

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

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No potential conflict of interest

### **Confidentiality Statement**

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

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

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

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

**Eligibility and randomisation:** This protocol describes a randomised trial for people in the community at higher risk of an adverse outcome from possible or confirmed SARS-CoV-2 infection, defined in accordance with the United Kingdom's National Health Service syndromic case definition (<https://www.nhs.uk/conditions/coronavirus-covid-19/symptoms/>). Participants are randomised to receive either usual care or a trial treatment in addition to usual care (see appendices for details of all trial arms). Participants can take part in the study if they are eligible to be randomised to at least one intervention arm, as well as the Usual Care arm.

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

**Response adaptive randomisation:** The initial randomisation ratio is fixed 1:1 for a comparison between two trial arms, but the trial has the capability for these proportions to be altered according to participants' responses to interventions. Pre-specified decision criteria allow for dropping a treatment for futility, declaring a treatment superior, or adding a new treatment to be tested. If at any point a treatment is deemed superior to the usual care arm, the superior treatment may replace the usual care arm as the new standard of care. In the context of the COVID-19 pandemic, the trial may continue as long as the pandemic persists.

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

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

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

**Efficient study design:** All enrolment (screening, informed consent, eligibility review and baseline data) and follow-up procedures (daily diary, hospitalisations and deaths) can be performed and captured online on the trial website or by telephone with a member of the trial team.

Randomisation is online and automatic following eligibility confirmation. Participant packs and medications are sent from the central study team directly to the participant.

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

**Numbers to be randomised:** The trial will continue until either superiority or futility is claimed for each intervention. We estimate that approximately 400 participants per arm (800 participants total if only a single intervention vs. Usual Care) will be required to provide 90% power for detecting an approximate difference of 2 days in median recovery time. We estimate that approximately 1500 participants per arm (3000 participants total if only a single intervention vs. usual care) will be required to provide 90% power for detecting a 50% reduction in the relative risk of hospitalisation and/or death.

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## 1. BACKGROUND and RATIONALE

We urgently need to know whether potential treatments for COVID-19-like-illness that are suitable for use in the community might help affected individuals recover more quickly and reduce the risk of hospitalisation and/or death.(1) PRINCIPLE is a platform trial designed to efficiently evaluate potential treatments for people with COVID-19-like-illness in the community, and who may be at higher risk of poorer outcomes. Eligible participants are those who meet the United Kingdom's National Health Service syndromic case definition (<https://www.nhs.uk/conditions/coronavirus-covid-19/symptoms/>), who are being managed in the community, and who are aged 65 and over, or 18 to 64 and experiencing shortness of breath as part of COVID-19 illness, or aged 18-64 with certain comorbidities (2-5), 7).

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

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

The primary analysis will include all participants as specified in the master statistical analysis plan and the adaptive design report. Clinical data, and information from swab and blood tests, where available, will be used to classify participants according to aetiology.

## 2. TRIAL DESIGN AND PROCEDURES

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

### 2.1 Participant Identification

#### 2.1.1 Trial Participants

The trial aims to include symptomatic participants with confirmed, or possible COVID-19 who meet the current NHS case definition for possible COVID-19, and who are well enough to remain in the community. This definition can be found here: <https://www.nhs.uk/conditions/coronavirus-covid-19/symptoms/>. Participants must be aged 65 and over, **OR** aged 18 to 64 and experiencing shortness of breath as part of COVID-19 illness, **OR** aged 18-64 with certain comorbidities.

Participants experiencing shortness of breath have a greater risk of severe and critical disease outcomes with COVID-19 (6).

The study is for people who have ongoing symptoms.

### 2.1.2 Inclusion Criteria

Inclusion requires the following:

1. Participant or their legal representative, is willing and able to give informed consent for participation in the study, and is willing to comply with all trial procedures
2. Suspected COVID-19 using the NHS syndromic definition, OR symptoms consistent with COVID-19\*, with a positive test for SARS-CoV-2 infection within the past 14 days
3. Symptoms must have started within the past 14 days and be ongoing

**AND**

4. Participant is aged 65 or over **OR**

Participant is aged 18- 64, and is experiencing shortness of breath as part of COVID-19 illness **OR**

Participant is aged 18-64 and has any of the following underlying health conditions

- a) Known weakened immune system due to a serious illness or medication (e.g. chemotherapy);
- b) Known heart disease and/or a diagnosis of high blood pressure
- c) Known chronic lung disease (e.g. asthma)
- d) Known diabetes
- e) Known mild hepatic impairment;
- f) Known stroke or neurological problem;
- g) Self-report obesity or body mass index  $\geq 35 \text{ kg/m}^2$

\*These symptoms may include, but are not limited to, shortness of breath, general feeling of being unwell, muscle pain, diarrhoea and vomiting.

### 2.1.3 Exclusion Criteria

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

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

## 2.2 Trial procedures

### 2.2.1 Recruitment

Recruitment is possible through a variety of mechanisms:

### 2.2.2 Face to face

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

### 2.2.3 Remote recruitment

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

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

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

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

Patient details will be provided in accordance with section 251 under the General Notice under the Health Service Control of Patient Information Regulations 2002, which applies only in England and Wales, providing patient information without consent for COVID-19 public health, surveillance and research purposes. The notice provides a temporary legal basis to avoid a breach of confidentiality for COVID-19 purposes.

For all recruitment models:

- Study Partner: at screening the potential participant will be asked to provide contact details for a Study Partner, to assist in completing trial procedures and to provide information on their behalf where necessary, but this is not a requirement for trial participation. However, it is strongly encouraged that participants who may be frailer

and/or lack capacity to consent make use of a study partner to facilitate their participation. In addition to family member or friend, the study partner may also be a carer or other suitable person.

- Participants may be asked if they wish to enrol in additional studies that do not conflict with the main PRINCIPLE trial. Those who do not screen as eligible for PRINCIPLE may be alerted to the possibility of participating in other approved trials.

## 2.3 Screening

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

## 2.4 Informed Consent

If participants meet the screening criteria, they will be asked to provide informed consent and a screening trial ID number will be assigned to them. Remote, paperless online/telephone consent is required, and appropriate during the pandemic. Participants will be able to download their consent form, or it may be printed by the central study team and delivered to participants with their study materials if they so prefer.

Written and summary versions of the PIS and ICF will be presented to participants detailing no less than: the exact nature of the trial; the known side-effects and risks involved in taking part. It will be clear that the participant is free to withdraw from the study at any time. A summary, pictorial PIS is available which can be read by those feeling very unwell, lack capacity or have low reading comprehension skills. Adequate time will be given to the participant to consider the information and to ask any questions about the trial before deciding whether to participate. After consent, the participant will enter online baseline information, including their address, contact details and those of a Study Partner.

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

recruiting clinicians will not endeavour to obtain consent for or recruit into the trial residents who, in addition to their lack of capacity, have a quality of life which can reasonably be considered as not acceptable to the potential participant.

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

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

## **2.5 Eligibility Assessment**

Eligibility of those who have provided appropriate consent can be checked at study sites or centrally by a medically qualified clinician or a research nurse, who is suitably trained and experienced and has been delegated this responsibility, and who has appropriate access to the participant's summary care record or relevant medical information. If a participant's summary care record cannot be accessed centrally, the clinician/delegate will contact the participant's primary care medical practice for information relevant to confirming eligibility. Participants will not be randomised to an arm if an exclusion criterion to that arm applies to them, but will need to have no exclusions relevant to at least one intervention and the usual care arm.

## **2.6 Randomisation**

Participants will be randomised using a fully validated and compliant web-based randomisation system called Sortition. Once deemed eligible, the clinician or a member of the trial team will randomise the participant, to one of the arms they are eligible for (at least two arms, usual care and at least one intervention), automatically by Sortition. Full details of response adaptive randomisation are described in section [5.2.2](#).

The participant, legal representative if applicable, trial team and participant's GP will be notified electronically of the treatment allocation. If the participant does not have an email address, they will be notified by telephone. The research team may also send the GP or Care Home an email or letter via secure systems, containing personally identifiable data and treatment allocation.

## **2.7 Blinding and code-breaking**

PRINCIPLE is an open-label trial. The participant, legal representative if applicable and the recruiting clinician will know the participant's allocation. Therefore, no unblinding or code breaking is required. However, those managing the data will be blind to participant allocation.

The trial team and recruiting clinicians will be blinded to emerging results. During the course of the trial, only the unblinding statisticians and the independent members of the Data Monitoring and Safety Committee will have access to the unblinded interim results.

## 2.8 Baseline Assessments

Once randomised, study medication (if so randomised), and a participant pack will be sent to participants, from their general practice, study team, Public Health England (PHE) or other approved central service (or collected from a general practice or pharmacy). Participants may be offered a swab test as part of standard care. Where possible, and availability of sampling kits allows, one sample will be taken as close to study entry as possible to assess COVID-19 status and other viral aetiologies. While the aim is to have a swab result for all patients, where swabs are unavailable, patients may still participate and be included in the primary intention to treat analysis only.

## 2.9 Subsequent Visits

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

Participants will be sent a link to their online diary, which they will be asked to complete for 28 days. They will be asked to rate the severity of symptoms, record contacts with the health services (including hospital admission), record medication use and new infections in the household. It is becoming increasingly apparent the COVID-19 infection may have a considerable negative impact on well-being (7) and so the five questions of WHO-5, validated for measuring wellbeing over time, will be presented at baseline and on days 14 and 28. We will not ask for WHO-5 questions to be completed for participants who lack capacity. We will capture ethnicity and care home residency at baseline and day 28 (if missed at baseline).

All participants receive a call from the trial team on day 2/3 to confirm that they have received a participant pack, and trial medication (if randomised to a trial medication), and to explain that they should complete the daily diary for 28 days even if they feel better or their swab result is negative. The trial team calls participants/study partners on days 7, 14 and 28 if they do not have internet access or have *not* completed their diary for at least 2 consecutive days prior to the call. No more than six contact attempts will be made at each of these follow-up points.

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

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

The RCGP RSC will report to the central trial office at regular intervals about healthcare contacts in the participant's clinical records, as they are able to download this information centrally. This will be used as confirmation and a back-up for information obtained directly from study participants and other data sources outlined above. If obtaining data is not possible using this



route, the GP surgery will be contacted to request a limited notes review. Participant records will be accessed up to twelve months following enrolment to ascertain follow up data from enrolment to day 28. Data will be collected as close to real time as possible; RCGP RSC, EMIS and NHS Digital and other sources of routinely collected data will be utilised if required. To investigate the impact of trial interventions on the longer-term effects of COVID-19, we will use these data collection methods to follow-up participants, for up to 10 years.

## 2.10 Qualitative Sub-study

A qualitative sub-study will be nested within the trial, to capture data to understand how patients conceptualise their illness and how they respond to taking medication(s) as part of the trial. Once participants have completed the trial, we will interview their respective clinicians to explore their views of taking part in trials during a pandemic. Healthcare professionals will also be asked about their experiences of taking part in the trial. See *supplementary material F* for further details. Participants who lack capacity will not be invited to participate in the qualitative sub study.

## 2.11 Early Discontinuation/Withdrawal of Participants

Each participant, or their legal representative on the participant's behalf, has the right to withdraw from the study at any time. For those that lack capacity, expression of dissent in any form will be taken as an indication they do not wish to be included and they will be withdrawn. In addition, the Investigator may discontinue a participant from the study at any time if the Investigator considers it necessary for any reason including:

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

The reason for withdrawal will be recorded on the CRF. Data that has already been collected about the participant will be kept and used.

## 2.12 Definition of End of Trial

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

# 3 TRIAL INTERVENTIONS

IMP information can be found in the relevant ISAs.

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



NHS volunteers, or it can be collected from the pharmacy by the participant or someone on their behalf.

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

## **4 SAFETY REPORTING**

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

### **4.1 Procedures for Reporting Adverse Events and Serious Adverse Events**

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

Hospitalisation and/or death due to confirmed or possible SARS-Cov-2 infection is a primary outcome, we will collect this data using a risk-adapted approach and will not report such SAEs. SAEs other than hospitalisation or death due to COVID-19 must be reported by the person who has discovered the SAE or nominated delegate within 24 hours of becoming aware of the event. The sponsor or delegate will ensure it is reviewed by the CI or other delegated personnel for relatedness and expectedness as soon as possible taking into account the reporting time for a potential SUSAR according to the relevant competent authority. If the event has not resolved, at the 28 day time point the SAE will be reviewed again to see if resolution has occurred. If the event is considered 'resolved' or 'resolving' no further follow up is required. If not, the event must be followed up until such a time point.

*See Supplementary Material D for definitions of adverse events*

#### **4.1.1. Other events exempt from immediate reporting as SAEs**

Hospitalisations will be defined as at least a one night admission to hospital. Hospitalisation for a pre-existing condition, including elective procedures planned prior to study entry, which has not worsened, does not constitute an SAE, and standard supportive care for the disease under study are not SAEs and do not require SAE reporting.

#### **4.1.2. Procedure for immediate reporting of Serious Adverse Events**

- Trial team will complete an SAE report form for all reportable SAEs.

- GP practice/trial team/RCGP will provide additional, missing or follow up information in a timely fashion.
- If necessary the participant may be contacted to provide additional, missing or follow up information as required.

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

#### 4.1.3 Expectedness and Causality

For SAEs that require reporting, expectedness of SARs will be determined according to the relevant RSI section of the Summary of Product Characteristics/IB. The RSI will be the current Sponsor and MHRA approved version at the time of the event occurrence.

#### Assessment of Causality

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

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

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

#### 4.2 SUSAR Reporting

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

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

#### 4.3 Development Safety Update Reports

The DSUR will be developed and submitted annually on the anniversary date that the trial receives Clinical Trial Authorisation +60 days. Due to the nature of this trial and the importance of sharing

the science of COVID-19 and the drug, internationally, we expect to produce reports to the UK Government and regulatory agency more frequently upon request.

## 5 STATISTICS

### 5.1 Master Statistical Analysis Plan (M-SAP)

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

### 5.2 Open Adaptive Platform Trial

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

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

#### 5.2.1 Co-Primary Endpoints & Analyses

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

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

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

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

If the Bayesian posterior probability of superiority (a log hazards ratio greater than 0 corresponding to quicker recovery) for a treatment versus Usual Care is sufficiently large (e.g.  $\geq 0.99$ ), the null hypothesis will be rejected and the intervention will be deemed superior to Usual Care with respect to time to recovery. The exact threshold of the superiority decision criterion (e.g. 0.99) will be determined *a priori* via simulation to control the one-sided Type I error of the study at approximately 0.025, and will be specified in the Adaptive Design Report (Appendix to the M-SAP). The Adaptive Design Report will also specify appropriate methodology for the primary analysis when the Usual Care arm is replaced by a superior treatment, and for when the comparison of a treatment versus Usual Care includes non-concurrent randomisations.

The second co-primary endpoint is hospital admission or death due to possible SARS-CoV-2 infection. The corresponding analysis will be a Bayesian generalised linear model of hospitalisation/death regressed on treatment and stratification covariates (age, comorbidity). Let  $\delta_j$  denote the log odds ratio comparing the odds of hospitalisation/death for persons in treatment group  $j$  versus persons in the Usual Care arm. A corresponding Bayesian posterior distribution will be derived for the estimated log odds ratio. If the first co-primary endpoint hypothesis (for time to recovery) is rejected for intervention  $j$ , the second co-primary hypothesis for intervention  $j$  be tested:

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

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

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

### 5.2.2 Adaptive Design

The pre-specified design will allow adaptations to the trial based on the observed co-primary endpoint data. These adaptations include the declaration of success or futility of an intervention at an interim analysis, the addition or removal of treatment arms, and changes in the randomisation probabilities. Adaptations will occur at a given interim analysis if pre-specified conditions are satisfied. The adaptive algorithm will be documented in the Adaptive Design

Report, including pre-specified criteria for decisions regarding futility or effectiveness of interventions and/or replacing interventions in the trial.

### 5.2.3 Interim Analyses

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

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

### 5.2.4 Allocation & Response Adaptive Randomisation

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

### 5.2.5 Sample Size Justification

Given the open perpetual trial structure, the trial does not have a finite ending based on sample size. Rather, the trial will continue until either superiority or futility is claimed for each intervention, or until the pandemic expires in the population. We estimate that approximately 400 participants per arm (800 participants total if only a single intervention vs. Usual Care) will be required to provide 90% power for detecting a hazard ratio of 1.3 (approximate difference of 2 days in median recovery time). This calculation is based on the assumption of an exponential distribution for time to recovery with a median of 9 days in the Usual Care arm, with some adjustments for missing data and multiple interim analyses. On average, we expect fewer participants to be required when there is a large treatment benefit or complete lack of benefit. For example, if the true hazard ratio is 1.5 (3 day benefit in median time to recovery), on average only 150 subjects per arm are required to provide sufficient power. The primary advantage of the

adaptive design is the ability to adapt the sample size to the observed data, thus addressing the primary hypothesis as quickly and as efficiently as possible.

We estimate that approximately 1500 participants per arm (3000 participants total if only a single intervention vs. usual care) will be required to provide 90% power for detecting a 50% reduction in the relative risk of hospitalisation and/or death. This calculation is based on the assumption of an underlying 5% combined hospitalisation and/or death rate in the Usual Care arm, with an intervention lowering the hospitalisation and/or death rate to 2.5%, with some adjustments for the multiple interim analyses. We expect fewer participants to be required to detect a 50% reduction if the event rate in the Usual Care arm is greater than 5%.

### **5.2.6 Virtual Trial Simulations**

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

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

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

## **5.3 Primary Analysis Population**

The primary analysis population is defined as all randomised participants according to the groups they were randomly allocated to as specified in the M-SAP. All other analysis populations will be defined in the M-SAP.

## **5.4 Procedures for Reporting Unplanned Deviation(s) from the Master Statistical Analysis Plan**

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

## **5.5 Qualitative sub-study analysis**

Audio-recordings of interviews will be transcribed verbatim and transcripts analysed using thematic analysis. Patient and HCP interviews transcripts will be analysed separately but findings will be compared and triangulated if deemed appropriate. Thematic analysis allows the research team to take a pragmatic approach to data collection, remaining grounded in the data but ensuring that the analysis answers the research objectives. NVivo software will be used to assist with the organisation and coding of data. Codes will be compared with one another to create



categories, grouping similar codes together. A thematic framework will be developed to code all data and represent key themes for both sets of interviews.

## **6 DATA MANAGEMENT**

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

### **6.1 Source Data**

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

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

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

### **6.2 Access to Data**

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

### **6.3 Data Recording and Record Keeping**

In accordance with the principles of Good Clinical Practice and the recommendations and guidelines issued by regulatory agencies, the design, conduct and analysis of this trial is focussed on issues that might have a material impact on the wellbeing and safety of study participants (in the community with suspected or confirmed SARS-CoV-2 infection) and the reliability of the results that would inform the care for future patients.

The critical factors that influence the ability to deliver these quality objectives are:

- to minimise the burden on thousands of busy clinicians working in an overstretched primary care setting and undertaking research during a major epidemic
- to ensure that suitable patients have access to the trial medication
- to provide information on the study to patients and clinicians in a timely and readily digestible fashion but without impacting adversely on other aspects of the trial or the patient's care

- to collect comprehensive information on the mortality and disease status

In assessing any risks to patient safety and well-being, a key principle is that of proportionality. Risks associated with participation in the trial must be considered in the context of usual care. At present, there are no proven treatments for COVID-19 for clinicians in the community to prescribe safely with a sound evidence base.

Although data entry should be mindful of the desire to maintain integrity and audit trails, in the circumstances of this epidemic, the priority is on the timely entry of data that is sufficient to support reliable analysis and interpretation about treatment effects.

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

## 7 QUALITY ASSURANCE PROCEDURES

The study will be conducted in accordance with the current approved protocol, GCP, relevant regulations and PC-CTU Standard Operating Procedures. All PIs, coordinating centre staff and site staff will receive training in trial procedures according to GCP where required. Regular monitoring will be performed according to GCP using a risk-based approach. Data will be evaluated for compliance with the protocol and accuracy in relation to source documents where possible.

