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

**Internal Reference Number / Short title:** PRINCIPLE

**Ethics Ref:** 20/SC/0158

**IRAS Project ID:** 281958

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

**Date and Version No:** 21 April 2020 version 2.1
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1. LAY SUMMARY
The risk of complications from suspected COVID-19 coronavirus infection is generally greater in people aged 50 years and older with underlying health conditions, and in those aged 65 years and older. The infection is having a devastating effect on people’s health and society. (1-4) So far, there are no specific treatments for COVID-19 that have been proven in well-conducted clinical trials to be effective. Most cases of probable COVID-19 infections are being managed in the community. An ideal treatment for patients with suspected COVID-19 infection in the community would be safe, with few side-effects, can be provided by existing NHS services, and helps patients recover quicker and without having to go to hospital.

Setting up a new clinical trial each time a potential treatment becomes available is time consuming and inefficient (5-7). We propose establishing a platform, randomised controlled trial in primary care that can rapidly test low-risk treatments for people at higher risk of poorer outcomes from the illness. Using an efficient, open (no placebo) clinical trial design in conditions of current usual care, our trial aims to give rapid answers about the effectiveness of trial treatments. The platform trial will be flexible. It will allow further treatments to be added into the trial while the trial is already in progress, should such suitable treatments become available.(5) This is particularly important as new candidate treatments are being considered on a regular basis. The overall goal is to find treatments suitable for widespread use in the community that will help affected people recover sooner, and without needing to be admitted to hospital.

2. SYNOPSIS

<table>
<thead>
<tr>
<th>Trial Title</th>
<th>Platform Randomised trial of Interventions against COVID-19 In older peoPLE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Internal ref. no. (or short title)</td>
<td>PRINCIPLE</td>
</tr>
<tr>
<td>Trial registration</td>
<td>ISRCTN 86534580</td>
</tr>
<tr>
<td>Sponsor</td>
<td>University of Oxford</td>
</tr>
<tr>
<td>Funder</td>
<td>UKRI/NIHR</td>
</tr>
<tr>
<td>Clinical Phase</td>
<td>III</td>
</tr>
<tr>
<td>Trial Design</td>
<td>Pragmatic, platform, randomised controlled trial of interventions for COVID-19 in PRIMARY CARE</td>
</tr>
<tr>
<td>Trial Participants</td>
<td>Patients ≥50-64 years with comorbidities detailed below, and aged ≥65 with or without comorbidity presenting within 14 days since onset of symptoms with a new continuous cough and/or high temperature during time of prevalent COVID-19 infections</td>
</tr>
<tr>
<td>Sample Size</td>
<td>Approximately 3000 (1500 per arm) but may be increased if additional arms are introduced and may also be modified in the light of emerging data.</td>
</tr>
<tr>
<td>Planned Trial Period</td>
<td>The trial will start as soon as permissions are in place and procedures and structures implemented. The platform trial will be ongoing until cases of COVID-19 wane to a low level and/or there are no new interventions that require evaluation in pragmatic randomised controlled trial in primary care. March 2022 has been decided as the formal end date at this stage, but that may need to be amended, depending on circumstances prevailing at the time.</td>
</tr>
<tr>
<td>Planned Recruitment period</td>
<td>The first inclusion is planned for as soon as possible, and the duration of the trial will depend on evolving circumstances.</td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th>Objectives</th>
<th>Outcome Measures</th>
<th>Timepoint (s)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary</strong></td>
<td>To assess effectiveness of trial treatments in reducing the need for hospital admission or death, for patients aged ≥50 years with serious comorbidity, and aged ≥65 with or without comorbidity and suspected COVID-19 infection during time of prevalent COVID-19 infections</td>
<td>Hospital admission or mortality related to suspected COVID-19</td>
</tr>
<tr>
<td><strong>Secondary</strong></td>
<td>To explore whether trial treatment reduces 1) Duration of severe symptoms 2) Time taken to self-report recovery 3) Contacts with the health services 4) Consumption of antibiotics 5) Hospital assessment without admission 6) Oxygen administration 7) Intensive Care Unit admission 8) Mechanical ventilation 9) To determine if effects are specific to those with the infections syndrome but who test positive for COVID-19 10) Duration of hospital admission 11) Viral shedding 12) Negative effects on well being</td>
<td>1-2 Patient report on day they feel to have recovered 3. Contacts with health services reported by patients and/or captured by reports of patients ‘medical records where the practice is a member of RSC 4. Bi-weekly reports from participants primary care medical records 5-8 and 10 patient report/carer report/medical record in primary care and hospital care 9. Swab results either at baseline or day 5 for COVID-19 will indicate an “Intention to Treat Infected” group within the overall cohort for sub analysis. Blood test on recovery (optional) for evidence of COVID-19 infection. 11. Follow up swabs at day 5 (if available) will indicate ongoing shedding allowing for comparison between groups 12. WHO-5 Well Being Index</td>
</tr>
</tbody>
</table>
Qualitative sub-study

