	Qualification (MD...)	MBChB, Dip Child Health, MRCGP, MD, FRCGP, HonFFPH
	Address		Country	United Kingdom
	Post Code			
	Country			

IN12

◉ NHS/HSC Site			Forename	Christopher
○ Non-NHS/HSC Site			Middle name	
			Family name	Butler
			Email	christopher.butler@phc.ox.ac.uk
	Organisation name	South West Peninsula	Qualification (MD...)	MBChB, Dip Child Health, MRCGP, MD, FRCGP, HonFFPH
	Address		Country	United Kingdom

Post Code

Country

IN13

◉ NHS/HSC Site

○ Non-NHS/HSC Site

Forename	Christopher
Middle name	
Family name	Butler
Email	christopher.butler@phc.ox.ac.uk
Organisation name	North Thames
Qualification (MD...)	MBChB, Dip Child Health, MRCGP, MD, FRCGP, HonFFPH
Address	
Country	United Kingdom

Post Code

Country

IN14

◉ NHS/HSC Site

○ Non-NHS/HSC Site

Forename	Christopher
Middle name	
Family name	Bulter
Email	christopher.butler@phc.ox.ac.uk
Organisation name	South London
Qualification (MD...)	MBChB, Dip Child Health, MRCGP, MD, FRCGP, HonFFPH
Address	
Country	United Kingdom

Post Code

Country

IN15

◉ NHS/HSC Site

○ Non-NHS/HSC Site

Forename	Christopher
Middle name	
Family name	Butler
Email	christopher.butler@phc.ox.ac.uk
Organisation name	North West London
Qualification (MD...)	MBChB, Dip Child Health, MRCGP, MD, FRCGP, HonFFPH
Address	
Country	United Kingdom

Post Code

Country

PART D: Declarations

D1. Declaration by Chief Investigator

1. The information in this form is accurate to the best of my knowledge and belief and I take full responsibility for it.

2. I undertake to fulfil the responsibilities of the chief investigator for this study as set out in the UK Policy Framework for Health and Social Care Research.

3. I undertake to abide by the ethical principles underlying the Declaration of Helsinki and good practice guidelines on the proper conduct of research.

4. If the research is approved I undertake to adhere to the study protocol, the terms of the full application as approved and any conditions set out by review bodies in giving approval.

5. I undertake to notify review bodies of substantial amendments to the protocol or the terms of the approved application, and to seek a favourable opinion from the main REC before implementing the amendment.

6. I undertake to submit annual progress reports setting out the progress of the research, as required by review bodies.

7. I am aware of my responsibility to be up to date and comply with the requirements of the law and relevant guidelines relating to security and confidentiality of patient or other personal data, including the need to register when necessary with the appropriate Data Protection Officer. I understand that I am not permitted to disclose identifiable data to third parties unless the disclosure has the consent of the data subject or, in the case of patient data in England and Wales, the disclosure is covered by the terms of an approval under Section 251 of the NHS Act 2006.

8. I understand that research records/data may be subject to inspection by review bodies for audit purposes if required.

9. I understand that any personal data in this application will be held by review bodies and their operational managers and that this will be managed according to the principles established in the Data Protection Act 2018.

10. I understand that the information contained in this application, any supporting documentation and all correspondence with review bodies or their operational managers relating to the application:

    - Will be held by the REC (where applicable) until at least 3 years after the end of the study; and by NHS R&D offices (where the research requires NHS management permission) in accordance with the NHS Code of Practice on Records Management.
    - May be disclosed to the operational managers of review bodies, or the appointing authority for the REC (where applicable), in order to check that the application has been processed correctly or to investigate any complaint.
    - May be seen by auditors appointed to undertake accreditation of RECs (where applicable).
    - Will be subject to the provisions of the Freedom of Information Acts and may be disclosed in response to requests made under the Acts except where statutory exemptions apply.
    - May be sent by email to REC members.

11. I understand that information relating to this research, including the contact details on this application, may be held on national research information systems, and that this will be managed according to the principles established in the Data Protection Act 2018.