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

### 7.1 Risk assessment and Monitoring

A risk assessment and monitoring plan will be prepared before the study opens and will be reviewed as necessary over the course of the study to reflect significant changes to the protocol or outcomes of monitoring activities. Monitoring will be performed by the PC-CTU Quality Assurance Manager or delegate. The level of monitoring required will be informed by the risk assessment.

### 7.2 Trial committees

The responsibilities of each group are as follows:

- Data Monitoring and Safety Committee (DMSC) - to review the data at each interim analysis as described in the Statistical Analysis section, as the updates to the randomisation scheme occur in order to ensure that the process is working correctly and to review and monitor the accruing data to ensure the rights, safety and wellbeing of the



trial participants. Composition, and roles and responsibilities of the DMSC are detailed in the DMSC charter.

- Trial Steering Committee (TSC) - the Trial Steering Committee ensure the rights, safety and wellbeing of the trial participants. They will make recommendations about how the study is operating, any ethical or safety issues and any data being produced from other relevant studies that might impact the trial. Composition, and roles and responsibilities of the TSC are detailed in the TSC charter.
- Trial Management Group (TMG) - is responsible for the day-to-day running of the trial, including monitoring all aspects of the trial and ensuring that the protocol is being adhered to. It will include Co-Investigators and will meet weekly in the first instance. . Composition, and roles and responsibilities of the TMG are detailed in the TMG charter.
- A core project team (PT) from within the TMG will meet weekly or as required for operational decision making (met daily at the start of the trial).

## 8 PROTOCOL DEVIATIONS

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

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

## 9 SERIOUS BREACHES

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

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

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

## 10 ETHICAL AND REGULATORY CONSIDERATIONS

### 10.1 Declaration of Helsinki

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

### 10.2 Guidelines for Good Clinical Practice

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

### **10.3 Approvals**

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

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

### **10.4 Other Ethical Considerations**

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

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

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

### **10.5 Reporting**

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

### **10.6 Transparency in Research**

Prior to the recruitment of the first participant, the trial will have been registered on a publicly accessible database. Results will be uploaded to the European Clinical Trial (EudraCT) Database within 12 months of the end of trial declaration by the CI or their delegate. Where the trial has been registered on multiple public platforms, the trial information will be kept up to date during the trial, and the CI or their delegate will upload results to all those public registries within 12 months of the end of the trial declaration.

### **10.7 Participant Confidentiality**

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

## **10.8 Expenses and Benefits**

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

## **11 FINANCE AND INSURANCE**

### **11.1 Funding**

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

The Department of Health & Social Care have provided the following drugs free of charge for trial Use: Hydroxychloroquine

### **11.2 Insurance**

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

### **11.3 Contractual arrangements**

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

## **12 PUBLICATION POLICY**

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

## **13 DEVELOPMENT OF A NEW PRODUCT/ PROCESS OR THE GENERATION OF INTELLECTUAL PROPERTY**

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

## **14 ARCHIVING**

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

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**16 APPENDIX A: SCHEDULE OF PROCEDURES**

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

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

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

**17 APPENDIX B: AMENDMENT HISTORY**

<b>Amendment No.</b>	<b>Protocol Version No.</b>	<b>Date issued</b>	<b>Author(s) of changes</b>	<b>Details of Changes made</b>
1 (SA1)	1.1		Emma Ogburn; Chris Butler; Gail Hayward	Inclusion criteria: change 'known heart disease' to 'Known heart disease and/or hypertension'; Exclusion criteria: exclude patients taking the following drugs: penicillamine, amiodarone, ciclosporin, chloroquine. Update section 9.6 to include vision changes and lowering of blood sugar. Update change in Funder and update Investigator list to reflect UKRI funder bid.
2 (SA2)	2.0		Emma Ogburn; Chris Butler; Gail Hayward, Hannah Swayze	Inclusion of TSC; central facility to distribute patient packs; addition of third arm; update of secondary outcomes to include WHO wellbeing questions; qualitative sub study; sign posting to other RCGP RSC study; eligibility confirmation by research nurse.
3 (SA3)	2.1		Hannah Swayze; Chris Butler; Emma Ogburn; Gail Hayward	Trial rationale; secondary outcomes to include blood test; 14 days of covid-19 symptoms; call to participant at day 2; poster
4 (SA4)	2.1		<i>No changes to the protocol</i>	
5 (SA5)	3.0		Hannah Swayze; Chris Butler; Emma Ogburn; Gail Hayward	Updated Azithromycin information; broadening of inclusion criteria; first interim analysis; primary analysis details; care home materials; administrative and typographical updates; study partner letter; recruitment via social media, care homes and pharmacies; GPs prescribe trial medication; eligibility to at least one intervention arm as well as the



				Usual Care arm; ICF may be sent to participants.
6 (SA6)	4.0		Chris Butler; Emma Ogburn; Gail Hayward; Ben Saville; Ly-Mee Yu; Hannah Swayze	Updating inclusion criteria; updating the rationale and evidence for safety of hydroxychloroquine; inclusion of a new arm, doxycycline; AE reporting for hydroxychloroquine arm; typographical clarifications.
7 (NS1)	4.0		<i>No changes to the protocol</i>	
8 (SA7)	5.0		Chris Butler; Emma Ogburn; Ben Saville; Ly-Mee Yu; Hannah Swayze	Including a second primary outcome, time to recovery, change to sample size estimation, new eligibility criteria: obesity, formatting changes, blood test process.
9 (SA8)	5.0		<i>No changes to the protocol</i>	
10 (SA9)	5.0		<i>No changes to the protocol</i>	
11 (NS2)	5.0		<i>No changes to the protocol</i>	
12 (SA10)	6.0		Chris Butler; Emma Ogburn; Hannah Swayze	Addition of inhaled corticosteroid treatment arm, enrolment to additional trials, long-term follow-up, access to NHS Digital Pillar 2 test data, removal of investigators, additional trial contact with participants for up to 12 months, changes to objectives/outcomes/time-points, removal of sampling from study
13 (NS3)	6.1		Sharon Tonner	Removal of patient already taking a treatment arm medication as an exclusion
14 (NS4)	6.1		<i>No changes to the protocol</i>	
15 (SA11)	6.2		Sharon Tonner, Hannah Swayze	Inclusion of patients who lack capacity to consent, discontinuation of azithromycin arm
16 (SA12)	7.0		Chris Butler; Emma Ogburn; Hannah Swayze;	Addition of colchicine treatment arm. Data management proportional approach. Discontinuation of doxycycline

			Emily Bongard; Julie Allen; Jienchi Dorward; Oliver Van Hecke	arm. Stylistic and typographical updates. Funding arrangements. Inclusion criteria - to include those aged 18 or over. Rephrasing secondary outcome: daily rating of how well participant feels. Statistical analysis.
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Lists details of all protocol amendments whenever a new version of the protocol is produced.

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

## 18 APPENDIX C: USUAL CARE ARM

### 1. Background and rationale

COVID-19 disproportionately affects people with comorbidities, more severe illness, and who are older. The disease causes considerable morbidity and mortality in this population group in particular, and is having a devastating effect on people's health, and society in the UK and internationally.(2-4, 8) So far, there are no specific treatments for COVID-19 that have been proven in rigorous clinical trials to be effective and that can be used in the community. Clinicians managing possible COVID-19 in the community will make clinical judgements about best treatment based on the clinical situation, but care is usually supportive to begin with, unless patients deteriorate and require hospital admission (<https://www.nice.org.uk/guidance/ng163>). The National Institute for Health and Care Excellence does not recommend the immediate use of antibiotics unless there are signs of pneumonia (<https://www.nice.org.uk/guidance/ng163>).

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

### 2. Changes to outcome measures

None

### 3. Detail of intervention

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

#### a. Investigational Medicinal Product (IMP) description

Not applicable

#### b. Storage of IMP

Not applicable

### 4. Safety reporting

Mechanisms for safety reporting are outlined in the trial protocol.

## 19 APPENDIX D: USUAL CARE PLUS HYDROXYCHLOROQUINE ARM (DISCONTINUED)

### 1. Background and rationale

#### a. Evidence for potential Hydroxychloroquine benefits in COVID-19

A candidate intervention for COVID-19, a drug called hydroxychloroquine, has become available following early evaluation in some studies in China.(9, 10) Hydroxychloroquine is a hydroxylated version of the drug chloroquine.(10, 11) Both agents are commonly in use as anti-malarials, and are used in a variety of auto-immune diseases. They have received significant recent interest as potential modifiers of disease activity in COVID-19. (10, 12, 13) Hydroxychloroquine is already available within the NHS on prescription for other indications, and has a generally benign safety profile.(14) Chloroquine is available to buy in the UK over the counter in some formulations and is used as antimalarial prophylaxis and treatment.

Chloroquine is known to block virus infection by increasing endosomal pH required for virus/cell fusion, as well as interfering with the glycosylation of cellular receptors of SARS-CoV-2.(5) Besides its antiviral activity, chloroquine has an immune-modulating activity, which may synergistically enhance its antiviral effect *in vivo*.(11) Chloroquine is widely distributed in the whole body, including lungs, after oral administration.(10) The EC<sub>90</sub> value of chloroquine against the 2019-nCoV in Vero E6 cells was 6.90 µM in one study (9) which can be clinically achievable as demonstrated in the plasma of rheumatoid arthritis patients who received 500 mg administration.(14)

Hydroxychloroquine has been found to be effective against intracellular micro-organisms including malaria and intracellular bacteria *Coxiella burnetii* and *Tropheryma Whipplei*.(11) Both chloroquine and hydroxychloroquine have been shown to have *in vitro* antiviral activity against SARS coronavirus in a number of studies.(11) Most recently activity against SARSCOV2 was shown to be greater for hydroxychloroquine than chloroquine (15).

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

1. **The Mahévas study** was an observational study that assessed whether hydroxychloroquine reduced the need for transfer to ICU in patients already sick enough to be hospitalised.(16) It focussed on sicker patients with hypoxic pneumonia, some requiring ITU care. It did not find a difference in transfers to ICU. So the question and population in the Mahevas study are very different compared to PRINCIPLE. Most importantly, unlike PRINCIPLE, the Mahevas study is **not a randomised clinical trial**. Numbers were relatively small (n=181), and it is at high risk of bias due to the observational design.

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

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

**2. The Tang study** was a hospital-based, randomised study and included 150 patients; randomisation was done using sealed envelopes.(17) The trial found no difference in the proportion of patients with two sequential negative swab results.

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

**3. The Mehra study** published in the Lancet on 22.05.2020 reported an association between hydroxychloroquine use and cardiac events and mortality amongst patients hospitalised with COVID-19.(18) The *observational* study design is inherently susceptible to bias, the study data integrity has been queried given the homogeneity of the baseline characteristics, the adequacy of the adjustment for confounders cannot be assessed from the published methods, and the registries used are in a different patient population compared to PRINCIPLE. Patients were much sicker and more advanced in the illness than in PRINCIPLE. The authors themselves state that "*Randomised clinical trials will be required before any conclusion can be reached regarding benefit or harm of these agents (hydroxychloroquine and chloroquine) in COVID-19 patients.*" The authors also state "These data do not apply to the use of any treatment regimen used in the ambulatory, out-of-hospital setting." This study has proved hugely controversial on social media, with a number of methodological and data integrity concerns already raised, for example:

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

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

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

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

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

**Regarding safety**, multivariable adjusted analyses with inverse probability weighting revealed no significant association between treatment with hydroxychloroquine and intubation or death (HR 1.04 (95% CI 0.82 – 1.32)). Whilst the patient population in this study is different to that of PRINCIPLE, it is interesting that the findings contrast with those of a recent Lancet study published by Mehra *et al*. One possible reason for the difference is that patients receiving interventions like hydroxychloroquine in the study by Mehra *et al* were sicker than those in the study’s control group. This may have arisen through use of crude measures to account for baseline disease severity (qSOFA score and SpO<sub>2</sub> < 94%) in their propensity score matching model, and may also explain the big differences seen in patients requiring mechanical ventilation between controls (7.7%) and those in intervention groups (20-21.6%).

**5. Boulware** and colleagues conducted a Covid-19 postexposure prophylaxis, placebo controlled randomised trial of hydroxychloroquine in 821 asymptomatic patients; 11.8% of those taking hydroxychloroquine vs 14.3 of those taking placebo experienced a new illness compatible with COVID-19 (absolute difference -2.4%) but this difference was not statistically significant, indicating no evidence of benefit from the hydroxychloroquine. (20)

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



### Earlier studies of hydroxychloroquine for COVID-19

**1. Chen** and colleagues conducted a *randomised* controlled trial to test the effectiveness of hydroxychloroquine in 30 adult patients who tested positive for COVID-19 in China.(21) Patients in the treatment group received 400mg of hydroxychloroquine for 5 days, while the control group received usual care. The result of a nasopharyngeal swab on Day 7 was used as the primary outcome. The intention- to- treat analysis revealed that the treatment group did not differ from the control group in the number of patients testing negative for COVID-19 on Day 7 (13 versus 14 patients), nor the duration of illness (all  $P>0.05$ ).

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

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

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

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

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



## In summary

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

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

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

## 2. Eligibility criteria specifically related to hydroxychloroquine

Inclusion criteria:

Exclusion criteria:

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

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

- Known congenital or documented QT prolongation
- Known retinal disease

### 3. Outcome measures related to hydroxychloroquine

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

### 4. Detail of intervention

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

#### a. Investigational Medicinal Product (IMP) description

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

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

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

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

#### b. Storage of IMP

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

For hydroxychloroquine, GP practices can order a supply of trial medication from Public Health England using the existing ImmForm process. GPs will be provided with an envelope by the trial team which will be labelled appropriately for trial medication, and they will add the patient's details to this label. This pack, containing instructions on using the medication will be provided to the patient or their representative.

### **c. SmPC precautions and concomitant medication**

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

#### **i. Precautions**

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

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

#### **ii. Concomitant medication**

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

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

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

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

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

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

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

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

### **iii. Pregnancy and Breastfeeding**

A moderate amount of data on pregnant women (between 300 – 1000 pregnancy outcomes), including prospective studies in long-term use with large exposure, have not observed a significant increased risk of congenital malformations or poor pregnancy outcomes. Hydroxychloroquine crosses the placenta. Only limited non-clinical data are available for hydroxychloroquine, data on chloroquine have shown developmental toxicity at high supratherapeutic doses and a potential risk of genotoxicity in some test systems. Therefore, hydroxychloroquine sulfate should be avoided in pregnancy except when, in the judgement of the physician, the individual potential benefits outweigh the potential hazards. Careful consideration should be given to using hydroxychloroquine during lactation, since it has been shown to be excreted in small amounts in human breast milk, and it is known that infants are extremely sensitive to the toxic effects of 4-aminoquinolines.

Pregnancy and breastfeeding are exclusion criteria for the hydroxychloroquine arm of the PRINCIPLE trial.

## **5. Safety reporting**

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

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

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

## 20 APPENDIX E: USUAL CARE PLUS AZITHROMYCIN ARM (DISCONTINUED)

### 1. Background and rationale

#### a. Evidence for potential Azithromycin benefits in COVID-19

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

Firstly, Azithromycin appears to have some anti-viral mechanisms. In COVID-19, Azithromycin appears to inhibit viral replication and therefore reduces shedding. In the small open observational trial of Gautret *et al* the addition of azithromycin to hydroxychloroquine (HCQ) (at 200 tds for 10 days) in 6 of the 14 HCQ subjects of the total 36 COVID-19 patients in the study significantly reduced viral shedding at 3 days to 15% (one subject) versus 70% in the HCQ arm and 95% in the indirect control arm, with no shedding at 6 days in the combination arm versus 50% and 90% respectively.(22) Azithromycin was also used in some Chinese observational and interventional studies.

Azithromycin has also been shown to be active *in vitro* against Zika and Ebola viruses,(23-25) and to prevent severe respiratory tract infections when administrated to patients suffering viral infection.(26) Inhibition of viral infections by azithromycin may be linked to its suppressive effect on the production of viral interferon.(27) Longer term administration of low dose azithromycin in COPD has been shown to suppress proinflammatory cytokine production, potentiate macrophage phagocytosis and anti-inflammatory cytokine expression.(28-30) Azithromycin use is also associated with a decrease in the expression of human HLA (human leukocyte antigen) complex molecules in the respiratory tract, including HLA-A, HLA-B, HLA-DPA1, HLA-DRA, HLA-DRB4.(31)

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

An important secondary pathway to severe illness and death with COVID-19 may be secondary infection and sepsis in the immune-compromised state, especially secondary community or hospital acquired pneumonia. Older people are more susceptible to pneumonia because of comorbidities, a weakened immune system and are therefore more likely to die.(32) The onset of pneumonia in the elderly can often be rapid, and for severe pneumonia, the prognosis is poor: as many as one in five will die.(32) Severe pneumonia is more prevalent the older you are and in those with more serious underlying diseases.(33) The leading cause of death is respiratory insufficiency. Death has been shown to increase in those not responding to initial antimicrobials, and consequently, the initial selection of the agent is important.

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

Medicare inpatients over 65 with pneumonia found that initial treatment with a second-generation cephalosporin plus macrolide ([HR, 0.71; 95% CI, 0.52-0.96), a non-pseudomonas third-generation cephalosporin plus a macrolide (HR, 0.74; 0.60-0.92), or a fluoroquinolone alone (HR, 0.64; 0.43-0.94) was associated with lower 30-day mortality.(34)

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

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

## **2 Changes to outcome measures**

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

## **3 Eligibility criteria specifically related to azithromycin**

Inclusion criteria: No changes

Exclusion criteria:

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

## **4 Detail of intervention**

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

### **a. Investigational Medicinal Product (IMP) description**

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

Special instructions:

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

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

Marketing authorisation number: PL 00289/1570

### **b. Storage of IMP**

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

### **c. SmPC precautions and concomitant medication**

#### **i. Precautions**

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

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

#### **ii. Concomitant medications**

Effects of other medicinal products on azithromycin:

#### *Antacids*

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

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

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



### *Fluconazole*

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

### *Nelfinavir*

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

### *Rifabutin*

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

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

### *Terfenadine*

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

### *Cimetidine*

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

Effect of azithromycin on other medicinal products:

#### *Ergotamine derivatives*

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

#### *Digoxin and colchicine (P-gp substrates)*

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

#### *Coumarin-Type Oral Anticoagulants*

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

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

#### *Cyclosporin*

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

#### *Theophylline*

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

#### *Trimethoprim/sulfamethoxazole*

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

#### *Zidovudine*

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

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

#### *Astemizole, alfentanil*

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

#### *Atorvastatin*

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

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

#### *Carbamazepine*

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

#### *Cisapride*

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

#### *Cetirizine*

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

#### *Didanosins (Dideoxyinosine)*

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

#### *Efavirenz*

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

#### *Indinavir*

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

#### *Methylprednisolone*

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

#### *Midazolam*

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

#### *Sildenafil*

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

#### *Triazolam*

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

### **iii. Fertility, pregnancy and lactation**

#### *Pregnancy*

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

### **5 Safety reporting**

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

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

## 21 APPENDIX F: USUAL CARE PLUS DOXYCYCLINE ARM (DISCONTINUED)

### 1. Background and rationale

#### a. Evidence for potential doxycycline benefits in COVID-19

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

The rationale for testing doxycycline is based on three reasons:

Firstly, doxycycline may have direct antiviral activity against SARS-CoV-2 based on computer modelling. Analysing all the proteins encoded by SARS-CoV-2 genes and then predicting potential targets by performing target-based virtual ligand screening, doxycycline ranked in the group of compounds with the highest binding affinity to 3CLpro (3-chymotrypsin-like protease). 3CLpro is the main protease in SARS-CoV-2 which is critical in the life-cycle of the virus (35).

