

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 ≥ 35 kg/m²*

*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 or **0800 138 0880** or you may contact the University of Oxford Clinical Trials and Research Governance (CTRG) office on 01865 616480, or the head of CTRG, email ctrig@admin.ox.ac.uk.

What will happen to my data?

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.

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

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.