1. To explore patient experiences of consulting, being tested and taking (trial) medication for suspected COVID-19. To explore healthcare professionals’ views of taking part in research during pandemics.

1. Telephone interview with patient.

Telephone interview with healthcare professional.

1. After 28 days.

Once practice has completed recruitment.

Intervention(s)

All trial interventions are detailed in the Appendices. Further interventions may be added or replaced during the course of the trial, subject to suitable interventions becoming available and all necessary approvals being first obtained.

Comparator

In the first instance, this will be a two-arm trial, with the intervention am being usual care plus a trial drug and the comparator being usual care. There will be no placebo control in this study in the first instance. Additional arms may be added as the trial progresses. These will be detailed in the Appendices. If a trial arm that included a study drug is shown to be superior, then that will become the standard of care (usual care) in the trial and any further interventions will be compared against that intervention.

3. ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
</tr>
</thead>
<tbody>
<tr>
<td>AE</td>
<td>Adverse event</td>
</tr>
<tr>
<td>AR</td>
<td>Adverse reaction</td>
</tr>
<tr>
<td>CI</td>
<td>Chief Investigator</td>
</tr>
<tr>
<td>CRF</td>
<td>Case Report Form</td>
</tr>
<tr>
<td>CT</td>
<td>Clinical Trials</td>
</tr>
<tr>
<td>CTA</td>
<td>Clinical Trials Authorisation</td>
</tr>
<tr>
<td>CTRG</td>
<td>Clinical Trials and Research Governance</td>
</tr>
<tr>
<td>DMSC</td>
<td>Data Monitoring Committee / Data Monitoring and Safety Committee</td>
</tr>
<tr>
<td>DSUR</td>
<td>Development Safety Update Report</td>
</tr>
<tr>
<td>GCP</td>
<td>Good Clinical Practice</td>
</tr>
<tr>
<td>GP</td>
<td>General Practitioner</td>
</tr>
<tr>
<td>HRA</td>
<td>Health Research Authority</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
</tr>
<tr>
<td>--------------</td>
<td>-------------</td>
</tr>
<tr>
<td>HCP</td>
<td>Healthcare professional</td>
</tr>
<tr>
<td>IB</td>
<td>Investigators Brochure</td>
</tr>
<tr>
<td>ICF</td>
<td>Informed Consent Form</td>
</tr>
<tr>
<td>ICH</td>
<td>International Conference on Harmonisation</td>
</tr>
<tr>
<td>IMP</td>
<td>Investigational Medicinal Product</td>
</tr>
<tr>
<td>MHRA</td>
<td>Medicines and Healthcare products Regulatory Agency</td>
</tr>
<tr>
<td>NHS</td>
<td>National Health Service</td>
</tr>
<tr>
<td>NIHR</td>
<td>National Institute of Health Research</td>
</tr>
<tr>
<td>RES</td>
<td>Research Ethics Service</td>
</tr>
<tr>
<td>PHE</td>
<td>Public Health England</td>
</tr>
<tr>
<td>PI</td>
<td>Principal Investigator</td>
</tr>
<tr>
<td>PIL</td>
<td>Participant/ Patient Information Leaflet</td>
</tr>
<tr>
<td>R&amp;D</td>
<td>NHS Trust R&amp;D Department</td>
</tr>
<tr>
<td>RCGP RSC</td>
<td>Royal College of General Practitioners Research Surveillance Centre</td>
</tr>
<tr>
<td>REC</td>
<td>Research Ethics Committee</td>
</tr>
<tr>
<td>RSI</td>
<td>Reference Safety Information</td>
</tr>
<tr>
<td>SAE</td>
<td>Serious Adverse Event</td>
</tr>
<tr>
<td>SAR</td>
<td>Serious Adverse Reaction</td>
</tr>
<tr>
<td>SDV</td>
<td>Source Data Verification</td>
</tr>
<tr>
<td>SMPC</td>
<td>Summary of Medicinal Product Characteristics</td>
</tr>
<tr>
<td>SOP</td>
<td>Standard Operating Procedure</td>
</tr>
<tr>
<td>TSC</td>
<td>Trial Steering Committee</td>
</tr>
<tr>
<td>SUSAR</td>
<td>Suspected Unexpected Serious Adverse Reactions</td>
</tr>
<tr>
<td>TMF</td>
<td>Trial Master File</td>
</tr>
</tbody>
</table>
4. BACKGROUND AND RATIONALE