Secondly, doxycycline has known anti-inflammatory effects in various human diseases by inhibiting mitogen-activated protein kinase (MAPK) and SMAD pathways (36), as well as potent antioxidant properties (37). Doxycycline reduces the hyperinflammation associated with severe COVID-19 by antagonising metalloproteinases such as MMP9 that are linked with lung injury, including SARS and ARDS (38).

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

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

An important secondary pathway to severe illness and death with COVID-19 may be secondary infection and sepsis in the immune-compromised state, especially secondary community or hospital acquired pneumonia. Older people are more susceptible to pneumonia because of comorbidities, a weakened immune system and are therefore more likely to die. (32) The onset of pneumonia in the elderly can often be rapid, and for severe pneumonia, the prognosis is poor: as many as one in five will die. (32) Severe pneumonia is more prevalent the older you are and in those with more serious underlying diseases. (33) The leading cause of death is respiratory insufficiency. Death has been shown to increase in those not responding to initial antimicrobials, and consequently, the initial selection of the agent is important. Common causative organisms in the elderly admitted to the hospital with pneumonia include *Haemophilus influenza*, *Staphylococcus aureus*, *Streptococcus pneumoniae* and less commonly, atypical organisms, such as *Mycoplasma pneumoniae* and *Klebsiella pneumoniae*. All these organisms fall under doxycycline's antimicrobial spectrum.

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

treated in the community if: the likely cause is bacterial or; it is unclear whether the cause is bacterial or viral and symptoms are more concerning or; they are at high risk of complications (older or frail patients, pre-existing comorbidity or have a history of severe illness following previous lung infection).(39) Doxycycline will have at least as broad a spectrum of action as azithromycin in terms of bacterial infections with the potential anti-viral and anti-inflammatory effects.

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

## **2. Changes to outcome measures**

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

## **3. Eligibility criteria specifically related to doxycycline**

Inclusion criteria: No changes

Exclusion criteria:

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

## **4. Detail of intervention**

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

### **a. Investigational Medicinal Product (IMP) description**

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

Special instructions:

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

The marketing authorisation holder is:

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

**b. Storage of IMP**

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

**c. SmPC precautions and concomitant medication**

**i. Precautions**

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

**ii. Concomitant medications**

*Warfarin*

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

**5. Safety reporting**

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

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



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

### 1. Background and rationale

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

Inhaled corticosteroids (ICS) are a commonly prescribed class of medication throughout the world. They are reasonably cheap and have been used widely for the last 60 years. The inhaled action and type2 pneumocyte target of COVID make ICS a potential therapeutic agent in COVID-19(40). They have been shown to be very effective in improving asthma and COPD care over the long term, where the recommendation is that most, if not all, patients with asthma should be prescribed an inhaled corticosteroid(41)·(42) and up to 90% of patients with COPD in the UK are prescribed ICS(43). The rationale of ICS is to reduce the inflammatory process that underlies exacerbations, which can be triggered by viruses in asthma and COPD. Systemic corticosteroids have been found to be effective at reducing mortality amongst hospitalised patients with COVID-19 [46, 47], but it is not known whether pre-hospital treatment with ICS is also beneficial.

Further evidence is as described below:

#### Evidence from the ARDS literature

ICS in patients at risk of acute respiratory distress syndrome (ARDS) have been shown to improve physiology and reduce inflammatory markers(44). In patients admitted to hospital at risk of ARDS or acute lung injury, there was an almost 50% reduction of ARDS in patients that were using ICS pre-admission, even controlling for covariates such as age, gender and chronic respiratory disease(45). Moreover, this ICS effect can also be seen to improve pulmonary physiology(46).

#### Potential mechanism of efficacy

Recently published *in vitro* data suggest a role for ICS inhibition of coronavirus replication in infected epithelial cells(47), whilst there is an indication that there is accelerated hyperinflammation at the onset of SARS-CoV-2 infection(48), which potentially can be modified by anti-inflammatory therapy. This suggests a plausible mechanism for ICS efficacy against COVID-19 in which ICS has a dual role: firstly, toning down the inflammatory “runaway train” (ARDS-like) response affecting a minority of COVID-19 patients; and secondly, inhibiting viral replication. It has long been known that the ICS effect on epithelial cells is as a direct consequence of gene transcription(49), and investigation of gene expression of ACE2 and TMPRSS2 in the sputum of asthmatic patients has very recently demonstrated lower expression of these key receptors in the presence of ICS(50). Furthermore, ICS attenuates expression of the ACE2 receptor in human and murine *in vitro* and *in vivo* models(51). This is of relevance as the SARS-CoV-2 mechanism of action is upon direct action of the ACE2 receptor, a receptor highly expressed on epithelial cells in the oral mucosa and type 2 alveolar cells and the serine protease TMPRSS2 for SARS-CoV-2 spike protein priming(52, 53). Furthermore, there is experimental evidence that inhaled corticosteroids inhibit coronavirus replication *in vitro*(54, 55). SARS-CoV-2 binds to cells via the angiotensin converting enzyme 2 (ACE2) receptor. ACE2 is highly expressed on epithelial cells in the oral mucosa and type 2 alveolar epithelial cells. The use of inhaled corticosteroids as a therapy suggests it would target the cells of interest. Furthermore, the primary action of the inhaled steroids is on the type 2 pneumocytes where viral replication is going to be at its most, where we know that ACE2 receptor expression is high.

## 2. Changes to outcome measures

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

## 3. Eligibility criteria specifically related to ICS

Inclusion criteria:

Age criteria: Patients aged  $\geq 65$  years, or Patients aged 50-64 years and meeting at least one of the following criteria:

- Known weakened immune system due to a serious illness or medication (e.g. chemotherapy);
- Known heart disease and/or a diagnosis of high blood pressure;
- Known asthma or lung disease;
- Known diabetes;
- Known mild hepatic impairment;
- Known stroke or neurological problem;
- Self-report obesity or body mass index  $\geq 35 \text{ kg/m}^2$

Exclusion criteria:

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

## 4. Detail of intervention

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

### a. Investigational Medicinal Product (IMP) description

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

### b. Storage of IMP

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

**c. SmPC precautions and concomitant medication**

**iii. Precautions**

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

**iv. Concomitant medications**

Largely, there is no restriction to concomitant medications using inhaled budesonide. The SmPC states that concomitant treatment with ketoconazole, HIV protease inhibitors or other potent CYP3A inhibitors may increase systemic budesonide levels, but that this is of little clinical significance for a short term treatment of 2 weeks, which is the duration of IMP use in the trial.

**5. Safety reporting**

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

Common and/or potential side effects from IMP include:

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

These are all reversible upon ceasing IMP.

## 23 APPENDIX H: USUAL CARE PLUS COLCHICINE

### 1. Background and rationale

#### a. Evidence for potential benefits of colchicine in COVID-19 illness

Colchicine is licenced and widely used in the UK for the treatment of acute gout and has been investigated as a possible treatment for COVID-19. Reyes and colleagues (56) have summarised existing clinical evidence for colchicine for COVID-19 thus:

“A retrospective single-centre study of 87 ICU patients with COVID-19 demonstrated a lower risk of death in patients on colchicine (adjusted HR 0.41, 95% CI 0.17 to 0.98).(57) The Greek Effects of Colchicine in COVID-19 (GRECCO-19) trial was the first prospective open-label randomised trial evaluating colchicine versus usual care in early hospitalised patients. This study of 105 patients found a significant reduction in the primary clinical outcome of a two-point deterioration on WHO disease severity scale.(58) An Italian study compared 122 hospitalised patients who received colchicine plus standard-of-care (lopinavir/ritonavir, dexamethasone or hydroxychloroquine) with 140 hospitalised patients receiving standard-of-care alone. Colchicine had a significant mortality benefit versus controls (84% vs 64% survival).(59) A third prospective study randomised 38 hospitalised COVID-19 patients to colchicine or placebo in a double-blinded manner.(60) Patients receiving colchicine had less need for supplemental oxygen at day 7 (6% vs 39%) and were more likely to be discharged at day 10 (94% vs 83%). Colchicine subjects also had greater reduction of CRP, and no increase in serious adverse events.”

More recently, a systematic review and meta-analysis (in preprint) supports the notion that colchicine lowers the risk of mortality (HR of 0.25, 95% CI [0.09, 0.66], six studies, n=5,033) However, the summary point estimate from the three included RCTs showed a signal towards mortality benefit that was not statistically significant among patients receiving colchicine versus placebo (OR 0.49, 95% CI [0.20, 1.24]).(61)

The COLCORONA randomised clinical trial has now reported in a pre-print.(62) It randomised 4488 patients to treatment with colchicine (0.5 mg twice daily for 3 days and once daily thereafter) or placebo for 28 days. The primary endpoint occurred in 4.7% of the patients in the colchicine group and 5.8% of those in the placebo group (odds ratio, 0.79; 95.1% confidence interval (CI), 0.61 to 1.03; P=0.08). Among the 4159 patients with PCR-confirmed COVID-19, the primary endpoint occurred in 4.6% and 6.0% of patients in the colchicine and placebo groups, respectively (odds ratio, 0.75; 95% CI, 0.57 to 0.99; P=0.04). In these patients with PCR-confirmed COVID-19, the odds ratios were 0.75 (95% CI, 0.57 to 0.99) for hospitalization due to COVID-19, 0.50 (95% CI, 0.23 to 1.07) for mechanical ventilation, and 0.56 (95% CI, 0.19 to 1.66) for death. Serious adverse events were reported in 4.9% and 6.3% in the colchicine and placebo groups (P=0.05); pneumonia occurred in 2.9% and 4.1% of patients (P=0.02). Diarrhoea was reported in 13.7% and 7.3% in the colchicine and placebo groups (P<0.0001).

This large-scale study of early treatment in those 18 years and over with more severe illness or comorbidity suggests that colchicine treatment early on in the illness reduces the need for hospitalisation or COVID-19. However, the study did not assess impact on recovery, so we don't

know from this study if colchicine reduced symptom burden. This is important as those receiving colchicine, predictably, experienced more gastrointestinal side-effects. The study did not recruit to target and some of the findings are not statistically significant. However, these findings need replication before this drug can be considered for routine use for COVID-19.

Another Phase 3 trial in Canadian pre-hospital and hospital settings is investigating colchicine paired with aspirin or interferon beta (ACTCOVID). The trial is still in progress ([www2.phri.ca/ACT-COVID-19/](http://www2.phri.ca/ACT-COVID-19/)).

### **b. Potential mechanism of action**

Colchicine is a broad-spectrum anti-inflammatory agent.(63-66) Colchicine inhibits cellular transport and mitosis by binding to tubulin and preventing its polymerisation as part of the cytoskeleton transport system.(67) Several of the biological therapies that have been studied and/or used in the setting of severe COVID-19 target some of the same pathways as colchicine, including IL-1 $\beta$  (ie, anakinra) and IL-6 (ie, tocilizumab and sarilumab). Colchicine differs from these agents in having pleiotropic mechanisms of action, being less potent on any single target, and being an oral agent. Potential benefits of colchicine compared to these biological therapies when used in the midst of cytokine storm, are that colchicine is not immunosuppressive, is not known to increase risk of infection, and is inexpensive.

There is evidence that the inflammasome is activated in COVID-19 and that the degree of activation is correlated with disease severity.(68) Inflammasomes are key components of effective host immune responses to pathogens. Excessive inflammasome activation (specifically NLRP3 inflammasome) is implicated in chronic inflammatory diseases such as inflammatory bowel disease, rheumatoid arthritis and gout, and with ARDS and ALI (acute lung injury) pathology following respiratory viral infections. Additionally, colchicine may have relevance to COVID-19 associated inflammatory pathology that include: inhibition of neutrophil chemotaxis in response to cytokines, inhibition of NF $\kappa$ B activation (a protein complex that controls transcription of DNA, cytokine production and cell survival) or expression, inhibition of neutrophil adhesion to endothelium, inhibition of neutrophil respiratory burst and reactive oxygen species generation, reduced TNF receptor expression on macrophages and endothelial cells and increased TGF $\beta$  expression(67) Of note though is that many of these latter actions of colchicine occur at much lower concentrations that are required for NLRP3 inflammasome activation in response to MSU crystals. Symptoms such as fever, joint and muscle ache, and headache may be ameliorated by a general anti-inflammatory action.

Therefore, when used early in the course of COVID-19, colchicine may prevent the progression from inflammatory activation to a hyperinflammatory state. The potential benefits of colchicine may therefore be maximised when used in the community, where earlier treatment could alleviate symptom burden, and prevent disease progression, hospitalisation and adverse outcomes.

## **2. Changes to outcome measures**

The addition of the usual care plus colchicine arm will not require any changes to outcome measures.

### 3. Eligibility criteria specifically related to colchicine

Inclusion criteria: No changes required

Exclusion criteria:

- Hypersensitivity to the active substance or to any of the excipients listed in section (Lactose, Pregelatinised Maize Starch, Stearic Acid, Purified Talc, Purified Water, Ethanol 96%)
- Known or suspected pregnancy
- Breastfeeding
- Women of childbearing potential (premenopausal female that is anatomically and physiologically capable of becoming pregnant\*) and not prepared to use highly effective contraception for the 28 day duration of follow up in the study\*\*
- Known blood dyscrasias
- Known severe renal impairment or requiring dialysis
- Known severe hepatic impairment
- Currently taking any of the following drugs: colchicine, clarithromycin, erythromycin, ketoconazole, itraconazole, voriconazole, HIV protease inhibitors (e.g. ritonavir, atazanavir), cobicistat, verapamil, diltiazem, cyclosporin, quinidine, disulfiram, grapefruit juice
- Inflammatory bowel disease or chronic diarrhoea

\* As recorded by the participant on the screening form and confirmed on Day 3 telephone call

*\*\*Highly effective methods have typical-use failure rates of less than 1% and include male or female sterilisation and long-acting reversible contraceptive (LARC) methods (intrauterine devices and implants). Women using another method of contraception, such as a combined hormonal method, progestogen only pill or injection, are eligible **if** they are willing to use an additional barrier method (e.g. male condom) for the 28 day duration of follow-up in the trial.*

The Patient Information Sheet Appendix, which the participant must read prior to providing informed consent, will clearly state the exclusion criteria listed above and the participant will be asked if they meet any of these exclusion criteria at the screening stage of the trial. The assessing clinician will then review the participant's responses against their medical record to confirm eligibility.

### 4. Detail of intervention

Participants randomised to the usual care plus colchicine arm will receive usual clinical care as per NHS guidelines, plus 500 micrograms of colchicine to be taken each day for 14 days. We will use the IMP distribution methods described in the protocol to deliver IMP to participants.

Pharmacokinetic modelling shows that for a given dose of colchicine plasma exposure is greater in older (especially female) people than younger people; the target patient population for this study will be predominantly older subjects. Colchicine is also subject to accumulation in leucocytes- a target cell in this COVID19. Taking these factors into account and given the relatively



narrow therapeutic index of colchicine, the dosing regimen will be 500 microgrammes daily for 14 days. A loading dose such as that used in the COLCORONA study and the use of a higher daily dose increases the risk of dose related adverse drug reactions (ADRs). Given the outpatient setting for this study with limited opportunity for laboratory and clinical monitoring, the proposed dose is expected to achieve a balance between clinically meaningful exposure in target cells while minimising the risk of ADRs. Some other studies have treated for longer than 14 days (7) but the natural history of COVID19 is that in most cases the course of disease for that individual has been established within 2 weeks.

It is acknowledged that the total dose of colchicine administered in this study (7 mg) is modestly greater than that recommended for treatment of acute gout (6 mg) but the proposed regimen has been designed to minimise the risk of ADRs.

Note: The British National Formulary advises a maximum total of 6mg per treatment course for acute gout (1mg less than the total for this study). However, the treatment course for gout is given over up to three days at 500mcg 2-4 times per day initially. In the PRINCIPLE Trial, the treatment will be spread over two weeks at a lower daily dose.

We propose a shorter duration and no loading dose compared to the COLCORONA study (62), given the incidence of side-effects found in that study, and that by two weeks, most patients with COVID-19 have either recovered or been hospitalised. Therefore, the window of opportunity for a positive benefit is mainly over two weeks, and a shorter duration without a loading dose will minimize risk of side-effects, while offering potential benefit. There are no dose-findings studies for colchicine in COVID-19. Our proposed dosing regime is based on expert pharmacological opinion and an appraisal of side-effects balanced against potential benefit in a large-scale community study without face-to-face recruitment and monitoring.

#### **a. Investigational Medicinal Product (IMP) description**

Colchicine 500 microgram ( $\mu$ g) tablets. The tablets are for oral administration. One tablet to be taken daily by mouth for 14 days (14 tablets in total).

Special instructions: Tablets should be swallowed whole with a glass of water.

#### **Manufacturer:**

The Marketing Authorisation holder is:

Accord-UK Ltd

(Trading style: Accord)

Whiddon Valley

Barnstaple

Devon

EX32 8NS

Marketing authorisation number is: PL 0142/0918

#### **Labelling and QP release:**

Vertical Pharma Resources Ltd (trading as IPS Pharma), 41 Central Avenue, West Molesey, KT8 2QZ, UK



Authorisation number: WDA(H) 32879

**b. Storage of IMP**

Colchicine: This medicine does not need any special storage conditions, but we will ask participants to store the medication at room temperature. The medication will be stored in locked cupboards in restricted access rooms in the Nuffield Department of Primary Care Health Sciences; in locked cupboards in restricted access rooms in GP Practices; in Pharmacies.

**c. SmPC Precautions, concomitant medications, pregnancy and lactation****i. SmPC Precautions**

Colchicine is a commonly prescribed drug in UK primary care and has a well-described safety profile due to its regulatory assessments for the authorisation in gout. Typical treatment doses for acute gout are 500 micrograms 2–4 times a day until symptoms relieved, maximum 6 mg per course.

Colchicine is teratogenic in animal studies and contraindicated in patients with severe renal (including patients undergoing haemodialysis) or severe hepatic impairments. Colchicine may cause severe bone marrow depression (agranulocytosis, aplastic anaemia, thrombocytopenia) and blood cell dyscrasia.

Colchicine is potentially toxic with a narrow therapeutic window.

Symptoms of acute overdosage may be delayed (3 hours on average): nausea, vomiting, abdominal pain, haemorrhagic gastroenteritis, volume depletion, electrolyte abnormalities, leucocytosis, hypotension in severe cases. The second phase with life threatening complications develops 24 to 72 hours after drug administration: multisystem organ dysfunction, acute renal failure, confusion, coma, ascending peripheral motor and sensory neuropathy, myocardial depression, pancytopenia, dysrhythmias, respiratory failure, consumption coagulopathy.

Patients at particular risk of toxicity are those with renal or hepatic impairment, gastrointestinal or cardiac disease, and patients at extremes of age. However, colchicine has a good safety profile when used according to the established therapeutic guidelines, and toxicity is rare if the recommended doses are not exceeded.

In PRINCIPLE, we exclude patients with known severe renal and known liver impairment, and have used a cautious dosing regimen, with no loading dose and low daily dose, to minimise risk in participants with other less severe co-morbidities. Our dosing schedule is also shorter in duration than the 30 days used in the large scale, remotely managed COLCORONA trial.<sup>(62)</sup> In addition, we will mitigate the risk of toxicity by asking each participant taking colchicine the number of tablets remaining via their diary entry to ensure drug accountability.

**ii. Concomitant medications**

Colchicine is a substrate for both CYP3A4 and the transport protein P-gp. In the presence of CYP3A4 or P-gp inhibitors, the concentrations of colchicine in the blood increase. Toxicity, including fatal cases, have been reported during concurrent use of CYP3A4 or P-gp inhibitors such as macrolides (clarithromycin and erythromycin), ciclosporin, ketoconazole, itraconazole, voriconazole, HIV protease inhibitors, calcium channel blockers (**verapamil** and **diltiazem**) and disulfiram.