12. I understand that the main REC or its operational managers may share information in this application or supporting documentation with the Medicines and Healthcare products Regulatory Agency (MHRA) where it is relevant to the Agency's statutory responsibilities.

13. Where the research is reviewed by a REC within the UK Health Departments Research Ethics Service, I understand that the summary of this study will be published on the website of the Health Research Authority (HRA) together with the contact point for enquiries named below. Publication will take place no earlier than 3 months after the issue of the ethics committee's final opinion or the withdrawal of the application.

Contact point for publication*(Not applicable for R&D Forms)*

HRA would like to include a contact point with the published summary of the study for those wishing to seek further information. We would be grateful if you would indicate one of the contact points below.

- ◯ Chief Investigator
- ◯ Sponsor
- ◯ Study co-ordinator
- ◯ Student
- ◯ Other – please give details
- ◯ None

Access to application for training purposes *(Not applicable for R&D Forms)*

Optional – please tick as appropriate:

☐ I would be content for members of other RECs to have access to the information in the application in confidence for training purposes. All personal identifiers and references to sponsors, funders and research units would be removed.

This section was signed electronically by Professor Christopher Butler on 10/12/2020 14:44.

Job Title/Post:	Profesor of primary care
Organisation:	University of Oxford
Email:	christopher.butler@phc.ox.ac.uk

D2. Declaration by the sponsor's representative

If there is more than one sponsor, this declaration should be signed on behalf of the co−sponsors by a representative of the lead sponsor named at A64-1.

I confirm that:

1. This research proposal has been discussed with the Chief Investigator and agreement in principle to sponsor the research is in place.

2. An appropriate process of scientific critique has demonstrated that this research proposal is worthwhile and of high scientific quality.

3. Any necessary indemnity or insurance arrangements, as described in question A76, will be in place before this research starts. Insurance or indemnity policies will be renewed for the duration of the study where necessary.

4. Arrangements will be in place before the study starts for the research team to access resources and support to deliver the research as proposed.

5. Arrangements to allocate responsibilities for the management, monitoring and reporting of the research will be in place before the research starts.

6. The responsibilities of sponsors set out in the UK Policy Framework for Health and Social Care Research will be fulfilled in relation to this research.

7. The statutory responsibilities of sponsors set out in the Medicines for Human Use (Clinical Trials) Regulations 2004 will be undertaken in relation to this trial.

   Please note: *The declarations below do not form part of the application for approval above. They will not be considered by the Research Ethics Committee.*

8. Where the research is reviewed by a REC within the UK Health Departments Research Ethics Service, I understand that the summary of this study will be published on the website of the National Research Ethics Service (NRES), together with the contact point for enquiries named in this application. Publication will take place no earlier than 3 months after issue of the ethics committee's final opinion or the withdrawal of the application.

9. Specifically, for submissions to the Research Ethics Committees (RECs) I declare that any and all clinical trials approved by the HRA since 30th September 2013 (as defined on IRAS categories as clinical trials of medicines, devices, combination of medicines and devices or other clinical trials) have been registered on a publically accessible register in compliance with the HRA registration requirements for the UK, or that any deferral granted by the HRA still applies.

This section was signed electronically by Clinical Trial and Research Governance CTRG Sponsorship on 10/12/2020 14:03.

Job Title/Post:	Elaine Chick
Organisation:	University of Oxford
Email:	

NIHR | National Institute for Health Research

CLINICAL RESEARCH NETWORK
COORDINATING CENTRE
Minerva House
5 Montague Close
London
SE1 9BB

Tel: 020 3328 6700
Fax: 020 7636 5138
Email: crn@nihr.ac.uk
www.nihr.ac.uk

21st December 2020

Dear Chris

RE: Amendment to PRINCIPLE: Platform Randomised trial of INterventions against COVID-19 In older peoPLE

Thank you for submitting the amendment of the PRINCIPLE study to the NIHR Urgent Public Health Group for review. It was agreed to support the amendment, subject to ethical permission. If you have not already done so, it is recommended that you seek urgent regulatory approval for the amendment to your study as a National Priority UPH study.