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

We urgently need to know whether there are readily available treatments that might modify the course of COVID-19 infections, particularly amongst those who are at higher risk of complications. At the present time, those are higher risk appear to be people aged 50 and over with comorbidity and those aged 65 and over.(1-3, 13)

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

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

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

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

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

COVID 19

Europe is now the centre of the COVID-19 epidemic caused by the highly infectious SARS-COV2 virus.(4, 15) As of 22 March 2020 in the UK, 5,018 confirmed cases, and 233 deaths have been reported in the UK, and modelling studies suggest the pandemic will worsen rapidly in the UK and elsewhere.(4, 16)

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

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

And/or

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

A pragmatic trial

The aim of PRINCIPLE is to be the national Primary Care platform trial for UK COVID-19, assessing the effectiveness of trial treatments in reducing the need for hospital admission or death for patients with suspected COVID-19 infection aged ≥50 years with serious comorbidity, and aged ≥65 with or without comorbidity, and during time of prevalent COVID-19 infections in the context of current care delivery. Thus, the trial will need to be as streamlined as possible so that it fits with minimal disruption into routine care during a period of widespread infection and considerable pressure on the NHS and society. In line with common practice for pragmatic trials, this trial will be an open trial with no placebo control.(14, 19-21) The primary outcome is hospitalisation and death, with the decision to hospitalise being made by clinicians independent of the trial according to clinical criteria.

Platform trial

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

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

<table>
<thead>
<tr>
<th>Objectives</th>
<th>Outcome Measures</th>
<th>Timepoint(s) of evaluation of this outcome measure (if applicable)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary Objective</strong></td>
<td>Hospital admission or mortality related to suspected COVID-19</td>
<td>Within 28 days</td>
</tr>
<tr>
<td>To assess effectiveness of trial treatments in reducing the need for hospital admission or death, for patients aged ≥50 years with comorbidity, and aged ≥65 with or without comorbidity and suspected COVID-19 infection during time of prevalent COVID-19 infections</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Secondary Objectives</strong></td>
<td>1-2 Patient report on day they feel to have recovered 3. Contacts with health services</td>
<td>Daily online symptoms score. Telephone call or text day 7, 14 and 28 if data</td>
</tr>
<tr>
<td>To explore whether trial treatment reduces 1) Duration of severe symptoms 2) Time taken to self-report recovery</td>
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<tr>
<td>3) Contacts with the health services</td>
<td>reported by patients and/or captured by reports of patients ‘medical records where the practice is a member of RSC</td>
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<tr>
<td>4) Consumption of antibiotics</td>
<td>4. Bi-weekly reports from participants primary care medical records</td>
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<tr>
<td>5) Hospital assessment without admission</td>
<td>5-8 and 10 patient report/ carer report/ medical record in primary care and hospital care</td>
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<tr>
<td>6) Oxygen administration</td>
<td>9. Swab results either at baseline or day 5 for COVID-19 will indicate an “Intention to Treat Infected” group within the overall cohort for sub analysis. Blood test on recovery (optional) for COVID-19.</td>
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<td>7) Intensive Care Unit admission</td>
<td>11. Follow up swabs (if available) at day 5 will indicate ongoing shedding allowing for comparison between groups</td>
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<td>12. WHO-5 Well Being Index</td>
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<tr>
<td>9) To determine if effects are specific to those with the infections syndrome but who test positive for COVID-19</td>
<td>10) Duration of hospital admission</td>
<td></td>
</tr>
<tr>
<td>10) Duration of hospital admission</td>
<td>11) Viral shedding</td>
<td></td>
</tr>
<tr>
<td>11) Viral shedding</td>
<td>12) Negative effects on well being</td>
<td></td>
</tr>
</tbody>
</table>

**Qualitative sub study**

1) To explore patient experiences of consulting, being tested and taking (trial) medication for suspected COVID-19. To explore healthcare professionals’ views of taking part in research during pandemics.