Colchicine is contraindicated in patients with renal or hepatic impairment who are taking a P-gp inhibitor (e.g. ciclosporin, verapamil or quinidine) or a strong CYP3A4 inhibitor (e.g. ritonavir, atazanavir, indinavir, clarithromycin, telithromycin, itraconazole or ketoconazole).

Therefore, patients using the above medications will not be eligible for enrolment into the colchicine arm of PRINCIPLE.

### iii. Fertility, pregnancy and lactation

Pregnancy and breast-feeding are exclusions for the colchicine arm.

Women of childbearing potential (premenopausal female that is anatomically and physiologically capable of becoming pregnant) and not prepared to use highly effective contraception for the 28 day duration of follow up in the study are excluded from the trial.

## 5. Safety reporting

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

Common and/or potential side effects that may be associated with colchicine include:

Abdominal pain, diarrhoea\*, nausea, vomiting.

A meta-analysis of 35 randomised trials of colchicine versus placebo found that the most common and significant adverse effect was diarrhoea. The only other adverse effect that occurred at a greater frequency than placebo was a set of pooled gastrointestinal symptoms including nausea, vomiting, diarrhoea, abdominal pain, loss of appetite, and bloating.(69, 70)

Rare side effects that may be associated with colchicine:

Agranulocytosis; alopecia; bone marrow disorders; gastrointestinal haemorrhage; kidney injury; liver injury; menstrual cycle irregularities; myopathy; nerve disorders; rash; sperm abnormalities; thrombocytopenia

*\* Side effects that may be associated with COVID-19*

We will report SAEs as defined in the main protocol for hospitalisation and/or death. Participants record symptoms and adverse events on their diary card. Events rated as a 'major problem' will be assessed by a clinician for potential reporting as an SAE.

### **Drug Accountability**

We will telephone all participants on Day 3 after randomisation to confirm that they have received their medication. For those receiving a trial treatment, 3 attempts are made to contact the participant to confirm receipt of the medication.

If we are unable to contact patients in the colchicine group, we will confirm and log IMP receipt by checking the patient's daily diary, where they are asked on a daily basis whether they have taken their trial treatment and how many tablets they have left. We can also check via the DHL portal, whether the participant pack containing the medication has been received by the participant, for additional confirmation. IMP receipt will be logged on the central IMP log.

## 24. Supplementary Material

### A. Abbreviations

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

**B. Key Trial Contacts**

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

	<p>(0)20 7594 8704</p> <p><b>DMSC Members:</b> Prof Simon Gates          Cancer Research Clinical Trials Unit (CRCTU)          Institute of Cancer and Genomic Sciences          University of Birmingham          Edgbaston          Birmingham          B15 2TT  <a href="mailto:S.Gates@bham.ac.uk">S.Gates@bham.ac.uk</a></p> <p>Prof Gordon Taylor          College House,          University of Exeter, St Luke's Campus,          Heavitree Road,          Exeter, EX1 2LU, UK  <a href="mailto:g.j.taylor@exeter.ac.uk">g.j.taylor@exeter.ac.uk</a></p> <p>Prof Nick Francis          Primary Care and Population Science,          University of Southampton, Southampton, UK.  <a href="mailto:Nick.Francis@soton.ac.uk">Nick.Francis@soton.ac.uk</a></p> <p>Dr Patrick White          7th Floor          Capital House          Guy's          United Kingdom  <a href="mailto:Patrick.white@kcl.ac.uk">Patrick.white@kcl.ac.uk</a></p>
	<p><b>TSC Chair</b>          Prof Paul Little,          Primary Care and Population Science,          University of Southampton, Southampton, UK.  <a href="mailto:P.Little@soton.ac.uk">P.Little@soton.ac.uk</a></p> <p><b>TSC Members</b>          Prof Philip Hannaford,          NHS Professor of Primary Care          University of Aberdeen, Aberdeen, UK  <a href="mailto:p.hannaford@abdn.ac.uk">p.hannaford@abdn.ac.uk</a></p> <p>Prof Matt Sydes,          Professor of Clinical Trials &amp; Methodology,          MRC Clinical Trials Unit, University College of London, London, UK  <a href="mailto:m.sydes@ucl.ac.uk">m.sydes@ucl.ac.uk</a></p> <p><i>PPI representatives</i>          Ms Carol Green          Mr Tim Mustill</p>

### C. Objectives and Outcome Measures

	Objectives	Outcome Measures	Timepoint (s)
Primary	To assess the effectiveness of trial treatments in reducing 1) Time to recovery, for patients 2) Hospitalisation and/or death.	1) Time to self-reported recovery, defined as the first instance that a participant reports feeling recovered from possible COVID-19, and 2) Hospitalisation and/or death	Within 28 days of randomisation Patient report, Study Partner report, medical records, Daily online symptom scores
Secondary	To explore whether trial treatment will affect  1) Participant reported illness severity, reported by daily rating of how well participant feels. 2) Duration of severe symptoms and symptom recurrence 3) Contacts with the health services 4) Consumption of antibiotics 5) Hospital assessment without admission 6) Oxygen administration 7) Intensive Care Unit admission 8) Mechanical ventilation 9) Duration of hospital admission	1-3. Participant reports daily and monthly (after 28 days) symptoms. 4. Contacts with health services reported by patients and/or captured by reports of patients' medical records if the practice is a member of the RCGP RSC network 5. Bi-weekly reports from participants' primary care medical records 6-10. Patient report/carer report/medical record in primary and secondary care 11. WHO-5 Well Being Index 12. Reports of new infections in the household (from daily questionnaire) 13. Swab test results will indicate an "Intention to	Daily online symptom scores.  Telephone call or text on days 2, 7, 14 and 28 and once a month for 12 months if data is not obtained through the online diary.  GP notes review if available through Oxford RCGP RSC network; otherwise, other sources of routinely collected data after 28 days. Medical notes review for up to 10 years.  HES/ONS/EMIS/Medical record data linkage after 28 days if patients have been assessed in hospital  Swab result from medical records, the



	10) Negative effects on well being 11) New infections in household 12) To determine if effects are specific to those with a positive test for SARS-CoV-2	Treat Infected" group within the overall cohort for sub analysis. Blood test results on recovery (optional) for evidence of historic COVID-19	supporting laboratory and/or convalescent blood test result for evidence of historic COVID-19  WHO 5 Well Being Index at baseline, day 14, and day 28 and monthly for up to 12 months, either via online diary or telephone
Qualitative sub-study	1. To explore patients' experiences of consulting, being tested and taking (trial) medication for possible COVID-19. 2. To explore healthcare professionals' views of taking part in research during pandemics.	1. Telephone interviews with patients. 2. Telephone interviews with healthcare professionals.	1. After 28 days. 2. Once practice has completed recruitment.
Intervention(s)	All trial interventions are detailed in the Appendices. Further interventions may be added or replaced during the course of the trial, subject to suitable interventions becoming available and all necessary approvals being obtained.		
Comparator	In the first instance, this will be a two-arm trial, with the intervention arm being usual care plus a trial drug and the comparator being usual care. There will be no placebo control in this study. Additional arms may be added as the trial progresses. These will be detailed in the Appendices. If an intervention arm is shown to be superior, then this will become the new standard of care. However, the primary analysis of subsequent interventions will correspond to the comparison versus the original Usual Care arm.		



## D. Adverse Events

### Definitions

Adverse Event (AE)	Any untoward medical occurrence in a participant to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product.
Adverse Reaction (AR)	<p>An untoward and unintended response in a participant to an investigational medicinal product which is related to any dose administered to that participant.</p> <p>The phrase "response to an investigational medicinal product" means that a causal relationship between a trial medication and an AE is at least a reasonable possibility, i.e. the relationship cannot be ruled out.</p> <p>All cases judged by either the reporting medically qualified professional or the Sponsor as having a reasonable suspected causal relationship to the trial medication qualify as adverse reactions.</p>
Serious Adverse Event (SAE)	<p>A serious adverse event is any untoward medical occurrence that:</p> <ul style="list-style-type: none"> <li>• results in death</li> <li>• is life-threatening</li> <li>• requires inpatient hospitalisation or prolongation of existing hospitalisation</li> <li>• results in persistent or significant disability/incapacity</li> <li>• consists of a congenital anomaly or birth defect*.</li> </ul> <p>Other 'important medical events' may also be considered a serious adverse event when, based upon appropriate medical judgement, the event may jeopardise the participant and may require medical or surgical intervention to prevent one of the outcomes listed above.</p> <p>NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.</p> <p>*NOTE: Pregnancy is not, in itself an SAE. In the event that a participant or his/her partner becomes pregnant whilst taking part in a clinical trial or during a stage where the foetus could have been exposed to the medicinal product (in the case of the active substance or one of its metabolites having a long half-life) the pregnancy should be followed up by the investigator until delivery</p>

	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)	<p>A serious adverse reaction, the nature and severity of which is not consistent with the Reference Safety Information for the medicinal product in question set out:</p> <ul style="list-style-type: none"> <li>• in the case of a product with a marketing authorisation, in the approved summary of product characteristics (SmPC) for that product</li> <li>• in the case of any other investigational medicinal product, in the approved investigator’s brochure (IB) relating to the trial in question.</li> </ul>

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

## E. Data Recording and Record Keeping

The data will be entered into the CRFs in an electronic format by the participant, Trial Partner or trial team (using OpenClinica™ database via Sentry). OpenClinica™ is stored on a secure server – data will be entered in a web browser and then transferred to the OpenClinica Database by encrypted (Https) transfer. OpenClinica™ meets FDA part 11B standards. This includes safety data, laboratory data and outcome data. Safety data will also be collected through electronic diaries which are stored on a secure server.

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

## F. Qualitative Sub-study

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

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

Patients recruited to both the intervention and usual care arms will be purposively sampled across the recruiting period with approximately 15-20 patients in each arm (30-40 interviews in total). We will seek to obtain maximum variation in age and symptom severity (as reported in daily diary at baseline). When the research team receives responses from HCPs, they will collect basic demographics to purposively select participants based on practice location, practice size, practice patient recruitment and job role. We aim to complete 20-25 interviews with HCPs.

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

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

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

#### Data Collection:

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

# Colchicine 500 microgram Tablets

Summary of Product Characteristics Updated 05-Aug-2019 | Accord-UK Ltd

## 1. Name of the medicinal product

Colchicine 500microgram Tablets

## 2. Qualitative and quantitative composition

Each tablet contains 500 micrograms of colchicine.

### Excipient with known effect:

One tablet contains 59 mg lactose monohydrate (see section 4.4).

For the full list of excipients, see section 6.1.

## 3. Pharmaceutical form

Tablet.

A white to off white, round, 6 mm diameter, flat tablet with bevelled edges, debossed with "0.5" on one side.

## 4. Clinical particulars

### 4.1 Therapeutic indications

#### Adults

- Treatment of acute gout
- Prophylaxis of gout attack during initiation of therapy with allopurinol and uricosuric drugs

### 4.2 Posology and method of administration

#### Posology.

#### Adults

##### *Treatment of acute gout attack:*

1 mg (2 tablets) to start followed by 500 micrograms (1 tablet) after 1 hour.

No further tablets should be taken for 12 hours.

After 12 hours, treatment can resume if necessary with a maximum dose of 500 micrograms (1 tablet) every 8 hours until symptoms are relieved.

The course of treatment should end when symptoms are relieved or when a total of 6 mg (12 tablets) has been taken. No more than 6 mg (12 tablets) should be taken as a course of treatment.

After completion of a course, another course should not be started for at least 3 days (72 hours).

##### *Prophylaxis of gout attack during initiation of therapy with allopurinol and uricosuric drugs:*

500 micrograms twice daily.

The treatment duration should be decided after factors such as flare frequency, gout duration and the presence and size of tophi have been assessed.

#### Patients with renal impairment

Use with caution in patients with mild renal impairment. For patients with moderate renal impairment, reduce dose or increase interval between doses. Such patients should be carefully monitored for adverse effects of colchicine (see also section 5.2).

For patients with severe renal impairment, see section 4.3.

#### Patients with hepatic impairment

Use with caution in patients with mild/moderate hepatic impairment. Such patients should be carefully monitored for adverse effects of colchicine.

For patients with severe hepatic impairment, see section 4.3.

#### Elderly

Use with caution.

#### Method of Administration

For oral administration

Tablets should be swallowed whole with a glass of water

### 4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- Patients with blood dyscrasias
- Pregnancy
- Breastfeeding
- Women of childbearing potential unless using effective contraceptive measures
- Patients with severe renal impairment
- Patients with severe hepatic impairment
- Colchicine should not be used in patients undergoing haemodialysis since it cannot be removed by dialysis or exchange transfusion.
- Colchicine is contraindicated in patients with renal or hepatic impairment who are taking a P-glycoprotein (P-gp) inhibitor or a strong CYP3A4 inhibitor (see section 4.5)

### 4.4 Special warnings and precautions for use

Colchicine is potentially toxic so it is important not to exceed the dose prescribed by a physician with the necessary knowledge and experience.

Colchicine has a narrow therapeutic window. The administration should be discontinued if toxic symptoms such as nausea, vomiting, abdominal pain, diarrhea occur.

Colchicine may cause severe bone marrow depression (agranulocytosis, aplastic anaemia, thrombocytopenia). The change in blood counts may be gradual or very sudden. Aplastic anaemia in particular has a high mortality rate. Periodic checks of the blood picture are essential.

If patients develop signs or symptoms that could indicate a blood cell dyscrasia, such as fever, stomatitis, sore throat, prolonged bleeding, bruising or skin disorders, treatment with colchicine should be immediately discontinued and a full haematological investigation should be conducted straight away.

Caution is advised in case of:

- liver or renal impairment
- cardiovascular disease
- gastrointestinal disorders
- elderly and debilitated patients
- patients with abnormalities in blood counts

Patients with liver or renal impairment should be carefully monitored for adverse effects of colchicine (see section 5.2).

Co-administration with P-gp inhibitors and/or moderate or strong CYP3A4 inhibitors will increase the exposure to colchicine, which may lead to colchicine-induced toxicity including fatalities. If treatment with a P-gp inhibitor or a moderate or strong CYP3A4 inhibitor is required in patients with normal renal and hepatic function, a reduction in colchicine dosage or interruption of colchicine treatment is recommended (see section 4.5).

This medicinal product contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

### 4.5 Interaction with other medicinal products and other forms of interaction

Colchicine is a substrate for both CYP3A4 and the transport protein P-gp. In the presence of CYP3A4 or P-gp inhibitors, the concentrations of colchicine in the blood increase. Toxicity, including fatal cases, have been reported during concurrent use of CYP3A4 or P-gp inhibitors such as macrolides (clarithromycin and erythromycin), ciclosporin, ketoconazole, itraconazole, voriconazole, HIV protease inhibitors, calcium channel blockers (verapamil and diltiazem) and disulfiram (see section 4.4).

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

Colchicine is contraindicated in patients with renal or hepatic impairment who are taking a P-gp inhibitor (e.g. ciclosporin, verapamil or quinidine) or a strong CYP3A4 inhibitor (e.g. ritonavir, atazanavir, indinavir, clarithromycin, telithromycin, itraconazole or ketoconazole) (see section 4.3).

A reduction in colchicine dosage or an interruption of colchicine treatment is recommended in patients with normal renal or hepatic function if treatment with a P-gp inhibitor or moderate or strong CYP3A4 inhibitor is required (see section 4.4). A 4-fold reduction in colchicine dosage is recommended when co-administered with a P-gp inhibitor and/or a strong



CYP3A4 inhibitor. A 2-fold reduction in colchicine dosage is recommended when co-administered with a moderate CYP3A4 inhibitor.

The magnitude of interactions with strong and moderate CYP3A4 inhibitors as well as with P-gp inhibitors from performed *in vivo* studies is summarised in the table below:

Single dose of 0.6 mg colchicine without or with:	Number of subjects	% change in colchicine pharmacokinetic parameters		Guidance for dose reduction:
		C <sub>max</sub>	AUC <sub>0-t</sub>	
<b>Strong CYP3A4 inhibitors</b>				4-fold Acute gout regimen to be repeated no earlier than 3 days.
Clarithromycin 250 mg twice daily for 7 days	N=23	297	339	
Ketoconazole 200 mg twice daily for 5 days	N=24	190	287	
Ritonavir 100 mg twice daily for 5 days	N=18	267	345	
<b>Moderate CYP3A4 inhibitors</b>				2-fold Acute gout regimen to be repeated no earlier than 3 days.
Verapamil ER 240 mg once daily for 5 days	N=24	130	188	
Diltiazem ER 240 mg once daily for 7 days	N=20	129	177	
Grapefruit juice 240 ml twice daily for 4 days	N=21	93	95	
<b>Potent P-gp inhibitors</b>				4-fold Acute gout regimen to be repeated no earlier than 3 days.
Cyclosporin 100 mg single dose	N=23	324	317	

Given the nature of the side effects, caution is advised with concomitant administration of drugs that can affect the blood count or have a negative effect on hepatic and/or renal function.

In addition, substances such as cimetidine and tolbutamide reduce metabolism of colchicine and thus plasma levels of colchicine increase.

Grapefruit juice may increase plasma levels of colchicine. Grapefruit juice should therefore not be taken together with colchicine.

Reversible malabsorption of cyanocobalamin (vitamin B12) may be induced by an altered function of the intestinal mucosa.

The risk of myopathy and rhabdomyolysis is increased by a combination of colchicine with statins, fibrates, ciclosporin or digoxin.

#### 4.6 Fertility, pregnancy and lactation

##### Fertility

Colchicine administration in animals induces significant reductions in fertility.

##### Pregnancy

Colchicine is genotoxic *in vitro* and *in vivo*, and is teratogenic in animal studies (see section 5.3). Colchicine is therefore contraindicated in pregnancy (see section 4.3).

Women of childbearing potential have to use effective contraception during treatment.

##### Breastfeeding

Colchicine is excreted in breast milk. Therefore, use of colchicine is contraindicated in women who are breastfeeding (see section 4.3).

#### 4.7 Effects on ability to drive and use machines

No details are available regarding the influence of colchicine on the ability to drive and use machines. However, the possibility of drowsiness and dizziness should be taken into account.

#### **4.8 Undesirable effects**

The following adverse reactions have been observed.

The frequencies are listed under one of the following classifications:

Very common > 1/10

Common > 1/100 and < 1/10

Uncommon > 1/1000 and < 1/100

Rare > 1/10 000 and < 1/1000

Very rare < 1/10 000

Not known (cannot be estimated from the available data)

##### Blood and lymphatic system disorders

Not known: bone marrow depression with agranulocytosis, aplastic anemia and thrombocytopenia.

##### Nervous system disorders

Not known: peripheral neuritis, neuropathy.

##### Gastrointestinal system disorders

Common: abdominal pain, nausea, vomiting and diarrhoea.

Not known: gastrointestinal haemorrhage.

##### Hepatobiliary disorders

Not known: hepatotoxicity.

##### Skin and subcutaneous tissue disorders

Not known: alopecia, rash.

##### Musculoskeletal and connective tissue disorders

Not known: myopathy and rhabdomyolysis.

##### Renal and urinary disorders

Not known: renal damage.

##### Reproductive system and breast disorders

Not known: amenorrhoea, dysmenorrhoea, oligospermia, azoospermia.

##### Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme Website: [www.mhra.gov.uk/yellowcard](http://www.mhra.gov.uk/yellowcard) or search for MHRA Yellow Card in the Google Play or Apple App Store.

#### **4.9 Overdose**

Colchicine has a narrow therapeutic window and is extremely toxic in overdose. Patients at particular risk of toxicity are those with renal or hepatic impairment, gastro-intestinal or cardiac disease and patients at extremes of age.

Following colchicine overdose, all patients, even in the absence of early symptoms, should be referred for immediate medical assessment.