As you are no doubt aware, resources for supporting National Priority UPH studies are limited and therefore it is helpful for the UPH Group to have sight of amendments to studies. This will assist the UPH Group to review other studies submitted for UPH badging, and help to avoid the risk of conflict or duplication with UPH-badged studies. Therefore we would be grateful if you could inform the UPH Group of any future amendments to the study.

The NIHR CRN Research Delivery team will be updated on this amendment to the study, and a member of the team will be in touch with you shortly to discuss the support required. However, if there is something that you would like to discuss as a matter of urgency please get in touch with us through the urgentpublichealthcrn@nihr.ac.uk email address.

Finally, you may find the following information helpful:

Core datasets

To ensure key information needed by decision makers about the effects of interventions is included in your study, please consider the use of core outcome sets such as the COMET initiative http://www.comet-initiative.org/Studies/Details/1538

As outlined in the application form, a small dataset of information about your study will be uploaded to the NIHR website and linked to the Health Research Agency website. If you have any queries regarding sharing these data publicly, please contact covid19application@nihr.ac.uk

Media activity

If you wish to publicise this research in UK media (including social media), please notify pressoffice@nihr.ac.uk 24 hours in advance. The NIHR press office team is maintaining a centrally-held media grid for COVID-19 research. In the event that journalists contact you after information about your study is uploaded to the NIHR website and prior to any planned publicity, please contact the NIHR press office regarding an expedited approach.

ISRCTN registration

It is compulsory for **all** Urgent Public Health (UPH) badged studies to be entered on the ISRCTN registry. ISRCTN is able to offer same-day registration for UPH badged studies. To access this please contact info@ISRCTN.com before creating or logging into your ISRCTN account and making your ISRCTN application through the ISRCTN online submission portal. Alternatively, you can apply for your ISRCTN registration through our Central Portfolio Management System (CPMS) on receipt of your CPMS ID. Instructions on how to do this will be provided. All non-commercial studies badged as UPH are able to have their registration fee paid by the Department of Health and Social Care. Reimbursement is not possible if you have already applied and received an ISRCTN before confirmation of your UPH badging and inclusion on the NIHR CRN Portfolio.

Demographic data collection

Following NICE guidelines (https://www.nice.org.uk/covid-19/support-for-developers-of-medicinal-products-for-covid-19) a full range of baseline patient characteristics should be collected so that the relevance of the patient population to the NHS patient population can be evaluated. This includes sex, age, ethnicity, comorbidities, smoking status, residence in care home, functional status, and confinement status.

Patient Information Leaflets (PILs) translation

For UPH studies, the NIHR CRN is offering a PILs translation service which provides full and certified translation of PIL into languages specified. The aim of this service is to enable increased opportunity and equity for participation, increase the speed of trial delivery and reduce burden on sites and LCRNs. The following six languages are offered: Polish, Bengali, Urdu, Punjabi, French, Portuguese. Study teams can access this service through the Research Delivery Directorate.

PPIE and participation support for UPH studies

The CRN has a Public Advisory Forum to provide PPIE support to UPH studies. The forum consists of lay Research Champions who have been trained around health research and have received an induction around coronavirus research specifically. UPH study teams can seek involvement from the Public Advisory Group around any specific issues related to the design and delivery of UPH studies, by contacting crncc.ppie@leeds.ac.uk

To support UPH studies with any specific challenges around the participation of BAME communities in COVID-19 studies, the University of Leicester (NIHR ARC East Midlands) Centre for BME Health (https://centreforbmehealth.org.uk/) is offering expert guidance for study teams and research delivery teams. If you have specific enquiries about engaging BAME communities with your UPH study please contact ppie.crncc@leeds.ac.uk who will connect you with the Centre.

Future Study Amendments

If you plan to make an amendment to your research project, these should be submitted for NIHR Urgent Public Health Group review via the online submission form.

With best wishes

Nick Lemoine
Medical Director, NIHR Clinical Research Network

cc. Chelsea Drake NIHR CRN Head of Communications
Lead LCRN: Thames Valley and South Midlands
Research Delivery Directorate
Business Development and Marketing Directorate
Devolved Nations Representatives