1. Telephone interview with patient.

1. **After 28 days.**

**Intervention(s)**

All trial interventions are detailed in the Appendices. Further interventions may be added or replaced during the course of the trial, subject to suitable interventions becoming available and all necessary approvals being first obtained.

**Comparator**

In the first instance, this will be a two-arm trial, with the intervention arm being usual care plus a trial drug and the comparator being usual care. There will be no placebo control in this study in the first instance. Additional arms may be added as the trial progresses. These will be detailed in the Appendices. If a trial arm that included a
5. TRIAL DESIGN
This will be an open, prospective, individually randomised, platform, controlled clinical trial in community care. The trial will initially be two-arm, but additional arms may be added as the trial progresses.

The trial will be implemented in the first instance in practices that are already part of the RCGP RSC Network. Currently over 500 practices are part of this network, with 100 already offering a sentinel viral swabbing service which is being scaled up. Due to the pandemic, almost all practices in the UK have been asked to join the RCGP RSC Network.

6. PARTICIPANT IDENTIFICATION
6.1 Trial Participants
Patients ≥50 years with serious comorbidity, and patients aged ≥65 with or without comorbidity presenting in the community within 14 days since onset of symptoms, with a new continuous cough and/or high temperature during a time of prevalent COVID-19 infections.

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

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

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

7.1.1 Inclusion Criteria
- Participant is willing and able to give informed consent for participation in the study;
- Participant is willing to comply with all trial procedures;
- Onset of symptoms of possible COVID-19 in the community (continuous cough and/or high temperature) within 14 days of inclusion;
- Patients aged ≥50-64 years with any of the following listed comorbidities:
  - Known weakened immune system due to a serious illness or medication (e.g. chemotherapy);
  - Known heart disease and/or hypertension;
  - Known asthma or lung disease;
  - Known diabetes not treated with insulin;
- Known mild hepatic impairment;
- Known stroke or neurological problem;

OR

- Patients aged ≥65 with or without comorbidity

### 7.1.2 Exclusion Criteria

- Pregnancy;
- Breastfeeding;
- Known severe hepatic impairment;
- Known severe renal impairment;
- Known porphyria;
- Type 1 diabetes or insulin dependent Type 2 Diabetes mellitus;
- Known G6PD deficiency;
- Known myasthenia gravis;
- Known severe psoriasis;
- Known severe neurological disorders (especially those with a history of epilepsy—may lower seizure threshold);
- Previous adverse reaction to, or currently taking, hydroxychloroquine, chloroquine, azithromycin or other macrolides or ketolides
- Patients taking the following drugs: penicillamine, amiodarone, sotalol, ciclosporin, digoxin, chloroquine, bromocriptine, cabergoline, ergotamine, ergometrine, methysergide or any ergot derivatives.
- Already taking antibiotics for an acute condition
- Patient currently admitted in hospital
- Known congenital or documented QT prolongation
- Known allergy to soya or peanut due to the risk of hypersensitivity reactions
- Known retinal disease;
- Almost recovered (generally much improved and symptoms now mild or almost absent)
- Judgement of the recruiting clinician deems ineligible.

## 8 TRIAL PROCEDURES

### 8.1 Recruitment

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

People who are concerned about COVID-19 continue to contact their general practices in large numbers. In the first instance, we will ask participating general practices to record whether a person phoning about COVID-19 is potentially eligible for the study. The practice will then ask the person if they are interested in finding out about potential trial participation or seek verbal consent if they are happy to be contacted by the trial team to discuss this further. If they are, information will be provided verbally and online either by the GP surgery or their contact details passed to the trial team who will provide such information on how they might join the study. Full information will be available to view on a web site and subsequently on the Participant Information Sheet (PIS). A simplified Participant Information Leaflet may also be provided to...
supplement the full PIS. This information will inform potentially eligible and interested patients about how to access further trial information and consider participation, as well as the procedures involved in joining the study, and what participation would involve. Practices can also choose to screen contacts from the previous (up to) 14 days for potentially eligible participants to be approached to discuss participation.