##### Clinical:

Symptoms of acute overdosage may be delayed (3 hours on average): nausea, vomiting, abdominal pain, hemorrhagic gastroenteritis, volume depletion, electrolyte abnormalities, leukocytosis, hypotension in severe cases. The second phase with life threatening complications develops 24 to 72 hours after drug administration: multisystem organ dysfunction, acute renal failure, confusion, coma, ascending peripheral motor and sensory neuropathy, myocardial depression, pancytopenia, dysrhythmias, respiratory failure, consumption coagulopathy. Death is usually a result of respiratory depression and cardiovascular collapse. If the patient survives, recovery may be accompanied by rebound leukocytosis and reversible alopecia starting about one week after the initial ingestion.

##### Treatment:

No antidote is available.

Elimination of toxins by gastric lavage within one hour of acute poisoning.

Consider oral activated charcoal in adults who have ingested more than 0.1mg/kg bodyweight within 1 hour of presentation and in children who have ingested any amount within 1 hour of presentation.

Haemodialysis has no efficacy (high apparent distribution volume).

Close clinical and biological monitoring in hospital environment.

Symptomatic and supportive treatment: control of respiration, maintenance of blood pressure and circulation, correction of fluid and electrolytes imbalance.

The lethal dose varies widely (7 - 65 mg single dose) for adults but is generally about 20 mg.

## 5. Pharmacological properties

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: drugs for gout, with no effect on uric acid metabolism. ATC code: M04AC01

In the AGREE (Acute Gout Flare Receiving Colchicine Evaluation) study low- and high-dose colchicine were compared using a randomized, placebo-controlled design. The high-dose prolonged colchicine regimen (4.8 mg total over 6 hours) was compared with a placebo and a low-dose abbreviated regimen (1.8 mg total over 1 hour, i.e. 1.2 mg followed by 0.6 mg in 1 hour). Both colchicine regimens were significantly more effective than placebo, with 32.7% responders in the high-dose group, 37.8% responders in the low-dose group, and 15.5% responders in the placebo group ( $P = 0.034$  and  $P = 0.005$ , respectively, versus placebo). The results at the primary 24-hour end point demonstrate superior safety of low-dose colchicine, without loss of efficacy, relative to high-dose colchicine for early acute gout flare (self-administered within 12 hours of flare onset). The pharmacokinetic analysis performed in this study showed that the colchicine plasma concentration was decreased substantially from about 12 hours after administration in healthy volunteers.

Colchicine prophylaxis (0.6 mg twice daily) during initiation of allopurinol for chronic gouty arthritis reduced the frequency and severity of acute flares, and reduced the likelihood of recurrent flares. Treatment may be continued for up to 6 months, based on clinical data. Prospective randomized controlled trials are needed to further evaluate flare prophylaxis for up to 6 months, after 6 months, and over time.

The mechanism of action of colchicine in the treatment of gout is not clearly understood. Colchicine is considered to act against the inflammatory response to urate crystals, by possibly inhibiting the migration of granulocytes into the inflamed area. Other properties of colchicine, such as interaction with the microtubules, could also contribute to the operation. Onset of action is approximately 12 hours after oral administration and is maximal after 1 to 2 days.

### 5.2 Pharmacokinetic properties

Colchicine is rapidly and almost completely absorbed after oral administration. Maximum plasma concentrations are met usually after 30 to 120 minutes. The terminal half-life is 3 to 10 hours. Plasma protein binding is approximately 30%. Colchicine is partially metabolised in the liver and then in part via the bile. It accumulates in leucocytes. Colchicine is largely excreted (80%) in unchanged form and as metabolites in the faeces. 10-20% is excreted in the urine.

#### Renal impairment

Colchicine is significantly excreted in urine in healthy subjects. Clearance of colchicine is decreased in patients with impaired renal function. Total body clearance of colchicine was reduced by 75% in patients with end-stage renal disease undergoing dialysis.

The influence of renal impairment on the pharmacokinetics of colchicine was assessed in a study in patients with familial Mediterranean fever (FMF), 5 women and 4 men, with ( $n=4$ ) and without ( $n=5$ ) renal impairment. The mean age was 30 years (range 19-42 years). All 5 patients with renal impairment had biopsy-proven amyloidosis; 4 were on routine hemodialysis and 1 had a serum creatinine CL of 15 ml/min. They could therefore be classified as having severe renal impairment. Subjects received 1 mg colchicine except for 1 subject with cirrhosis who received 500 micrograms. A 4-fold decrease in colchicine CL was observed in subjects with renal impairment compared to those with normal renal function ( $0.168 \pm 0.063$  l/h/kg vs.  $0.727 \pm 0.110$  l/h/kg). The terminal half-life was  $18.8 \pm 1.2$  h for subjects with severe renal impairment and  $4.4 \pm 1.0$  h for those with normal renal function. The volume of distribution was similar between groups. The patient with cirrhosis had a 10-fold lower CL compared to the subjects with normal renal function.

#### *Paediatric population*

No pharmacokinetics data are available in children.

### 5.3 Preclinical safety data

#### Genotoxicity

In one study, a bacterial test indicated that colchicine has a slight mutagenic effect.

However, two other bacterial tests and a test in *Drosophila melanogaster* found that colchicine was not mutagenic.

Tests have shown that colchicine induces chromosomal aberrations and micronuclei, and causes some DNA damage.

### Teratogenicity

Tests in animals have shown that colchicine is teratogenic.

## **6. Pharmaceutical particulars**

### **6.1 List of excipients**

Lactose monohydrate  
Microcrystalline cellulose  
Pregelatinised starch  
Sodium starch glycolate  
Magnesium stearate

### **6.2 Incompatibilities**

Not applicable.

### **6.3 Shelf life**

2 years

### **6.4 Special precautions for storage**

Store in the original package in order to protect from light.

### **6.5 Nature and contents of container**

White opaque PVC/ plain push through aluminum foil.  
Blisters : 20 and 100 tablets.  
Not all pack sizes may be marketed.

### **6.6 Special precautions for disposal and other handling**

No special requirements for disposal.

## **7. Marketing authorisation holder**

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

## **8. Marketing authorisation number(s)**

PL 0142/0918

## **9. Date of first authorisation/renewal of the authorisation**

07.04.2015

Renewal approved: 10/12/2018

## **10. Date of revision of the text**

30/07/2019

## **Company Contact Details**

Accord-UK Ltd

### **Address**

Whiddon Valley, Barnstaple, Devon, EX32 8NS, UK

### **Telephone**

+44 (0)1271 385 200

### **Medical Information Direct Line**

+44 (0)1271 385 257

### **WWW**

[www.accord-healthcare.co.uk](http://www.accord-healthcare.co.uk)

### **Fax**

+44 (0)1271 346 106

### **Medical Information e-mail**

[Medinfo@accord-healthcare.com](mailto:Medinfo@accord-healthcare.com)





## Colchicine

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

The study medication you have been given is called **Colchicine**. You have been given Colchicine 500 microgram tablets.

### Dose and Administration

The **Colchicine tablets** are for taking by mouth (oral administration). You should take one **Colchicine** tablet (500 micrograms) each day for 14 days.

Administration: Tablets should be swallowed whole with a glass of water.

If you are a woman of childbearing potential, you must use highly effective contraceptives for the 28 day duration of the trial.

If you miss a dose, take the missed dose as soon as you remember. Please skip the missed dose if it is almost time for your next scheduled dose. Do not take extra medicine to make up the missed dose.

If you decide that you no longer wish to take the medication, you can take your medication to your local pharmacy for disposal, when you are able to.

### Side-Effects

Please see the **Colchicine** appendix included in your participant pack, for a list of possible side-effects and what to do if you experience any of these.

You will be able to tell us if you are experiencing any of these symptoms in your daily diary.



This medication can cause rare allergic reactions. **If you develop any problems please stop taking the medication immediately and seek clinical advice.**

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

### **Precautions:**

Please do not take the medication if you have a known allergy to colchicine or any of these inactive substances: lactose, Pregelatinised Maize Starch, Stearic Acid, Purified Talc, Purified Water or Ethanol 96%.

You cannot take **Colchicine** with any of the following medication:

- Colchicine, clarithromycin, erythromycin, ketoconazole, itraconazole, voriconazole, HIV protease inhibitors (e.g. ritonavir, atazanavir), cobicistat, verapamil, diltiazem, cyclosporin, quinidine, disulfiram.
- Please do not consume grapefruit juice whilst taking the medication.

If any of these apply, please do not take the trial medication and speak to your GP and trial team.

### **Storage:**

Please store at room temperature in the original package in order to protect from light.

We will ask you to record how many tablets you have remaining each day in your daily diary.

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



Study Title	PRINCIPLE
EudraCT No	2020-001209-22
Version Number, Date	v1.0 19.02.2021

Description of information needed	Label Text
<b>Name, address and telephone number of the sponsor</b> (the main contact for information on the product, clinical trial and emergency unblinding)	University of Oxford Joint Research Office 1st floor, Boundary Brook House Churchill Drive, Headington Oxford OX3 7GB Tel: +44 (0)1865572224 Fax: +44 (0)1865572228
<b>Pharmaceutical dosage form, route of administration, quantity of dosage units,</b> and in the case of open trials, the name/identifier and strength/potency;	<b>Colchicine</b> 500 micrograms tablets (pack of 14)  The colchicine tablets are for oral administration.
<b>Batch and/or code number</b> to identify the contents and packaging operation;	
<b>Trial reference code</b> allowing identification of the <u>trial, site, investigator and sponsor</u> if not given elsewhere;	PRINCIPLE trial. University of Oxford Chief Investigator: Prof. Chris Butler
<b>Trial subject identification number</b> /treatment number and where relevant, the visit number;	
<b>Kit/Pack number</b>	
<b>Investigator</b> (if not included previously)	
<b>Directions for use</b> (reference may be made to a leaflet or other explanatory document intended for the trial subject or person administering the product)	<b>Colchicine</b> 500 micrograms tablets. Take 1 tablet each day for 14 days.  Special instructions: Tablets should be swallowed whole with a glass of water.
<b>“For clinical trial use only”</b> or similar wording;	For clinical trial use only
<b>Storage conditions</b>	Store at room temperature in the original package in order to protect from light
<b>Period of use</b> (use-by date, expiry date or re-test date as applicable), in month/year format and in a manner that avoids any ambiguity	14 days  Expiry date: month/year  Shelf life is 2 years
<b>“keep out of reach of children”</b> except when the product is for use in trials	Keep out of reach of children



where the product is not taken home by subjects	
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# Visual identity guidelines

Ensuring your communications materials are  
professional and credible

# Introduction

These guidelines are intended to supplement the University of Oxford 'Oxford blue: Visual identity guidelines' toolkit which can be found at

[www.ox.ac.uk/branding\\_toolkit](http://www.ox.ac.uk/branding_toolkit)

The toolkit includes information on:

- University branding marks and logo
- The brand colours
- Typography
- Exhibitions and signage
- Brand marks on stationery
- Writing and style guide
- Brochures and other printed items
- Stationery and conference items
- Photography

This document aims to provide additional information on how to use Nuffield Department of Primary Care Health Sciences logos.

If you have any questions about applying this visual identity, please contact:

Dan Richards-Doran, Communications Manager  
[dan.richards-doran@phc.ox.ac.uk](mailto:dan.richards-doran@phc.ox.ac.uk)

# Why apply a visual identity?

The University of Oxford needs to present a consistent identity to ensure instant recognition of our global brand among a wide variety of audiences around the world. This identity is a graphical expression of who we are and what we represent as an organisation.

The University produces a great deal of communications materials across an increasingly diverse range of media. It is therefore vital that the University logo appears prominently, making our communications:

- Professional
- Clear
- Consistent
- Instantly recognisable.

Combining the University of Oxford logo with the department logo creates a relationship between the two, demonstrates hierarchy and clearly aligns the department and its activities with the globally recognised Oxford brand.

However, the department brand goes far beyond applying a visual identity. The strength of our research, our work in the community, the people of our department and our relationship with the University's long-standing reputation for excellence in teaching and medical sciences all count towards building and maintaining this globally recognised brand image.

**The University of Oxford and department logos should be placed together in a prominent position (preferably in the corner) at all times on all official documents, stationery and digital applications.**

## Typography

There are several University of Oxford typefaces, the main one being Foundry Sterling. For clarity, consistency and ease of use, the department has chosen to use Arial as a standard typeface, and Foundry Sterling on commercially printed/promotional materials. This can be downloaded at:

[www.ox.ac.uk/public-affairs/branding-toolkit/downloads](http://www.ox.ac.uk/public-affairs/branding-toolkit/downloads)

Foundry Sterling has been chosen for its clarity and readability and should be used on all printed materials such as leaflets and brochures.

Text of letters/memos:	Arial
Internal documents:	Arial
Powerpoint presentations:	Arial
Emails:	Arial
Web and digital applications:	PT Sans
Commercially printed materials:	Foundry Sterling
Letterheads/compliment slips:	Arial

Please do not use Calibri

Complimentary typefaces are also available, such as Minion Pro, for use in design where there is a need for an additional complimentary font.

## Colour – Oxford blue

The colour associated with the University is Oxford blue, this is recognised worldwide as our identifying colour.



**Oxford blue (Pantone 282)**



**Process (CMYK) for use in printing**

C=100 M=80 Y=0 K=60



**Screen (RGB) for digital/web use**

R=0 G=33 B=71

A range of complimentary colours are available for use in graphic design including backgrounds and typography. A list of these can be found in the branding toolkit:

[www.ox.ac.uk/public-affairs/branding-toolkit/downloads](http://www.ox.ac.uk/public-affairs/branding-toolkit/downloads)

## Department accent colour – purple

The department has adopted purple as an accent colour for our design and publications.



**Process (CMYK) for use in printing**

C=35 M=100 Y=50 K=21



**Screen (RGB) for digital/web use**

R=138 G=23 B=81

## The department logo

The standard department logo includes the University of Oxford logo as part of its design. Generally both elements should always be joined, either completely together or on the same line. The department name in logo form should never appear in isolation without the University of Oxford logo in close proximity.

### Exclusion zone

As with the University of Oxford logo, the department logo is protected by an invisible exclusion zone where no graphic material other than the background should appear. This is to ensure it remains free of visual interference. The exclusion zone should be a minimum of 0.3x where X is the width of the blue rectangle logo. The only exclusion is in the case of partner branding, such as using the CEBM logo.

### Reversed version

The logo has most impact on a white or very light background. Where this is not possible, a reversed version of the logo exists where the department name is in white. Never use this on a lighter background.

### Small logo

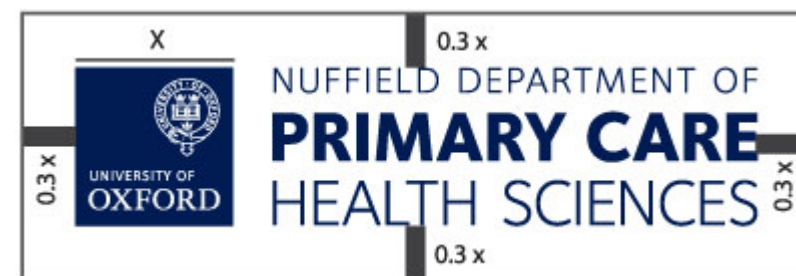
The minimum quadrangle size is 24mm width. Smaller versions of the logo are available for use down to 15mm width. This size works well on infographics.

### Avatar

The Oxford square can be used in isolation as an avatar, i.e. on Twitter.



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# Stationery templates

A range of stationery templates have been produced for use by all department staff to standardise how our visual identity is applied.

Letterheads, compliment slips and email signatures have been produced for the Radcliffe Primary Care Building, the Gibson Building and Old Road Campus. Specific letterhead and compliment slips have been produced for HERG, CEBM, VBHC, and PC-CTU. Other research groups should use the standard department letterhead.

Please use Arial for the body text of these templates.

Do not change these templates or create new ones without consulting the Communications and Events Manager.

All available templates can be downloaded from the department intranet:  
[www.phc.ox.ac.uk/intranet/department-administration/comms/brandguidelines/](http://www.phc.ox.ac.uk/intranet/department-administration/comms/brandguidelines/)





## Powerpoint template

After journal publications, powerpoint is one of the most widely used communication tools for scientists, used in teaching, presentations and promotional activities.

This is one of the most important places to apply the correct visual identity and several versions of the powerpoint template have been produced.

On the standard template (top) the department and University logos have been split for impact, which is also the case on the department website.

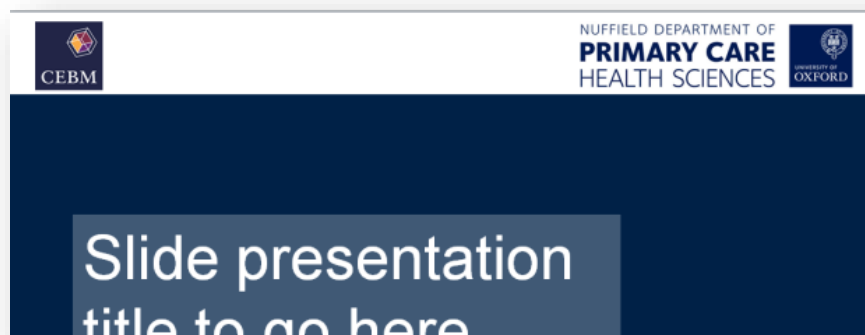
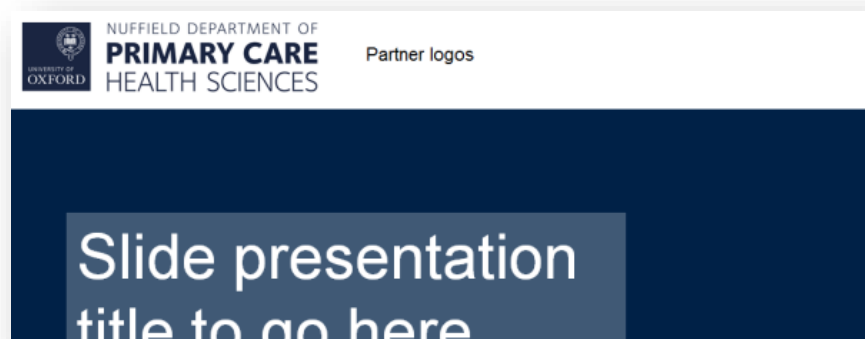
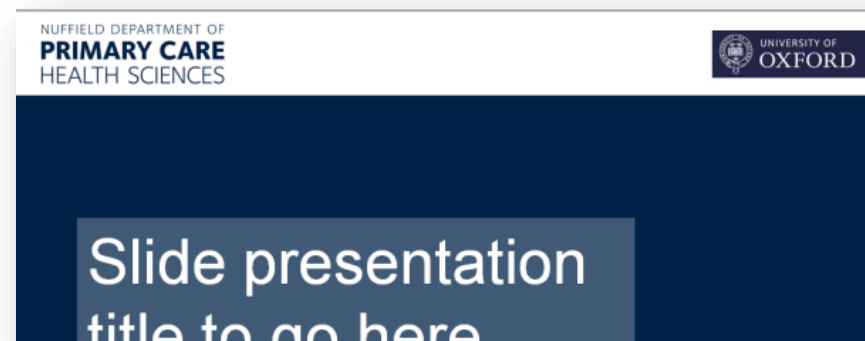
Where a partner logo is being used and the department leads on the research, the department and university logos should be used together in the top left (middle).

If the CEBM/PC-CTU logos are used, then the University and department logo appears on the right and the additional logo on the left (bottom).

This logo order can also be applied to the top of department websites.

