

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 provides researchers with the practical support they need to make clinical studies happen in the NHS 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, you must complete a NIHR Clinical Research Network (CRN) Portfolio Application Form (PAF) immediately after completing this project filter question and before submitting other applications. Failing to complete the PAF ahead of other applications e.g. HRA Approval, may mean that you will be unable to access NIHR CRN Support for your study.

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 familiar 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
Post Code	OX2 6GG
Country	UNITED KINGDOM

Work E-mail	christopher.butler@phc.ox.ac.uk
* Personal E-mail	christopher.butler@phc.ox.ac.uk
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.

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 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 well established 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 part 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 at 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
- 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 is willing and able to give informed consent for participation in the study.
- Participant is willing to comply with all trial procedures
- Onset of symptoms of possible COVID-19 in the community (continuous cough and/or high temperature) within 7 days of inclusion
- Patients aged ≥ 50 -64 years with any of the following listed comorbidities:
 - known weakened immune system due to a serious illness or medication (e.g. chemotherapy)
 - known heart disease
 - 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 ineligible

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 (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 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.

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)*

- Access to medical records by those outside the direct healthcare team
- Access to social care records by those outside the direct social care team
- Electronic transfer by magnetic or optical media, email or computer networks
- Sharing of personal data with other organisations
- Export of personal data outside the EEA
- 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
- Storage of personal data on any of the following:
 - Manual files (includes paper or film)
 - NHS computers
 - Social Care Service computers
 - Home or other personal computers
 - 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 from 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
- Review within a multi-centre research group
- Review within the Chief Investigator's institution or host organisation
- 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
- Other review by independent statistician
- Review by company statistician
- Review by a statistician within the Chief Investigator's institution
- 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	
Work Address	Oxford University Hospitals NHS Foundation Trust, Headley Way, Headington, Oxford
Post Code	OX3 9DU
Telephone	
Fax	
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
 Work Address Department of Primary Care Health Sciences
 Radcliffe Observatory Quarter

Post Code OX2 6GG
 Telephone 01865 617 283
 Fax
 Mobile
 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
 Employer University of Oxford
 Work Address Department of Primary Care Health Sciences
 Radcliffe Observatory Quarter

Post Code OX2 6GG
 Telephone +44 (0)1865 289357
 Fax
 Mobile
 Work Email gail.hayward@phc.ox.ac.uk

Title Forename/Initials Surname
 Dr Oliver van Hecke

Post NIHR Academic Clinical Lecturer
 Qualifications MBChB (Pret) DMJ (Clin) MRCGP FRACGP DPhil
 Employer University of Oxford
 Work Address Department of Primary Care Health Sciences
 Radcliffe Observatory Quarter

Post Code OX2 6GG
 Telephone +44 (0)1865 289300
 Fax
 Mobile
 Work Email oliver.vanhecke@phc.ox.ac.uk

	Title	Forename/Initials	Surname
	Professor	Martin	Llewellyn
Post	Professor in Infectious Diseases		
Qualifications	BSc, FRCP, DTMH, PhD)		
Employer	University of Sussex		
Work Address	Medical Research Building		

Post Code	BN1 9PS
Telephone	BN1 9PS
Fax	
Mobile	
Work Email	M.J.Llewelyn@bsms.ac.uk

	Title	Forename/Initials	Surname
	Prof	Ly-Mee	Yu
Post	Associate Professor and Deputy Director Academic (Primary Care Clinical Trials Unit)		
Qualifications	M.Sc., DPhil		
Employer	University of Oxford		
Work Address	Department of Primary Care Health Sciences Radcliffe Observatory Quarter		

Post Code	OX2 6GG
Telephone	+44 (0)1865 617199
Fax	
Mobile	
Work Email	ly-mee.yu@phc.ox.ac.uk

	Title	Forename/Initials	Surname
	Dr	Emma	Ogburn
Post	CTU Director of Operations		
Qualifications	BSc. (Hons) PhD		
Employer	University of Oxford		
Work Address	Department of Primary Care Health Sciences Radcliffe Observatory Quarter		

Post Code	OX2 6GG
Telephone	
Fax	
Mobile	
Work Email	emma.ogburn@phc.ox.ac.uk

	Title	Forename/Initials	Surname
	Ms	Julie	Allen
Post	Senior Trial Manager		
Qualifications			
Employer	University of Oxford		
Work Address	Department of Primary Care Health Sciences Radcliffe Observatory Quarter		

Post Code OX2 6GG
 Telephone
 Fax
 Mobile
 Work Email Julie.allen@phc.ox.ac.uk

Title Forename/Initials Surname
 Dr Emily Bongard
 Post Senior Trial Manager
 Qualifications BSc (Hons), MSc, PhD
 Employer University of Oxford
 Work Address Department of Primary Care Health Sciences
 Radcliffe Observatory Quarter

Post Code OX2 6GG
 Telephone
 Fax
 Mobile
 Work Email emily.bongard@phc.ox.ac.uk

Title Forename/Initials Surname
 Dr Hannah Swayze
 Post Senior Trial Manager
 Qualifications BSc, PhD
 Employer University of Oxford
 Work Address Department of Primary Care Health Sciences
 Radcliffe Observatory Quarter