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

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

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

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

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

During this process, we will ask the potential participant to, if possible, include a phone number and email address for a Study Partner, who may provide assistant to the study participant in completing trial procedures. Identifying a Study Partner is not a requirement of study participation, merely a suggested mechanism to aid participation for consenting patients.

Eligibility can be checked at study sites. In addition, eligibility can be checked centrally by a medically qualified clinician or a Research Nurse suitably trained and experienced who has been delegated this responsibility, with appropriate access to the participant’s medical records. If participant’s medical notes cannot be accessed centrally, the clinician/delegate will contact the participants GP for information to enable the study team to confirm eligibility.

Once informed consent has been obtained, and eligibility confirmed, participants will be randomised via a secure online link using our in-house Sortition module. The participant, trial team and participant’s GP will be notified electronically of what treatment allocation they have been randomised to. The participant and GP can review the PIS and completed ICF at any time using a secure log-in access code.

All participants will be provided with 2 sampling kits for self-sampling by their practice, study team, Public Health England (PHE) or other central service, if sampling kits are available. One sample will be taken as close to study entry as possible, to assess COVID-19 status, and the second five days after enrolment to assess COVID-19 status and viral shedding. Where swabbing facilities are unavailable, for example, if there is no supply of suitable swabs, patients may still participate in the trial and be included in the intention to
treat analysis only.

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

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

Once recruited, participants will be issued with an online link where they will be asked to record the presence and severity of a few simple symptoms each day. Where online data is not being entered by participants, the research team will contact the participants and/or their study partner following days 2, 7, 14 and 28. The study team will make no more than three attempts to contact the participant/Trial Partner at each of these follow-up points. We will also obtain consent to ascertain relevant data from hospital records about length of stay and ICU admission and ventilation.

The RCGP RSC will report to the central trial office at least twice weekly about healthcare contacts in the participating patient’s clinical records, as they are able to download this information centrally for study participants. This will be used as confirmation and a back-up for information obtained directly from study participants and other data sources outlined above. Where notes review is not possible using this route – for example, where a patient has been recruited through an urgent or unscheduled care contact and therefore their registered GP practice has not been involved and does not wish to register with the RCGP RSC, the registered GP surgery will be contacted separately by the trials team to request a limited notes review.

8.2 Screening and Eligibility Assessment

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

8.3 Informed Consent

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

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

8.4 Randomisation

Participants will be randomised using a fully validated and compliant web-based randomisation system called Sortition. At the baseline assessment, the recruiter or a member of the trial team will enter the participant’s baseline data into the online system, which will then enable the randomisation to take place. The randomisation process will take only a few moments via the online system and will not delay trial participation. Full details of response adaptive randomisation are described in section 11.2.4.

8.5 Blinding and code-breaking

PRINCIPLE will be an open-label trial. The participant and the recruiting clinician will know the participant’s allocation. Therefore, no unblinding or code breaking is required in the event of a relevant emergency. However, those managing the data will be blind to participant allocation.

The trial team and recruiting clinicians will be blinded to emerging results. During the course of the trial, only those on the Data Safety & Monitoring Committee will have access to the unblinded interim results.

8.6 Baseline Assessments

Once eligibility is confirmed, participants will be randomised using Sortition online. A sampling kit with two sets of swabs and an insert containing instructions will be sent to the participant’s home for self-sampling as soon after study inclusion as possible and then again 5 days later, unless a sample can be taken face-to-face by the general practice, or another facility soon after inclusion, in which case the initial self-swab will not be necessary. While the aim is to have a swab result for all patients, if a swab cannot be done for supply or other logistical reasons, this will not exclude the patient form participating in the study. However, they will only be analysed in the intention to treat analysis. All participants, whether in the intervention or control group, will be asked to provide swab or self-swab at study enrolment and day 5, if swabbing facilities for this are available. If participants take their own swab, they will put it in the secure container and double bag, and post it to the PHE laboratory supporting the study. Participants will be told how study materials and any medication they are randomised to receive can be obtained, either through collection at a pharmacy, GP practice, or by home delivery. GPs will be able to issue the study medication directly to participants, it may be issued centrally from the trial team.