## Poster template

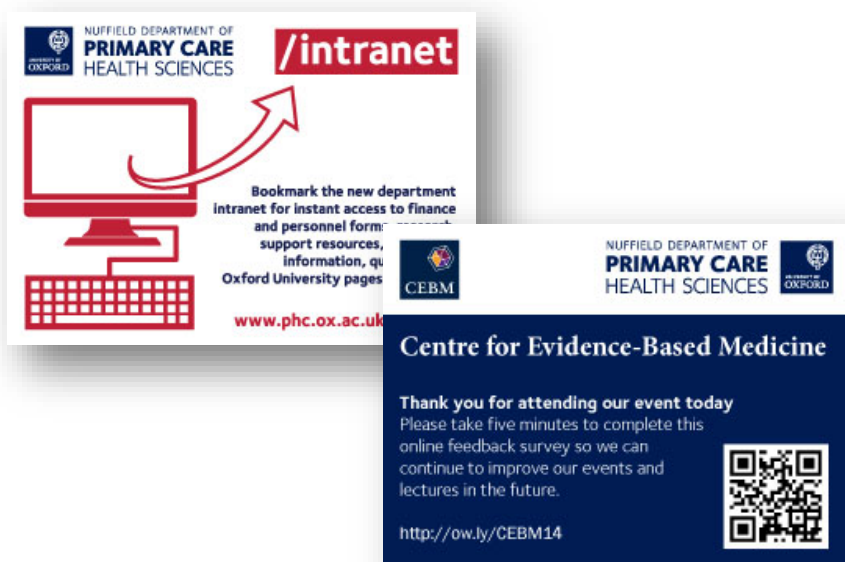
A0 landscape and portrait poster templates are also available. When creating a poster ensure you also include your funder's logos. You may wish to consult their own brand guidelines for information on logo placement.



## Logo placement in design

The department logo should always appear in a prominent location in either corner of the design, either at the top or the bottom. Central placement of the logo should be avoided, unless there is no other option due to the narrow width of the item being branded.

The department logo comes in two versions to allow for either left or right placement. Logo placement on the left is preferred, unless a second logo is used as part of the branding, in which case the right-hand placement of the logo could be used.



## Infographics

When creating an infographic, always ensure the small version of the department logo is used in either the bottom left or top left.

Before creating your infographic, first consider whether it is appropriate for the audience it is intended for and how you will use it. Check your facts are not misleading or at risk of being taken out of context.

Please also remember to include a reference to the paper or journal, if applicable, to ensure your facts can be verified. This could be in short form rather than the full paper reference, e.g.:

Smith J *et al.* An RCT to test the new health intervention. Lancet 2017.  
DOI: 10.1016/S123-456(1)123-3

## Videos/animations

Please always include the department logo at the start of your videos or animations. The final slide should include your funder's logo, disclaimer and a link to find out more. Consult your funder's brand guidelines for guidance.



## Using the department logo as a partner

In certain circumstances the department logo will be used as part of a series of logos on promotional literature. The department logo should always be offered in standard form (see right) rather than just the square University of Oxford logo. **If there is only room for the University logo, then the department must always be credited in written form somewhere in the accompanying copy.**

For CEBM only, where the centre is working in partnership with another organisation, the University and CEBM logos may be used together without the department name incorporated into the logo. However the department must be credited in the accompanying copy.

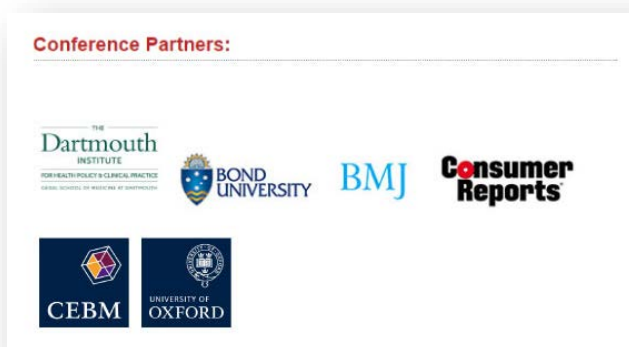


Photo credits: OUIImages/Nasir Hamid, Pixabay

## Images and photography

Augmenting your design materials with images can enhance their appearance and make them more eye-catching. Where possible, consider using images of people and places rather than cartoons of objects, since primary care research is about people.

A selection of photos are available on the department Z drive:

Z:\DPHPC\_slideshows\Department PHOTOS + VIDEOS

For stock photos, visit [www.shutterstock.com](http://www.shutterstock.com), select the photo you would like to use and contact the communications manager who will be able to purchase this for you using the department account.

Royalty free photos can be found at [www.pixabay.com](http://www.pixabay.com)

Please always credit the photographer.



## What not to do

Do not skew the logo, always ensure it is the correct proportions



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Do not recolour the logo



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Do not use the department logo without the Oxford logo visible in a prominent position.

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Do not use a low resolution version of the logo



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Do not add text within the exclusion zone, or augment the logo with additional information



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**General Practice Research Group**

## Design studio

The University provides an internal design service for the production of brochures, leaflets and posters, infographics and other print/digital content. Before consulting external agencies, it is advised to contact the Design Service first since they offer much more competitive rates.

[www.ox.ac.uk/designstudio](http://www.ox.ac.uk/designstudio)

The department administration team also offer limited design services, and can assist with the development of many types of publicity material.

Please consult the communications manager before developing a design brief.

## Before you publish your work

Before you complete your work, always get somebody else to read it to check for spelling and grammar.

Please send commercially printed publications and visual content, such as infographics and videos, to the department communications manager to sign-off prior to publication.

For all materials, remember to check:

- Spelling and grammar
- Logo placement
- Correct URL present
- Are your funder/other partners credited?
- Do you have appropriate imagery?
- If you are advertising an opportunity, is the call-to-action clear?

*Last updated: April 2017*

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

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

Date:

Hello,

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

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

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

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

You also need to be aged 65 years and over, or 18-64 years and experiencing shortness of breath as part of COVID-19 illness, or 18-64 years with certain underlying health conditions.

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

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

Yours Sincerely

The PRINCIPLE Study Team, University of Oxford

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

Participant Introductory Letter Version/Date: v1.2 12th February 2021, EudraCT number:2020-001209-22

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





**PRINCIPLE TRIAL: Patients registering on the NHS COVID-19 testing website will be sent a confirmation email with details of their NHS testing appointment. The following text will be included to signpost to the trial:**

### **Can you help the NHS?**

If you are over 18 and recently developed coronavirus symptoms, you may be able to take part in a clinical trial.

To find out more and check if you qualify, go to [URL].

# VOLUNTEERS NEEDED

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

Are you:

**Aged 65 or over?**

**OR 18 to 64** and experiencing shortness of breath as part of COVID-19 illness, with symptoms within the past 14 days?

**OR 18-64** with underlying health conditions, with symptoms within the past 14 days?

Please visit [www.principletrial.org](https://www.principletrial.org)

to find out how to take part in an Urgent Public Health clinical trial for COVID-19 treatments



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Primary Care | **PCU**  
Clinical Trials Unit

**NIHR** | National Institute  
for Health Research



UK Research  
and Innovation





# VOLUNTEERS NEEDED

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

**Are you aged 65 or over? Or 18 to 64 and experiencing shortness of breath as part of COVID-19 illness or do you have underlying health conditions? with symptoms within the past 14 days?**

**Please visit [www.principletrial.org](http://www.principletrial.org) to find out how to take part in an Urgent Public Health Clinical Trial for COVID-19 Treatments**



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Primary Care | ●●●●  
Clinical Trials Unit

*Advert, v1.1, 12.02.21.  
IRAS: 281958, REC:  
20/SC/058*





Radcliffe Observatory Quarter, Woodstock Road, Oxford. OX2 6GG  
Tel: 0800 138 0880 • [principle@phc.ox.ac.uk](mailto:principle@phc.ox.ac.uk) • [www.principletrial.org](http://www.principletrial.org)

Date:

Dear Dr \_\_\_\_\_,

Name of patient:

Patient's date of birth:

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

Further information about PRINCIPLE is available on the attached sheet or at  
[www.principletrial.org](http://www.principletrial.org)

A copy of your patients consent form is attached. **Please retain the consent form, along with this letter, in your patient's medical record.** Please note that your patient has given consent for us to gather information from their medical notes.

The treatment your patient has been randomised to receive is:

Trial Treatment: \_\_\_\_\_  
at [dose] for [duration]

**For patients in the active treatment arm, please put the drug details as an 'outside' prescription in your clinical record so that it is visible in the Emergency Care Summary if the patient contacts NHS24 or is admitted to hospital.**

Please report any Serious Adverse Events (SAEs) other than hospitalisation or death due to COVID-19 infection to the Scottish trial team within 24 hours.

[Any relevant other local information including local arrangements re swabs]

#### **PRINCIPLE Trial details**

Site ID:

Local trial team contact details:

PRINCIPLE Patient ID:

Many thanks.

The PRINCIPLE team

Page 1 of 2

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

GP Letter Scotland, **Version/Date: v2.1 12 February 2021, EudraCT number:2020-001209-22**

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

Radcliffe Observatory Quarter, Woodstock Road, Oxford. OX2 6GG  
Tel: 0800 138 0880 • [principle@phc.ox.ac.uk](mailto:principle@phc.ox.ac.uk) • [www.principletrial.org](http://www.principletrial.org)

## What is the PRINCIPLE trial?

The PRINCIPLE trial is one of three UK-wide COVID-19 trial platforms (the other two are in hospitals). It will evaluate a series of drugs which are potential treatments for COVID-19. More detailed information on which drugs are currently being evaluated can be found at [www.principletrial.org](http://www.principletrial.org)

### What do I have to do?

The Oxford and local trial teams will manage trial medication prescribing and dispensing and core data collection. You may be asked to help with follow-up data extraction (these will be done by the trial team for most patients, but it is important that we get complete data on death and hospital admission for patients who are lost to follow-up). We would also like you to report any serious adverse events which come to your attention to the Scottish Trial contact listed on the patient notification'.

### What are Serious Adverse Events (SAEs) and how do I report them?

A serious adverse event is any untoward medical occurrence that:

- results in death
- is life-threatening at the time of the event
- 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.

Hospitalisation and death due to COVID-19 are our trial primary outcomes so do not need reporting as SAEs. Please report SAEs to the **Scottish Trial contact listed on the patient notification**. The Trial Team will need to know the PRINCIPLE Patient ID, and a brief description of when the SAE happened and what it consisted of. The trial team is responsible for assessing if the adverse event is likely related or not to the trial medication, and for reporting to regulators.

Please report SAEs using the SAE form provided, which contains date of birth, but no other personal identifiable information.

### Can I refer patients to the trial?

Yes. If you see a patient who you think is likely to have COVID-19, then you can tell them to get in touch with the Oxford trial team to find out more. They can do this by any of:

Website: [www.principletrial.org](http://www.principletrial.org)  
Tel: 0800 138 0880  
email: [principle@phc.ox.ac.uk](mailto:principle@phc.ox.ac.uk)

**[Please include current per protocol eligibility criteria here]**

The Oxford trial team will then fully screen them for eligibility.

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

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

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

The study is called PRINCIPLE. It is run by the University of Oxford, and is funded by the UK government as a national priority study. The study aims to find treatments that reduce hospital admission and speed recovery for people with symptoms of COVID-19. People included in the study must be:

- aged **65 and over**, OR
- aged **18-64** and experiencing shortness of breath as part of COVID-19 illness, OR
- aged **18-64** with certain underlying health conditions

They will either receive usual care, or usual care plus a study drug. All study drugs are widely used to treat other conditions and have been assessed as being safe for use in this study.

All of the treatments in the PRINCIPLE trial have been approved by the UK- Medicines and Health Care Products Regulatory Agency (MHRA), as well as the Urgent Public Health panel of independent experts. The MHRA regulates the use of all medicines in the UK.

**You may be able to take part in this study if:**

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

**OR**

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

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

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

So, please make contact if you have **symptoms of COVID-19 and meet the age criteria detailed above!**

Yours Sincerely

[insert practice name]



# You could help the fight against COVID-19

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

**Anyone suspected or confirmed with COVID-19 may be eligible to join the PRINCIPLE trial** Symptoms to look out for include:



**New cough**



**High temperature**



**Loss or change in smell or taste**

## The PRINCIPLE trial is open to:

**Anyone aged 65 and above**

**Or**  
anyone aged 18-64 and experiencing shortness of breath as part of COVID-19 illness

**Or** anyone aged 18-64 with certain underlying health conditions such as:



**High blood pressure and/ or heart disease**



**Stroke or neurological problems**



**Diabetes not treated with insulin**



**Liver disease**



**Asthma or lung disease**



**Obesity or BMI  $\geq 35$  kg/m<sup>2</sup>**



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

To find out more or register for the study, please visit [www.principletrial.org](http://www.principletrial.org)

 **0800 138 0880**

 **principle@phc.ox.ac.uk**



NUFFIELD DEPARTMENT OF  
**PRIMARY CARE**  
HEALTH SCIENCES

Primary Care  
Clinical Trials Unit

**NIHR** | National Institute  
for Health Research



UK Research  
and Innovation



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

# Do you have suspected or confirmed COVID-19? Symptoms may include:



New cough



High temperature



Loss or change in smell or taste

## If you are either:

**Aged 65 and above**

**Or**  
aged 18-64 and experiencing shortness of breath as part of COVID-19 illness

**Or** aged 18-64 with certain underlying health conditions such as:



**High blood pressure and/or heart disease**



**Stroke or neurological problems**



**Known diabetes**



**Liver disease**



**Asthma or lung disease**



**Obesity or BMI ≥35 kg/m²**



**Weakened immune system due to serious illness or medication**

## You could be eligible to join the PRINCIPLE trial and help the fight against COVID-19

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

To find out more or register for the study, please visit [www.principletrial.org](http://www.principletrial.org)

☎ 0800 138 0880

✉ [principle@phc.ox.ac.uk](mailto:principle@phc.ox.ac.uk)

## ***Appendix 1***

### ***Inhaled Corticosteroid - Budesonide***

#### ***Drug Information***

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

#### ***Side-effects***

The common side effects are:

cough immediately after inhaling

mouth and throat pain

hoarse voice

oral candidiasis (thrush).



## **Appendix 2**

### **Colchicine**

#### **Drug Information**

Colchicine is a medicine which is licenced and widely used in the UK for the treatment of acute gout. Although is not currently used to treat infections like COVID-19, it has been investigated as a possible treatment for COVID-19.

#### **Colchicine Dose and Administration**

Colchicine is a new possible treatment for COVID-19, so the most effective dose is unknown. Studies like this are trying to find out how well the treatment works.

**An oral dose (by mouth) of a tablet of 500 microgram (µg) each day for 14 days (14 tablets in total), will be used in the trial.**

If you decide that you no longer wish to take the medication, you can stop at any time, and take your medication to your local pharmacy for disposal, when you are able to.

#### **Potential COVID-19 Treatment**

Several clinical studies have found that colchicine may help to treat COVID-19. However, we need more evidence from large clinical trials, about whether colchicine improves recovery from COVID-19 symptoms, which may reduce the number of people going into hospital with the disease. This is why we have included the treatment in the PRINCIPLE Trial. Colchicine has been recommended by the UK COVID-19 Therapeutics Advisory Panel (UK-CTAP) for the treatment of COVID-19, and approved by the Chief Medical Officer.

The use of colchicine in PRINCIPLE has also been approved by the UK- Urgent Public Health Panel. The panel is formed by a group of independent experts including patient representatives and healthcare professionals from across the four UK nations.

#### **Exclusion Criteria**

Before you are enrolled, you will be asked if you have any of the following reasons for NOT taking Colchicine, and you will be excluded from receiving colchicine if you do.

#### **Exclusions: If you have any of the following conditions you should not take Colchicine**

- Allergy to colchicine or any of these inactive substances: lactose, Pregelatinised Maize Starch, Stearic Acid, Purified Talc, Purified Water or Ethanol 96%.

- Known or suspected pregnancy
- Breastfeeding
- Women of childbearing potential (premenopausal female that is anatomically and physiologically capable of becoming pregnant) not willing to use highly effective contraceptives for 28 day duration of the trial.
- Known blood dyscrasias (a blood disorder)
- Known severe kidney impairment or requiring dialysis
- Known severe liver impairment
- Currently taking any of the following drugs: colchicine, clarithromycin, erythromycin, ketoconazole, itraconazole, voriconazole, HIV protease inhibitors (e.g. ritonavir, atazanavir), cobicistat, verapamil, diltiazem, cyclosporin, quinidine, disulfiram.
- Inflammatory bowel disease or chronic diarrhoea or malabsorption

You will also be asked to agree not to drink any grapefruit juice while taking colchicine.

**A registered nurse or doctor will review your answers to these screening questions against information obtained from your medical notes to check that you can take the treatment, once confirmed you will be enrolled into the trial.**

## **Contraception**

**It is important that women of childbearing potential must use highly effective contraceptives from enrolment until day 28 of follow up.**

### **Methods of contraception that are acceptable for the trial include the following:**

The implant, the coil, and male or female sterilisation will be acceptable for participating in the trial. The injection and most forms of hormonal contraception will also be considered acceptable for the trial, if used in combination with condoms or other barrier methods. However, condoms alone won't be sufficient during the study. You can discuss any questions you have about contraception during the study period with the trial team. If you were to become pregnant during the trial you must tell us immediately and you will be withdrawn from the study, although we will ask to follow you up for safety reasons.

**It is important to note that a barrier method on its own is not sufficient**

### ***Side-effects***

Below, we have listed some possible side-effects of colchicine. We will ask you to record whether you experience any of these symptoms in your daily diary. You will also receive a call from the

study team on Day 3 to check that you have received your participant pack and to answer any questions you may have. We will also ask in your daily diary about how many colchicine tablets you have left.

**Side effects that may be associated with Colchicine:**

The common side effects are:

- Abdominal pain
- Diarrhoea\*
- Nausea
- Vomiting

\*side-effects also seen with COVID-19

Rare side effects that may be associated with colchicine:

Low white blood cell count; hair loss; bone marrow disorders; gastrointestinal bleeding; kidney injury; liver injury; menstrual cycle irregularities; disease of muscle tissue; nerve disorders; rash; sperm abnormalities; low blood platelet count.



## **Platform Randomised trial of INterventions against COVID-19 In older people: The PRINCIPLE Trial**

### **PARTICIPANT INFORMATION LEAFLET**

The PRINCIPLE Trial is trying to find new treatments for COVID-19 that that can be used in the community. We hope to find treatments that help people recover quicker without needing to be admitted to hospital. We are inviting you to join this trial because we understand you are currently experiencing symptoms of COVID-19.

This leaflet gives information about the trial, including its aims, and tells you about the risks and benefits of taking part.

## *What is the purpose of the trial?*

### COVID-19

The risk of complications from COVID-19 is increased in people aged 65 and older; people aged 18 to 64 years with certain underlying health conditions; and people aged 18 to 64 years experiencing shortness of breath as part of COVID-19 illness. In these people COVID-19 can sometimes lead to significant medical problems, hospitalisation, and death.

Most people with COVID-19 are treated in the community. We urgently need to find treatments that are suitable for use in the community.

### The Trial

The purpose of this clinical trial is to find treatments that help those suffering with COVID-19 at home and in the community get better quicker and without needing to be treated in hospital. To be able to do this, we aim to test one or more suitable, possible treatments for COVID-19, as soon as they become available.

We are testing treatments that are well known and have been used for many years around the world, and already have a license for use in the UK.

All of the treatments in the PRINCIPLE trial have been approved by the UK- Medicines and Health Care Products Regulatory Agency (MHRA), as well as the Urgent Public Health panel of independent experts. The MHRA regulates the use of all medicines in the UK.

Please see Appendices for treatment specific information and the known common side-effects.

## *Can I take part?*

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

a new continuous cough

**or** a high temperature

**or** a loss of, or change in, normal sense of **taste or smell**

**OR**

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

Also, to join the trial, you need to be either:

***Aged 65 and over***

**OR**

***Aged 18-64, and experiencing shortness of breath\* as part of COVID-19 illness***

**OR**

***Aged 18-64 with any of the following underlying health conditions:***

- a) Known weakened immune system due to a serious illness or medication (e.g. chemotherapy);*
- b) Known heart disease and/or a diagnosis of high blood pressure*
- c) Known chronic lung disease (e.g. asthma)*
- d) Known diabetes*
- e) Known mild hepatic impairment;*
- f) Known stroke or neurological problem;*
- g) Self-report obesity or body mass index  $\geq 35$  kg/m<sup>2</sup>*

\*Shortness of breath can make it hard to breathe deeply and you may feel winded or as if you can't get enough air into your lungs. Unlike many other conditions that can cause shortness of breath, this symptom can persist and quickly escalate in people with COVID-19.