Post Code OX2 6GG
 Telephone
 Fax
 Mobile
 Work Email hannah.swayze@phc.ox.ac.uk

Title Forename/Initials Surname
 Professor Maria Zambon
 Post Director of Reference Microbiology
 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 maria.zambon@phe.gov.uk

	Title Forename/Initials Surname
	Dr Ben Saville
Post	Statistical Scientist
Qualifications	PhD
Employer	Berry Consultants
Work Address	3345 Bee Caves Road Suite 201 Austin, Texas, US
Post Code	78746
Telephone	(512) 213-6428
Fax	
Mobile	
Work Email	

	Title Forename/Initials Surname
	Dr Joanna Ellis
Post	Clinical Scientist
Qualifications	
Employer	National Infection Service, Public Health England
Work Address	Respiratory Virus Unit 61 Colindale Avenue London
Post Code	NW9 5EQ
Telephone	020 8327 6017
Fax	
Mobile	
Work Email	joanna.ellis@phe.gov.uk

	Title Forename/Initials Surname
	Gayatri Amirthalingam
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	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 Commercial status: Non-Commercial
 Academic
 Pharmaceutical industry
 Medical device industry
 Local Authority
 Other social care provider (including voluntary sector or private organisation)
 Other

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.

- 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

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?

UNITED KINGDOM

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 sulphhydryl 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 sulphhydryl 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

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.

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

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.

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.

3. Who will the samples be removed from?

- 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.

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.

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 result 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.

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 specimen for up to 5 years following their own approved processes.

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	<input checked="" type="radio"/> NHS/HSC Site <input type="radio"/> 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, MRCP, MD, FRCGP, HonFFPH
	Address	Country UNITED KINGDOM
	Post Code	OX3 9DU
	Country	GBR
IN2	<input checked="" type="radio"/> NHS/HSC Site <input type="radio"/> Non-NHS/HSC Site	
		Forename Christopher
		Middle name
		Family name Butler
	Organisation name	NIHR CRN:North East and North Cumbria
		Email christopher.butler@phc.ox.ac.uk
		Qualification (MD...) MBChB, Dip Child Health, MRCP, MD, FRCGP, HonFFPH
	Address	Country UNITED KINGDOM
	Post Code	
	Country	
IN3	<input checked="" type="radio"/> NHS/HSC Site <input type="radio"/> Non-NHS/HSC Site	
		Forename Christopher
		Middle name
		Family name Butler
	Organisation	NIHR CRN:North
		Email christopher.butler@phc.ox.ac.uk
		Qualification (MD...) MBChB, Dip Child Health, MRCP, MD, FRCGP, HonFFPH
	Address	
	Post Code	
	Country	

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, MRCP, 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, MRCP, 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

IN7

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

- 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
 Address
 Post Code
 Country
 Qualification (MD...)
 Country UNITED KINGDOM
 MBChB, Dip Child Health, MRCP, MD, FRCGP,
 HonFFPH

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
 Address
 Post Code
 Country
 Qualification (MD...)
 Country UNITED KINGDOM
 MBChB, Dip Child Health, MRCP, MD, FRCGP,
 HonFFPH

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, MRCP, MD, FRCGP,

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

Post Code
 Country

IN10

- 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:Kent,
 Surrey and
 Sussex

Qualification (MD...) MBChB, Dip Child Health, MRCGP, MD, FRCGP,
 HonFFPH

Country UNITED KINGDOM

Address

Post Code
 Country

IN11

- NHS/HSC Site
- Non-NHS/HSC Site

Forename Christopher

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

Country UNITED KINGDOM

Address

Post Code
 Country

IN12

- NHS/HSC Site
- Non-NHS/HSC Site

Forename Christopher

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

Country UNITED KINGDOM

Address

IN13

Post Code
Country

- NHS/HSC Site
- Non-NHS/HSC Site

Organisation name North Thames
Address

Forename Christopher
Middle name
Family name Butler
Email christopher.butler@phc.ox.ac.uk
Qualification (MD...) MBChB, Dip Child Health, MRCP, MD, FRCGP, HonFFPH
Country UNITED KINGDOM

Post Code
Country

IN14

- NHS/HSC Site
- Non-NHS/HSC Site

Organisation name South London
Address

Forename Christopher
Middle name
Family name Bulter
Email christopher.butler@phc.ox.ac.uk
Qualification (MD...) MBChB, Dip Child Health, MRCP, MD, FRCGP, HonFFPH
Country UNITED KINGDOM

Post Code
Country

IN15

- NHS/HSC Site
- Non-NHS/HSC Site

Organisation name North West London
Address

Forename Christopher
Middle name
Family name Butler
Email christopher.butler@phc.ox.ac.uk
Qualification (MD...) MBChB, Dip Child Health, MRCP, MD, FRCGP, HonFFPH
Country UNITED KINGDOM

Post Code
Country

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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 23/03/2020 18:52.

Job Title/Post: Professor 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 23/03/2020 18:53.

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