8.7 Subsequent Visits

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

Participant follow-up will be primarily online, where they will be asked to complete questions each day for 28 days. If not completed, the trial team will contact the participant and/or their Study Partner to obtain the information. In addition, at day 14 and 28 the World Health Organisation – Five Well-Being Index (WHO-5) will be administered, completed online or telephone call, at the preference of the participant.

Each day, participants, or their study partner, will be asked to rate the severity of a set number of symptoms, record contacts with the health services including hospital admission, record medication use, new infections in the household, and the five questions of WHO 5 Well Being Index on days 14 and 28. The latter instrument has been validated for measuring wellbeing over time. It is becoming increasingly
apparent the COVID-19 infection may have a considerable negative impact on well-being, exploring impact of interventions on this is important. (22)

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

The participants who consented to be contacted for an optional covid-19 blood test (if it becomes available) will be contacted by the study team within 6 months of completing the study and given more information in an additional participant information sheet and consent form, including where blood sampling will take place and that blood samples will not be stored.

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

Where notes review is not possible using these routes – for example where a patient has been recruited through an urgent or unscheduled care contact and therefore their registered GP practice has not been involved and does not wish to register with the RCGP RSC, the registered GP surgery will be contacted separately by the trials team to request a limited notes review.

8.8 Sample Handling

We will request two biological samples to test for COVID-19 from all consenting participants, the first at baseline and the second at day 5. Unless a swab can be taken face-to-face in the course of usual care, this will be a self-swab process with the practice generating the required forms. Once the swab has been taken it will be put in the regulation contained packaging, double bagged, and posted to the PHE laboratory that is supporting the study using their existing, safe, compliant processes. The trial team will utilise PHE and their existing processes and documentation. The trial team do not intend to store the swab once tested, and it won’t be stored for the purpose of this trial. The swab material will fall under PHE and not the trial remit, and PHE may retain the swab for up to 5 years.

If a blood test for covid-19 becomes available, participants who have consented to being contacted will receive further information about this test and give consent if they wish to take part. We anticipate participants will be informed of their blood test result and blood samples wont be stored.

8.9 Qualitative Sub-study

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

Recruitment:

When patient participants consent to take part in the trial, we will ask whether they would be happy to be contacted by telephone to be invited for a telephone interview. Patient participants will be contacted by telephone by a member of the research team within 3 months to invite them to participate after they
complete their day 28 follow up. The researcher will provide study information over the telephone. The Interview Patient PIS, and Interview Patient ICF will be available on the study website and will be emailed to participants if requested.

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

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

Patients recruited to both the intervention and usual care arms will be purposively sampled across the recruiting period with approximately 15-20 patients in each arm (30-40 interviews in total). We will seek to obtain maximum variation in age and symptom severity (as reported in daily diary on day 0).

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

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

Interviews:

Interviews will be conducted by telephone and all participants will be asked to provide verbal consent prior to interviews starting. The researcher will make a written record of this consent using the Qualitative ICFs which will be emailed to the participant. Interviews will be audio-recorded with participant’s permission.

Patient interviews will follow a semi-structured topic guide (Interview Patient Topic Guide) and ask about reasons for consulting and illness perceptions prior to the consultation, experiences of the consultation, the COVID-19 testing process (and result where the participant has been notified) and medication adherence. The topic guide will be informed by the Common Sense Model which describes how people perceive and cope with symptoms of illness.

HCP interviews will follow the Interview HCP Topic Guide and will ask about experiences of carrying out trial activities, recruiting patients and the work required to set up a clinical trial during a pandemic.

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

8.10 Early Discontinuation/Withdrawal of Participants

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

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

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The reason for withdrawal will be recorded on the CRF. Data that has already been collected about the participant will be kept and used. Swabs may be stored outside of the trial remit, for PHE purposes adhering to their retention policy. Optional covid-19 blood test samples will not be stored.

8.11 Definition of End of Trial

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

9 TRIAL INTERVENTIONS

9.1 Investigational Medicinal Product(s) (IMP) Description

_Trial Drug information can be found in the relevant Appendices._

9.2. Blinding of IMPs

There is no blinding of IMPs in the trial.