### ***Do I have to take part?***

No, taking part is entirely your choice and voluntary. It is up to you to decide whether to take part in the trial or not. A decision not to take part will not affect the standard of care you receive from the NHS in any way, now or in the future.

In certain circumstances, we are contacting people who may have recently tested positive for COVID-19, and information about this has been provided to the trial by NHS Digital in these unique pandemic circumstances. You have the right to opt out of any future communications

from PRINCIPLE should you wish to do so. If you do not wish to receive further communication from the trial, please let us know. PRINCIPLE will not keep your data should you choose not to take part. Please see the General Notice under the Health Service Control of Patient Information Regulations 2002 for more information (LINK). We will make a maximum of three attempts to contact you about the trial.

## ***What will happen to me if I take part?***

If you are interested in taking part, we will ask you to complete a short online form to see if you are eligible. If you do not have internet access or would like to telephone us instead, then you can contact us using the contact details at the end of the document.

### **Informed Consent**

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

### **Initial Questionnaire**

You will then complete some questions about you and how you are feeling. We will also collect some contact details such as your name, email address and telephone number. We will also ask you to provide details of a Trial Partner, if there is someone suitable for this. This could be a relative, spouse, friend or carer, if such a person is available, who we will contact for information about you if we are unable to get hold of you for whatever reason.

### **Randomisation**

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

You will receive an email or phone call to let you know which group you have been allocated to; your GP and the trial team will also receive this email. If we find that you cannot participate, we will let you know by email or phone.

### **Trial Treatment**

If you are randomised to the standard care plus trial treatment group, arrangements will be made

for the medication to be delivered to you. You will also receive instructions on how to take it and for how long, and you will be asked to confirm receipt of the medication via text or telephone call. Should your condition worsen at any time during the trial, you should not contact the trial team about this, but contact your GP or other usual services that are open to you.

### Follow-Up

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

We may contact you (email, text message or telephone call) once a month for up to 12 months after you enrol into the trial to collect information about ongoing symptoms, hospital visits and your well-being. Samples you have given or go on to give for COVID-19 in your standard care may also be used for national infection surveillance, if this is the case, we would like to access the results from any samples (including testing swabs and convalescent blood samples) held in your GP record or by PHE. In addition, we will collect information from your GP records and data held by central NHS bodies (such as NHS Digital) for long-term follow-up for up to 10 years, to help us better understand the long-term effects of COVID-19 and the trial treatments.

### Supporting other COVID-19 trials

Our main aim is to find treatments that can be used in the community and that are effective against COVID-19. We are working with other researchers to achieve this. You may receive information about other treatment trials from the PRINCIPLE trial platform.

### What happens if I am admitted to Hospital?

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

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



hospital admission that you may have during the follow up period.

#### **Optional Follow-up**

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

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

With any medicine, including ones that are already used within the NHS, there is a risk of side effects. Please see Appendices for details of the side-effects common to each drug. You will be asked to tell us if you are experiencing any of these symptoms in your daily diary, and you can also contact the trial freephone number to tell us.

### ***What are the possible benefits of taking part?***

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

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

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

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

### ***Expenses and Payments***

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

### ***What if there are any problems?***

If you have any questions about this trial, please contact the Trial Team (See Page 12 for contact details).

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

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

### ***What will happen to my data?***

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

As part of the trial enrolment process we may need to view your Summary Care Records (SCR) (<https://digital.nhs.uk/services/summary-care-records-scr/summary-care-records-scr-information-for-patients>) to check your medication, allergies, adverse reactions and 'Additional Information' to make sure that it is safe for you to take trial medication. A SCR is an electronic record of important patient information, created from GP medical records. SCR 'Additional Information' includes information recorded in your GP record about your significant illnesses and health problems, operations and vaccinations you have had in the past, how you would like to be treated (such as where you would prefer to receive care), what support you might need and who should be contacted for more information about you. SCRs can be seen and used by authorised staff in other areas of the health and care system involved in your direct care.

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

### ***What if relevant new information becomes available during the trial?***

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

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

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

### ***What will happen to the results of the trial?***

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

### ***Who is organising and funding the research?***

Funding has been provided by the National Institute for Health Research. PRINCIPLE has been set up by the Primary Care Clinical Trials Unit at the University of Oxford. In-kind contributions: Department of Health and Social Care provided hydroxychloroquine, free of charge.

### ***Who has reviewed the trial?***

All research in the NHS is looked at by an independent group of people called a Research Ethics Committee (REC). The REC is there to protect your safety, rights, wellbeing and dignity. This trial has been ethically reviewed and was approved by the South Central - Berkshire Research Ethics Committee (REC Reference: 20/SC/0158).

This trial has also received approval from the Medicines and Healthcare products Regulatory Agency (MHRA).

#### **Trial Team:**

Tel. 0800 138 0880

#### **Trial Email Address:**

[principle@phc.ox.ac.uk](mailto:principle@phc.ox.ac.uk)

### **PRINCIPLE Radio Advert**

COVID-19 has affected the lives of everybody within the UK and the rest of the world. Finding safe and effective treatments has been the drive of researchers at the University of Oxford and right now, you have an opportunity to help. PRINCIPLE is a national priority trial to find treatments for COVID-19. We are looking for volunteers aged 65 or over, or 18-64 years and experiencing shortness of breath as part of COVID-19 illness, or 18-64 years with certain underlying health conditions. s. To be eligible to take part, you must be unwell with Covid-19 symptoms, and have had them for less than 14 days. No face to face visits are needed. Please help us fight COVID-19 by visiting our website [www.principletrial.org](http://www.principletrial.org).

COVID-19 has affected the lives of everybody. Finding safe and effective treatments has been the drive of researchers at the University of Oxford and right now, you have an opportunity to help. We are looking for volunteers aged **18 or over** with COVID-19 symptoms to take part in a national priority trial. Please help us fight COVID-19 by visiting [www.principletrial.org](http://www.principletrial.org)



## **PRINCIPLE Trial – Social Media Post – version 1**

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

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

The trial is open to people aged 65 or over, or 18-64 years and experiencing shortness of breath as part of COVID-19 illness, or 18-64 years with certain underlying health conditions.

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

<http://www.principletrial.org>

## **PRINCIPLE Trial – Social Media Post – version 2**

PRINCIPLE is an Urgent Public Health clinical trial investigating treatments for people aged over 18, with COVID-19 symptoms. More details at [www.principletrial.org](http://www.principletrial.org) or click [HERE](#) to register as a patient from PRACTICE NAME.

## VOLUNTEERS NEEDED

Do you have suspected or confirmed COVID-19?

### Are you aged 65 or over?

**OR 18-64** and experiencing shortness of breath as part of COVID-19 illness, with symptoms within the past 14 days?

**OR 18-64** with underlying health conditions, with symptoms within the past 14 days?

Please visit  
[www.principletrial.org](http://www.principletrial.org)

to find out how to take part in an Urgent Public Health clinical trial for COVID-19 treatments

SCAN ME



## VOLUNTEERS NEEDED

Do you have suspected or confirmed COVID-19?

### Are you aged 65 or over?

**OR 18-64** and experiencing shortness of breath as part of COVID-19 illness, with symptoms within the past 14 days?

**OR 18-64** with underlying health conditions, with symptoms within the past 14 days?

Please visit  
[www.principletrial.org](http://www.principletrial.org)

to find out how to take part in an Urgent Public Health clinical trial for COVID-19 treatments

SCAN ME



## VOLUNTEERS NEEDED

Do you have suspected or confirmed COVID-19?

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**OR 18-64** and experiencing shortness of breath as part of COVID-19 illness, with symptoms within the past 14 days?

**OR 18-64** with underlying health conditions, with symptoms within the past 14 days?

Please visit  
[www.principletrial.org](http://www.principletrial.org)

to find out how to take part in an Urgent Public Health clinical trial for COVID-19 treatments

SCAN ME



## VOLUNTEERS NEEDED

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**OR 18-64** and experiencing shortness of breath as part of COVID-19 illness, with symptoms within the past 14 days?

**OR 18-64** with underlying health conditions, with symptoms within the past 14 days?

Please visit  
[www.principletrial.org](http://www.principletrial.org)

to find out how to take part in an Urgent Public Health clinical trial for COVID-19 treatments

SCAN ME



## VOLUNTEERS NEEDED

Do you have suspected or confirmed COVID-19?

### Are you aged 65 or over?

**OR 18-64** and experiencing shortness of breath as part of COVID-19 illness, with symptoms within the past 14 days?

**OR 18-64** with underlying health conditions, with symptoms within the past 14 days?

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SCAN ME



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SCAN ME



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SCAN ME



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SCAN ME



## PRINCIPLE video infographic script

### *\*Introduction\**

COVID-19 can lead to significant medical problems, hospitalisation, and sometimes death. So far, there are no treatments that have been proven in clinical trials to help people recover from COVID-19 while in the community.

We need to find treatments that help people recover quicker and reduce the need for them to go to hospital.

### *\*What the study involves\**

We are looking for people aged 18 years or over with symptoms including a cough OR temperature OR loss/change of smell/taste, starting within the past 14 days. OR you may have had a recent confirmed test for COVID-19 with any other symptoms.

Registering for the study can be completed online or over the phone and no face to face visits are required. You will be randomly assigned to receive usual care or medication. We will send everyone a participant pack directly to their home. If you have any questions at all you can contact the trial free phone number or your GP.

### *\*Summary\**

If you are unwell now with COVID-19 or **become unwell in the future**, please visit our website [www.principletrial.org](http://www.principletrial.org) for more information or to register for the trial. You can also call the team on 0800 138 0880

Please help us fight COVID-19 and consider registering for the PRINCIPLE Trial.



## Website Trial Advert

### Join a COVID-19 clinical trial

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

- You have had these symptoms for fewer than 15 days:
- new continuous cough or high temperature or a loss of, or change in, normal sense of taste or smell
- OR have a positive test for SARS-Co-V2 infection with COVID-19 symptoms in the past 14 days
- You are aged 65 and above,
- OR 18-64 and experiencing shortness of breath as part of COVID-19 illness,
- OR 18-64 with certain underlying health conditions.
  - **Find out more LINK**



Participant identifier

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Participant initials

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**Baseline CRF**

Introduction															
1.	Date of birth (DD/MMM/YYYY):	_ _ / _ _ _ / _ _ _ _													
2.	Sex	Male / Female / Other													
3.	Ethnicity:  White White and Black Caribbean White and Black Asian Any other Mixed/Multiple ethnic background Indian Pakistani Bangladeshi Chinese Any other Asian background African Caribbean Any other Black/African/Caribbean background Any other ethnic group, please describe	<table border="1"> <tr><td></td></tr> <tr><td></td></tr> <tr><td></td></tr> <tr><td></td></tr> <tr><td></td></tr> <tr><td></td></tr> <tr><td></td></tr> <tr><td></td></tr> <tr><td></td></tr> <tr><td></td></tr> <tr><td></td></tr> <tr><td></td></tr> <tr><td></td></tr> </table>													
3a)	If other, please describe: _____														
4.	Have you had a vaccination for COVID-19?	Yes <input type="checkbox"/> No <input type="checkbox"/>													
4a)	Have you had the first shot or the first and second shot?	First shot <input type="checkbox"/> First & Second shot <input type="checkbox"/>													
4b)	What date did you receive the first shot? (If exact date not known please provide the month and/or year).	_ _ / _ _ _ / _ _ _ _ Don't know <input type="checkbox"/>													
4c)	What date did you receive the second shot? (If exact date not known please provide the month and/or year).	_ _ / _ _ _ / _ _ _ _ Don't know <input type="checkbox"/>													

Participant identifier

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Participant initials

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**Baseline CRF**

5.	Have you had a test for COVID-19?	Yes <input type="checkbox"/> No <input type="checkbox"/>
5a)	What was the result?	Positive / Negative / Not yet received
5b)	Date of result	_ _ / _ _ _ / _ _ _ _
5c)	What was the result?	Positive / Negative / Not yet received
5d)	Date of result	_ _ / _ _ _ / _ _ _ _
6.	Are you a current smoker?	Yes <input type="checkbox"/> No <input type="checkbox"/>
6a)	Are you an ex-smoker?	Yes <input type="checkbox"/> No <input type="checkbox"/>
7.	Do you live in a residential, nursing or care home?	Yes <input type="checkbox"/> No <input type="checkbox"/>

**Do you have any of the following co-morbidities/conditions:**

8.	• Asthma, COPD or other lung disease	Yes <input type="checkbox"/> No <input type="checkbox"/>
9.	• Diabetes	Yes <input type="checkbox"/> No <input type="checkbox"/>
10.	• Heart problems (e.g. angina, heart attack, heart failure, atrial fibrillation, valve problems)	Yes <input type="checkbox"/> No <input type="checkbox"/>
11.	• Diagnosed with hypertension (high blood pressure)	Yes <input type="checkbox"/> No <input type="checkbox"/>
12.	• Liver disease	Yes <input type="checkbox"/> No <input type="checkbox"/>
13.	• Stroke or other neurological problem	Yes <input type="checkbox"/> No <input type="checkbox"/>
14.	• Weakened immune system due to a serious illness or medication (e.g. chemotherapy)	Yes <input type="checkbox"/> No <input type="checkbox"/>
15.	• Body mass index (BMI) at or above 35kg/m <sup>2</sup>	Yes <input type="checkbox"/> No <input type="checkbox"/>
16.	Are you taking ramipril, lisinopril, perindopril, captopril or enalapril?	Yes <input type="checkbox"/> No <input type="checkbox"/>

Participant identifier

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Participant initials

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### Baseline CRF

Symptoms														
Please rate the following symptoms today:														
17.	Fever	No problem / Mild problem / Moderate problem / Major problem												
18.	Cough	No problem / Mild problem / Moderate problem / Major problem												
19.	Shortness of breath	No problem / Mild problem / Moderate problem / Major problem												
20.	Muscle ache	No problem / Mild problem / Moderate problem / Major problem												
21.	Nausea / Vomiting	No problem / Mild problem / Moderate problem / Major problem												
22.	Diarrhoea	No problem / Mild problem / Moderate problem / Major problem												
23.	Loss of smell and/or taste	No problem / Mild problem / Moderate problem / Major problem												
24.	Headache	No problem / Mild problem / Moderate problem / Major problem												
25.	Abdominal pain	No problem / Mild problem / Moderate problem / Major problem												
26.	Generally feeling unwell	No problem / Mild problem / Moderate problem / Major problem												
27.	How well are you/participant feeling today? Please rate how you are feeling now using a scale of 1 – 10, where 1 is the worst you can imagine, and 10 is feeling the best you can imagine.													
<table border="1"> <tr> <td><b>Worst</b></td> <td>1</td> <td>2</td> <td>3</td> <td>4</td> <td>5</td> <td>6</td> <td>7</td> <td>8</td> <td>9</td> <td>10</td> <td><b>Best</b></td> </tr> </table>			<b>Worst</b>	1	2	3	4	5	6	7	8	9	10	<b>Best</b>
<b>Worst</b>	1	2	3	4	5	6	7	8	9	10	<b>Best</b>			

Participant identifier

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Participant initials

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**Baseline CRF**
**Antibiotics**

28.	Have you taken antibiotics since your illness started?	Yes <input type="checkbox"/>	No <input type="checkbox"/>
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**Healthcare Services**

Have you had contact with the following healthcare services since your illness started? Please answer Yes or No.

29.	GP	Yes <input type="checkbox"/>	No <input type="checkbox"/>
30.	Other primary Care services (e.g. walk-in services/pharmacist)	Yes <input type="checkbox"/>	No <input type="checkbox"/>
31.	NHS 111	Yes <input type="checkbox"/>	No <input type="checkbox"/>
32.	A&E	Yes <input type="checkbox"/>	No <input type="checkbox"/>
33.	Other	Yes <input type="checkbox"/>	No <input type="checkbox"/>
33a)	If 'Other' please specify: _____		

**Wellbeing**

Please indicate for each of the 5 statements which is closest to how you have been feeling over the past 2 weeks.

	Over the past 2 weeks...	All of the time	Most of the time	More than half the time	Less than half the time	Some of the time	At no time
34.	... I have felt cheerful and in good spirits	5	4	3	2	1	0
35.	... I have felt calm and relaxed	5	4	3	2	1	0
36.	... I have felt active and vigorous	5	4	3	2	1	0
37.	... I woke up feeling fresh and rested	5	4	3	2	1	0
38.	... my daily life has been filled with things that interest me	5	4	3	2	1	0

Completed by: Print name .....Sign .....Date \_\_ / \_\_ / \_\_

Participant identifier

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Participant initials

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### Eligibility CRF

Date eligibility completed: _____	
Participant NHS number: _____	
1.	<p>Please select the participant's age range:</p> <ul style="list-style-type: none"> <li>Less than 18 (<b>Ineligible</b>)</li> <li>18—49</li> <li>50—64</li> <li>65+</li> </ul> <div style="border: 1px solid black; padding: 5px; margin-top: 10px;"> <p>18—49—Eligible for UC or <b>COLCH</b></p> <p>50+ —Eligible for UC, <b>BUDE</b> or <b>COLCH</b></p> </div>
2.	<p>Does the participant have at least one of the comorbidities/conditions listed below?</p> <ul style="list-style-type: none"> <li>Weakened immune system due to a serious illness or medication (e.g. chemotherapy)</li> <li>Heart disease or high blood pressure</li> <li>Asthma or lung disease</li> <li>Known diabetes</li> <li>Liver disease</li> <li>Stroke or neurological problem</li> </ul> <div style="border: 1px solid black; padding: 5px; margin-top: 10px;"> <p>If Yes and age range = 18-49—Eligible for <b>COLCH</b></p> <p>If Yes and age range = 50-64—Eligible for <b>COLCH</b> and <b>BUDE</b></p> </div>
2a)	<p>If No, does the participant have a body mass index (BMI) at or above 35 kg/m<sup>2</sup>?</p>
2b)	<p>If No, is the participant experiencing shortness of breath as part of a Covid-19 illness? Shortness of breath can make it hard to breathe deeply and you may feel winded or as if you can't get enough air into your lungs. Unlike many other conditions that cause shortness of breath, this symptom can persist and quickly escalate in people with COVID-19.</p> <div style="border: 1px solid black; padding: 5px; margin-top: 10px;"> <p>If Yes—Eligible for <b>COLCH</b></p> <p>If No—<b>Ineligible</b></p> </div>
3.	<p>Is the participant able to use an inhaler?</p>
4.	<p>Is the participant currently admitted to hospital?</p>
5.	<p>Has the participant previously participated in the PRINCIPLE trial?</p>