9.3. Storage of IMP

GP practices can order a supply of trial medication from Public Health England using the existing Inform process. All GP practices in England are already set up on Inform, as they use this system to order influenza vaccines form Public Health England. GPs will be provided with an envelope by the study team which will be labelled appropriately for trial medication, and they will add the patient’s details to this label. This pack, containing instructions on using the medication will be provided to the patient or their representative. Medication may either be issued by the patient’s registered GP surgery or by a surgery acting as a hub for a number of local surgeries.

Alternatively, study medication will be repackaged by accredited licensed, central facility and may be delivered to primary care centres or to the Primary Care Clinical Trials Unit for further distribution to study participants as they are included. Distribution of trial packs to study participants will be tracked via courier or call/text message.

9.4. Compliance with Trial Treatment

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

9.5. Accountability of the Trial Treatment

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

9.6. Concomitant Medication

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

10 SAFETY REPORTING

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

<table>
<thead>
<tr>
<th>Adverse Event (AE)</th>
<th>Any untoward medical occurrence in a participant to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product.</th>
</tr>
</thead>
</table>
| Adverse Reaction (AR) | An untoward and unintended response in a participant to an investigational medicinal product which is related to any dose administered to that participant.  
The phrase "response to an investigational medicinal product" means that a causal relationship between a trial medication and an AE is at least a reasonable possibility, i.e. the relationship cannot be ruled out.  
All cases judged by either the reporting medically qualified professional or the Sponsor as having a reasonable suspected causal relationship to the trial medication qualify as adverse reactions. |
| Serious Adverse Event (SAE) | A serious adverse event is any untoward medical occurrence that:  
- results in death  
- is life-threatening  
- requires inpatient hospitalisation or prolongation of existing hospitalisation  
- results in persistent or significant disability/incapacity  
- consists of a congenital anomaly or birth defect*.  
Other ‘important medical events’ may also be considered a serious adverse event when, based upon appropriate medical judgement, the event may jeopardise the participant and may require medical or surgical intervention to prevent one of the outcomes listed above.  
NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.  
*NOTE: Pregnancy is not, in itself an SAE. In the event that a participant or his/her partner becomes pregnant whilst taking part in a clinical trial or during a stage where the foetus could have been exposed to the medicinal product (in the case of the active substance or one of its metabolites having a long half-life) the pregnancy should be followed up by the investigator until delivery for congenital abnormality or birth defect, at which point it would fall within the definition of “serious”. |
| Serious Adverse Reaction (SAR) | An adverse event that is both serious and, in the opinion of the reporting Investigator, believed with reasonable probability to be due to one of the trial treatments, based on the information provided. |
| Suspected Unexpected Serious Adverse Reaction (SUSAR) | A serious adverse reaction, the nature and severity of which is not consistent with the Reference Safety Information for the medicinal product in question set out:  
- in the case of a product with a marketing authorisation, in the approved summary of product characteristics (SmPC) for that product  
- in the case of any other investigational medicinal product, in the |
NB: to avoid confusion or misunderstanding of the difference between the terms “serious” and “severe”, the following note of clarification is provided: “Severe” is often used to describe intensity of a specific event, which may be of relatively minor medical significance. “Seriousness” is the regulatory definition supplied above.

10.2 Assessment results outside of normal parameters as AEs and SAEs
There are no additional assessment results in this study

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

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

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

10.4 Procedures for Reporting Adverse Events
All AEs will be collected from daily participant diaries, calls to participants/Study Partners and RCGP data downloads.

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

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

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

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

10.5.1. Other events exempt from immediate reporting as SAEs

Hospitalisations will be defined as at least a 1 night admission to hospital.

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

10.5.2. Procedure for immediate reporting of Serious Adverse Events

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

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

10.5.3 Expectedness

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

10.6 SUSAR Reporting

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

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

10.7 Development Safety Update Reports

The DSUR will be developed and submitted annually on the anniversary date that the trial receives Clinical Trial Authorisation +60 days. Due to the nature of this trial and the importance of sharing the science of COVID-19 and the drug, internationally, we expect to produce reports to the UK Government and regulatory agency more frequently upon request.
11 STATISTICS
11.1 Master Statistical Analysis Plan (M-SAP)
The statistical design and pre-specified analyses will be described in detail in a Master Statistical Analysis Plan (M-SAP) drafted by a Trial Statistician and signed off by the CI and Lead/senior statistician. The M-SAP will be accompanied by arm-specific appendices to describe any planned deviations from the M-SAP. A broad overview of the design and primary analyses is provided below.

11.2 Open Adaptive Platform Trial

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

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

11.2.1 Primary Endpoint & Analysis

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

$$H_0: \theta_j \geq 0$$

$$H_1: \theta_j < 0$$

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

11.2.2 Adaptive Design

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

11.2.3 Interim Analyses

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

If the Bayesian posterior probability of a clinically meaningful treatment effect (≥ 0.05 decrease in the proportion hospitalized/dead) is sufficiently small (e.g. < 0.01) the intervention arm will be dropped from the study for futility. If there are no other intervention arms available, the trial will be suspended; otherwise accrual continues to the remaining treatment arms. The exact futility threshold will be pre-specified in the M-SAP and determined via simulation.

11.2.4 Allocation & Response Adaptive Randomisation

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

11.2.5 Sample Size Justification

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

11.2.6 Virtual Trial Simulations

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

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

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

11.3 Primary Analysis Population

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

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

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

11.5 Qualitative sub-study analysis

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

12 DATA MANAGEMENT

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

12.1 Source Data

Source documents are where data are first recorded, and from which participants’ CRF data are obtained. These include, but are not limited to, hospital records (from which medical history and previous and concurrent medication may be summarised into the CRF), clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence.
If the participant fails to complete data online and after three attempts at contacting the participant/Trial Partner, the RCGP RSC may be utilised to obtain missing data. Data collected will include participant identifiable information and will be accessed at the University of Oxford according to PC-CTU Information Governance policies and GDPR. Data will only be held for the duration of which its required, this will be reviewed annually.

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

12.2 Access to Data

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

12.3 Data Recording and Record Keeping

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

Sentry is an online secure data entry system developed in-house at PC-CTU and hosted at Oxford. It is designed to collect sensitive data, such as participant contact details, and securely retain them separate from a trial’s clinical data. Sentry can also act as a central participant portal to manage online eligibility, eConsent and ePRO - acting as an intermediary between the participant and the clinical databases. Sentry is accessed via a secure HTTPS connection and all stored sensitive data is encrypted at rest to AES-256 standards.

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

For the qualitative sub-study:

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

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

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

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

13.1 Risk assessment

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

13.2 Monitoring

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

13.3 Trial committees

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

- DMSC- to review the data at each interim analysis as described in the Statistical Analysis section, as the updates to the randomisation scheme occur in order to ensure that the process is working correctly and to review and monitor the accruing data to ensure the rights, safety and wellbeing of the trial participants.

- TSC – the Trial Steering Committee ensure the rights, safety and wellbeing of the trial participants. They will make recommendations about how the study is operating, any ethical or safety issues and any data being produced from other relevant studies that might impact the trial.

- TMG- is responsible for the day-to-day running of the trial, including monitoring all aspects of the trial and ensuring that the protocol is being adhered to. It will include Co-Investigators and will meet weekly in the first instance. A core project team (PT) from within the TMG will meet daily as required for daily operational decision making.

14 PROTOCOL DEVIATIONS

A study related deviation is a departure from the ethically approved study protocol or other study document or process (e.g. consent process or administration of study intervention) or from Good Clinical
Practice (GCP) or any applicable regulatory requirements. Any deviations from the protocol will be documented in a protocol deviation form and filed in the study master file.

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

15 SERIOUS BREACHES

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

(a) the safety or physical or mental integrity of the trial subjects; or

(b) the scientific value of the research.

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

16 ETHICAL AND REGULATORY CONSIDERATIONS

16.1 Declaration of Helsinki

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

16.2 Guidelines for Good Clinical Practice

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

16.3 Approvals

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

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

16.4 Other Ethical Considerations

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

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

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

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

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16.5 Reporting

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

16.6 Transparency in Research

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

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

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

16.7 Participant Confidentiality

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

16.8 Expenses and Benefits

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

17 FINANCE AND INSURANCE

17.1 Funding

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

17.2 Insurance

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

17.3 Contractual arrangements

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

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18 PUBLICATION POLICY

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

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

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

20 ARCHIVING

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