Participant identifier

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Participant initials

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### Eligibility CRF

6.	Does the participant have a known allergy to inhaled corticosteroids?	Yes <input type="checkbox"/> No <input type="checkbox"/>
7.	Is the participant currently prescribed corticosteroids by inhaler, by mouth or had a corticosteroid injection in the past month?	Yes <input type="checkbox"/> No <input type="checkbox"/>
8.	Does the participant have any of the following conditions: <ul style="list-style-type: none"> <li>• Galactose intolerance</li> <li>• Lapp lactase deficiency</li> <li>• Glucose-galactose malabsorption</li> </ul>	Yes <input type="checkbox"/> No <input type="checkbox"/>
9.	Is the participant pregnant or planning on becoming pregnant within the next few weeks?	Yes <input type="checkbox"/> No <input type="checkbox"/>
10.	Is the participant breastfeeding or planning on starting during the course of the trial?	Yes <input type="checkbox"/> No <input type="checkbox"/>
11.	Is the participant a pre-menopausal female that is capable of becoming pregnant?	Yes <input type="checkbox"/> No <input type="checkbox"/>
11 a)	If yes, is the participant using a highly effective method of contraception* and prepared to use this for the 28 days of the study?  * The implant, the coil, and male or female sterilisation will be acceptable for participating in the trial. The injection and most forms of hormonal contraception will also be considered acceptable for the trial, if used in combination with condoms or other barrier methods. However, condoms alone won't be sufficient during the study.	Yes <input type="checkbox"/> No <input type="checkbox"/>
12.	Is the participant hypersensitive/allergic to any of the following: <ul style="list-style-type: none"> <li>• Colchicine</li> <li>• Lactose</li> <li>• Pregelatinised Maize Starch</li> <li>• Stearic Acid</li> <li>• Purified Water</li> <li>• Ethanol (96%)</li> </ul>	Yes <input type="checkbox"/> No <input type="checkbox"/>

Participant identifier

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Participant initials

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### Eligibility CRF

13.	Does the participant have a clinically significant blood dyscrasia?	Yes <input type="checkbox"/> No <input type="checkbox"/>
14.	Does the participant have a known severe renal impairment or require dialysis?	Yes <input type="checkbox"/> No <input type="checkbox"/>
15.	Does the participant have severe liver disease?	Yes <input type="checkbox"/> No <input type="checkbox"/>
16.	<p>Is the participant currently taking any of the following drugs:</p> <ul style="list-style-type: none"> <li>• Clarithromycin</li> <li>• Cobicistat</li> <li>• Colchicine</li> <li>• Cyclosporin</li> <li>• Diltiazem</li> <li>• Disulfiram</li> <li>• Erythromycin</li> <li>• HIV protease inhibitors (e.g. ritonavir, atazanavir)</li> <li>• Itraconazole</li> <li>• Ketoconazole</li> <li>• Quinidine</li> <li>• Verapamil</li> <li>• Voriconazole</li> </ul>	Yes <input type="checkbox"/> No <input type="checkbox"/>
17.	Does the participant have inflammatory bowel disease or chronic diarrhoea?	Yes <input type="checkbox"/> No <input type="checkbox"/>

Participant identifier

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Participant initials

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### Eligibility CRF

18.	Is there any other reason you would exclude this participant? If yes, please provide your reason in the comments box below.	Yes <input type="checkbox"/> No <input type="checkbox"/>
Comments: <hr/> <hr/> <hr/>		

#### KEY

Exclusion for all arms

Exclusion criteria from inhaled corticosteroids

Exclusion criteria from colchicine

#### NOTES

Q 1 – 5 = Inclusion criteria

Q5 onwards = Exclusion criteria

Completed by: Print name ..... Sign ..... Date \_\_ / \_\_ / \_\_

Reviewed by: Print name ..... Sign ..... Date \_\_ / \_\_ / \_\_



# Participant Pictorial Information Sheet

## Platform Randomised trial of Interventions against Covid-19 In older people

### PRINCIPLE Trial

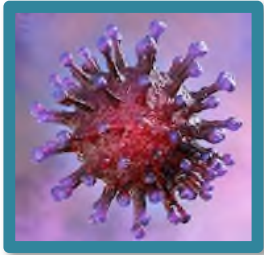

Platform Randomised trial of Interventions against COVID-19 In older people

Pictorial Participant Information Booklet v2.4, 12 February 2021,

**EudraCT number:2020-001209-22**

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

## What is the trial about?



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

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

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

# Who can take part?



Anybody aged 65 years or over.

**AND**

Anybody aged 18-64 and experiencing shortness of breath as part of COVID-19 illness.

5.

**AND**

- Anybody aged 18-64 with certain underlying health conditions: weakened immune system (e.g. taking chemotherapy)
- Known heart disease

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		<ul style="list-style-type: none"> <li>• Known asthma or lung disease</li> <li>• Known diabetes</li> <li>• Known Liver disease</li> <li>• Known stroke or neurological problem</li> <li>• Obesity</li> </ul> <p><b>WITH</b></p> <p>A new continuous cough or fever or a change in taste/smell OR You have had a <b>positive test</b> for SARS-Co-V2 infection which was taken fewer than 15 days ago, AND are unwell with symptoms of COVID-19.</p> <p><i>These symptoms may include, but are not</i></p>
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		<p><i>limited to, shortness of breath, general feeling of being unwell, muscle pain, diarrhoea, vomiting, fever and cough, and you must have had them for <b>fewer than 15 days</b>. If you are starting to feel better, this study isn't for you.</i></p>
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## What will happen if I take part?



	<p>6. If you develop a fever or a new continuous cough or change in taste/smell, OR if you have a positive test for SARS-Co-V2 infection with symptoms in the</p>
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		past 14 days, <b>please visit our trial website (see end of this leaflet).</b>
	7.	We will ask you to fill in a short form online, to check that you can take part
	8.	Your care will not be affected, whether or not you do take part in the trial.

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	<p>9.</p>	<p>If you are suitable to take part in the trial, you will be asked to fill in a consent form online, and to answer a few questions about yourself and your symptoms.</p>
	<p>10.</p>	<p>We will ask you to add details of a 'trial partner'. This is somebody that might be able help you with the study, and who we can also contact for information about how you are getting on.</p>




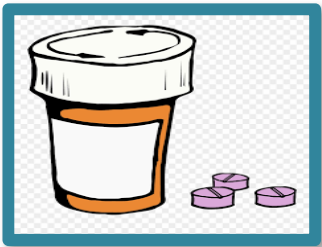
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	11.	The information that you give us will be shared with your GP and the study team, so that we can double check that everything is in order for you to take part.
	12.	If you can take part, you will be randomly (like tossing a coin) entered into a group:-
 <p>a) Usual care for your symptoms</p>	Or	 <p>b) You will receive one of the treatments that we are testing, in</p>

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		<p>addition to usual care for your symptoms.</p> <p>We will provide you with the trial medication and instructions on how to take it.</p>
	13.	<p>Whichever group you are in, we will ask you to answer a few questions each daily in an online diary for up to 28 days, so that we know how you are feeling.</p>

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	14.	<p>If you are unable to answer questions online, or forget to complete the questions, we might give you a phone call or send you a text message reminder.</p>
	15.	<p>If you are admitted to hospital, we would ask you, or someone close to you, to let us know.</p>
	16.	<p>If you agree to join the study, we will contact you at 28 days to see whether you are happy for us to arrange to speak with you in more detail about your</p>

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		<p>experience of taking part in the trial.</p> <p>Samples you have given or go on to give for COVID-19 in your standard care may also be used for national surveillance, if this is the case we would like to access the results from any samples (including testing swabs and convalescent blood samples) held in your GP record or by PHE.</p>
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Platform Randomised trial of Interventions against COVID-19 In older people

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# What will happen to my information?

	<p>17. We will use the information you give us to find out which treatments work. We may also look at your general practice and hospital medical records for further information about you and your illness.</p>
	<p>18. Any information that we collect about you will be kept safe. Your name will not go on any reports, presentations or publications.</p>

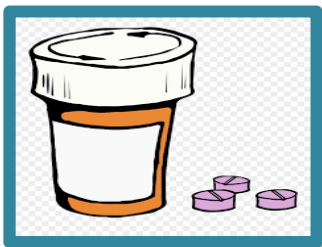
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## What are the disadvantages of taking part?

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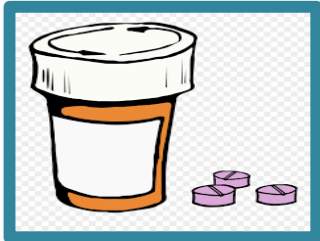
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## What are the benefits of taking part?

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


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## Will I be reimbursed for taking part?

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

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

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

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# What if there is a problem?

	25.	<p>If you have a concern about any aspect of this trial at any time, you can contact the trial team or the University of Oxford Clinical Trials and Research Governance (CTRG) office (Contact details below).</p>
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Platform Randomised trial of Interventions against COVID-19 In older people

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

## Trial contact details


	26.	<p>Trial team: <a href="mailto:principle@phc.ox.ac.uk">principle@phc.ox.ac.uk</a></p> <p>0800 138 0880</p> <p>Trial Website: <b><a href="http://www.principletrial.org">www.principletrial.org</a></b></p> <p>CTRG: <a href="mailto:ctrg@admin.ox.ac.uk">ctrg@admin.ox.ac.uk</a> 01865 616480</p>
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Platform Randomised trial of Interventions against COVID-19 In older peoPLE

Pictorial Participant Information Booklet v2.4, 12 February 2021,

**EudraCT number:2020-001209-22**

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

	<p>27. Thank you for taking the time to think about taking part in this trial.</p>
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**Thank you!**

Participant identifier

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Participant initials

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### Screening CRF

Date of completion: \_\_\_\_\_

1.	<p>Please select your age range:</p> <ul style="list-style-type: none"> <li>• Less than 18</li> <li>• 18—49</li> <li>• 50—64</li> <li>• 65+</li> </ul>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>
2.	Are you willing to give informed consent for participation in the study?	Yes <input type="checkbox"/> No <input type="checkbox"/>
3.	<p>Do you have a new continuous cough, and/or high temperature, and/or a loss of or change in your normal taste or sense of smell, which have been present for less than 15 days?</p> <p><b>Defined:</b> A new continuous cough - this means coughing 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) <b>and/or</b> A high temperature - this means you feel hot to touch on your chest or back (you do not need to take your temperature)</p>	Yes <input type="checkbox"/> No <input type="checkbox"/>
3a)	What date did you start to feel unwell with this illness (DD/MMM/YYYY)?	__ / __ / ____
3b)	Are you feeling almost recovered from this illness (i.e. generally much improved and your symptoms are now mild or almost absent)?	Yes <input type="checkbox"/> No <input type="checkbox"/>
4.	Have you had a positive test for COVID-19 infection?	Yes <input type="checkbox"/> No <input type="checkbox"/>
4a)	What date was this COVID-19 test taken?	__ / __ / ____
5.	<p>Are you unwell with symptoms of COVID-19?</p> <p>These symptoms may include, but are not limited to, shortness of breath, general feeling of being unwell, muscle pain, diarrhoea and vomiting.</p>	Yes <input type="checkbox"/> No <input type="checkbox"/>
5a)	What date did you start to feel unwell with this illness?	__ / __ / ____
5b)	Are you feeling almost recovered from this illness (i.e. generally much improved and your symptoms are now mild or almost absent)?	Yes <input type="checkbox"/> No <input type="checkbox"/>

Participant identifier

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Participant initials

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### Screening CRF

6.	Do you have at least one of the comorbidities/conditions listed below? <ul style="list-style-type: none"> <li>• Weakened immune system due to a serious illness or medication (e.g. chemotherapy)</li> <li>• Heart disease or high blood pressure</li> <li>• Asthma or lung disease</li> <li>• Known diabetes</li> <li>• Liver disease</li> <li>• Stroke or neurological problem</li> </ul>	Yes <input type="checkbox"/> No <input type="checkbox"/>
7.	Do you have a body mass index (BMI) at or above 35 kg/m <sup>2</sup> ? You can check your BMI here: <a href="https://www.nhs.uk/live-well/healthy-weight/bmi-calculator">https://www.nhs.uk/live-well/healthy-weight/bmi-calculator</a>	Yes <input type="checkbox"/> No <input type="checkbox"/>
8.	Are you experiencing shortness of breath as part of a Covid-19 illness? Shortness of breath can make it hard to breathe deeply and you may feel winded or as if you can't get enough air into your lungs. Unlike many other conditions that cause shortness of breath, this symptom can persist and quickly escalate in people with COVID-19.	Yes <input type="checkbox"/> No <input type="checkbox"/>
9.	Are you able to use an inhaler?	Yes <input type="checkbox"/> No <input type="checkbox"/>
10.	Are you currently admitted to hospital?	Yes <input type="checkbox"/> No <input type="checkbox"/>
11.	Have you previously participated in the PRINCIPLE trial?	Yes <input type="checkbox"/> No <input type="checkbox"/>
12.	Do you have a known allergy to inhaled corticosteroids?	Yes <input type="checkbox"/> No <input type="checkbox"/>
13.	Are you currently prescribed corticosteroids by inhaler, by mouth or had a corticosteroid injection in the past month?	Yes <input type="checkbox"/> No <input type="checkbox"/>
14.	Do you have any of the following conditions: <ul style="list-style-type: none"> <li>• Galactose intolerance</li> <li>• Lapp lactase deficiency</li> <li>• Glucose-galactose malabsorption</li> </ul>	Yes <input type="checkbox"/> No <input type="checkbox"/>

Participant identifier

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Participant initials

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### Screening CRF

15.	Are you pregnant or planning on becoming pregnant within the next few weeks?	Yes <input type="checkbox"/> No <input type="checkbox"/>
16.	Are you breastfeeding or planning on starting during the course of the trial?	Yes <input type="checkbox"/> No <input type="checkbox"/>
17.	Are you a pre-menopausal female that is capable of becoming pregnant?	Yes <input type="checkbox"/> No <input type="checkbox"/>
17 a)	If yes, are you using a highly effective method of contraception* and prepared to use this for the 28 days of the study?  * The implant, the coil, and male or female sterilisation will be acceptable for participating in the trial. The injection and most forms of hormonal contraception will also be considered acceptable for the trial, if used in combination with condoms or other barrier methods. However, condoms alone won't be sufficient during the study.	Yes <input type="checkbox"/> No <input type="checkbox"/>
18.	Are you hypersensitive/allergic to any of the following: <ul style="list-style-type: none"> <li>• Colchicine</li> <li>• Lactose</li> <li>• Pregelatinised Maize Starch</li> <li>• Stearic Acid</li> <li>• Purified Water</li> <li>• Ethanol (96%)</li> </ul>	Yes <input type="checkbox"/> No <input type="checkbox"/>
19.	Do you have a known blood disorder that requires regular hospital appointments?	Yes <input type="checkbox"/> No <input type="checkbox"/>
20.	Do you have a known severe kidney impairment or require dialysis?	Yes <input type="checkbox"/> No <input type="checkbox"/>
21.	Do you have severe liver disease?	Yes <input type="checkbox"/> No <input type="checkbox"/>

Participant identifier

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Participant initials

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### Screening CRF

22.	<p>Are you currently taking any of the following drugs:</p> <ul style="list-style-type: none"> <li>• Clarithromycin</li> <li>• Cobicistat</li> <li>• Colchicine</li> <li>• Cyclosporin</li> <li>• Diltiazem</li> <li>• Disulfiram</li> <li>• Erythromycin</li> <li>• HIV protease inhibitors (e.g. ritonavir, atazanavir)</li> <li>• Itraconazole</li> <li>• Ketoconazole</li> <li>• Quinidine</li> <li>• Verapamil</li> <li>• Voriconazole</li> </ul>	<p>Yes <input type="checkbox"/> No <input type="checkbox"/></p>
23.	Are you willing to not eat or drink grapefruit juice for 14 days?	<p>Yes <input type="checkbox"/> No <input type="checkbox"/></p>
24.	Do you have inflammatory bowel disease or chronic diarrhoea?	<p>Yes <input type="checkbox"/> No <input type="checkbox"/></p>

Comments: \_\_\_\_\_

25.	<p>Where did you hear about the trial?</p> <ul style="list-style-type: none"> <li>• GP</li> <li>• Facebook</li> <li>• Radio</li> <li>• Test Centre</li> <li>• Poster</li> <li>• Other healthcare provider</li> <li>• Pharmacy</li> <li>• Received call from trial team</li> <li>• Joint Dementia Research</li> <li>• Other</li> </ul>	<table border="1"> <tr><td></td></tr> <tr><td></td></tr> <tr><td></td></tr> <tr><td></td></tr> <tr><td></td></tr> <tr><td></td></tr> <tr><td></td></tr> <tr><td></td></tr> <tr><td></td></tr> <tr><td></td></tr> </table>										

Completed by: Print name ..... Sign ..... Date \_\_ / \_\_ / \_\_





Researchers at the University of Oxford are appealing for people with typical COVID-19 symptoms, aged 65 years and over, or 18-64 years and experiencing shortness of breath as part of COVID-19 illness, or 18-64 years with certain underlying health conditions., to take part in a COVID-19 treatment trial - PRINCIPLE.

Currently, there are no effective treatments available that have been shown through clinical trials to reduce disease burden in the community. PRINCIPLE is evaluating whether certain commonly used medicines, such as antibiotics, may prevent patients with COVID-19 from becoming more unwell and needing hospital care.

The research team are appealing for people experiencing symptoms that are likely to be caused by a COVID-19 infection, for fewer than 15 days, to join the trial. People may also be eligible to join if they have had a positive test for COVID infection which was taken less than 15 days ago, and are unwell with any symptoms.

There are no face to face visits involved and people can take part either online or over the phone. Anyone in the UK over 18 who is unwell with COVID symptoms may be able to take part and a participant pack will be couriered directly to patient's homes.

<Quote from healthcare provider making video>



NUFFIELD DEPARTMENT OF  
**PRIMARY CARE**  
HEALTH SCIENCES

Primary Care  
Clinical Trials Unit



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

**Translated video script, Version/Date: v1.1 12 February 2021, EudraCT number:2020-001209-22**

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

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

Date:

Hello,

I'm writing to let you know how you can support someone taking part in a research study to help find treatments for coronavirus / COVID-19.

The study is called PRINCIPLE and it is run by the University of Oxford. It aims to find treatments for people with symptoms of COVID-19, and who are aged 65 years and over, or 18-64 years and experiencing shortness of breath as part of COVID-19 illness, or 18-64 years with certain underlying health conditions. PRINCIPLE is supported by the UK government's Chief Medical Officer as a national priority study to find possible treatments for COVID-19.

People can get more information and sign up by telephoning 0800 138 0880 or at [www.principletrial.org](http://www.principletrial.org). There, they can also download a detailed patient information leaflet and a shorter summary that explains the study. All participants should understand the study before agreeing to take part. They will be able to nominate a 'Study Partner' (family, friend or carer e.g. care home staff) to help them with some of the things that will happen in the study. If you have any questions, please call/email the trial team, 0800 138 0880/principle@phc.ox.ac.uk.

Someone you know, who has already joined the PRINCIPLE study, may have asked you to be their Study Partner. Or you may know someone who is interested in joining and is thinking about asking you to be their Study Partner. The person joining the study has provided your contact details. Please see the Patient Information Sheet (<https://www.phctrials.ox.ac.uk/principle-trial/how-to-join>) for details about what will happen to personal data collected in the trial. The things that you could help with by being a Study Partner are described below:

What will happen in the study	How the Study Partner can help
People interested in joining the study will need to answer some questions on the telephone or online to check whether they are suitable, and provide consent.	Help with accessing information about the study and calling the study team on 0800 138 0880, or completing the online form at <a href="http://www.principletrial.org">www.principletrial.org</a> .  Provide your email and/or telephone number for the

	PRINCIPLE team to contact you as the Study Partner
Their GP, or a study nurse or doctor, will also check their medical notes to make sure it is safe for them to be in the study.	
Once signed up, the participant will either receive usual care, or usual care and a study medication which will be delivered from their GP, or directly from the study team. All study medications are already widely used in the NHS and have been approved as safe for use in this study.	Help the participant to take the medication according to instructions in the medication pack.
If they can access the internet, for the next 28 days we would like them to complete an online diary of their symptoms and medical care they have received. The trial team may also phone them or their study partner after 2, 7, 14 and 28 days to get this information, especially if accessing the internet is difficult.	Help the participant with completing the online diary and/or by receiving telephone calls after 2, 7, 14 and 28 days (these can be timetabled with the study team). The Study Partner can also complete the diary or take the telephone calls themselves if the participant is unable to do this (for example if they feel too unwell).

Many thanks for thinking about supporting this study to find treatments for COVID-19, your help is much appreciated.

Yours Sincerely,

The PRINCIPLE Trial Team