Platform Randomised Trial of Treatments in the Community for Epidemic and Pandemic Illnesses: 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. We will also assess less familiar treatments which might have beneficial effects for the treatment of COVID-19, but which do not yet 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/m^2

*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.

Some of the treatment we are testing in the study may not be licensed for use in the UK. We call these 'less well known treatments'. If you have been allocated to receive a less well known treatment, a member of our trial team will contact you within one day of joining the trial, as well as on Day 3. During the Day 1 call, a doctor or nurse will check you are still happy to take part in the study and explain specific side-effects. On Day 3, we will confirm that you gave received your participant pack, and read and understood the medication card provided. Please see the PIS appendices for further details about the trial treatments and those classed as less well known. You will also be able to call us at any time if you have any concerns about side effects caused by the treatment, using the trial freephone number: 0800 138 0880. If you are allocated to a less well known treatment and report any major side-effects (those that cause considerable limitation in your usual activity. Require medication or medical attention), and we are unable to contact you or your study partner, with your consent we will contact your GP directly. We will ask you to return any unused medication in a pre-paid envelope to the trial team, via courier.

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, or you can contact the trial freephone number. On a daily basis, if you are taking a less well known medication, the trial's clinical team will monitor specific, pre-defined potential side-effects that you report in your daily diaries, and contact you if required. Please see the medication specific appendices for details about which side-effects will be monitored for each treatment.

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 have informed the trial team of certain moderate or major side effects from taking a trial medicine not licenced in the UK, the trial team would like to contact you and/or your GP until you feel better.

If you wish to withdraw from the trial, please contact the trial team using the contact details at the end of this document. 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 the last page 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 ctrg@admin.ox.ac.uk.

What will happen to my data?

All information about you and your health will be kept private. The only people allowed to look at the information will be the doctors running the trial, the trial team and the regulatory authorities who check that the 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 on the last page).

Who is organising and funding the research?

Funding has been provided the by UKRI and 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, and Favipiravir, 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 - Favipiravir

Drug Information

Favipiravir is an oral (i.e. taken by mouth) antiviral that is licensed in Japan for use as a treatment for flu, and has been used in clinical trials for Ebola. Although it is not currently licensed for use in the UK or routinely used, Favipiravir is proven to have a good safety profile and in a number of clinical trials the drug has been shown to improve recovery from COVID-19 symptoms and may therefore be an effective treatment for COVID-19.

Favipiravir Dose and Administration

Favipiravir 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.

For this trial, nine tablets (1800mg) favipiravir to be taken orally twice a day on day one, and then four tablets (800mg) twice daily for four days (50 tablets in total).

You should avoid excessive exposure to sunlight or artificial ultraviolet light for the five days whilst taking favipiravir.

You must not take more than 6 paracetamol tablets in 24 hours whilst for the five days whilst taking favipiravir.

If you decide that you no longer wish to take the medication, you will be asked to return your medication to the trial team in the pre-paid envelope, via courier.

Potential COVID-19 Treatment

Several small clinical studies have found that favipiravir may help to treat COVID-19. However, we need more evidence from large clinical trials, which is why we have included the treatment in the PRINCIPLE Trial. Favipiravir has been highly recommended by the UK COVID-19 Therapeutics Advisory Panel (UK-CTAP) for the treatment of COVID-19.

The use of favipiravir in PRINCIPLE has 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 meet any of the following reasons for NOT taking favipiravir. If you meet ANY of the following criteria, you will automatically be excluded from

receiving favipiravir.

Exclusions: If you meet any of the following criteria you should not take Favipiravir

- Aged <50 years
- Known or suspected pregnancy
- Breastfeeding
- Women of childbearing potential (premenopausal female that is anatomically and physiologically capable of becoming pregnant), or male with a partner of childbearing potential, not willing to use highly effective contraceptive for 28 day duration of the trial.
- Known allergy to favipiravir
- Currently taking favipiravir
- Known history of gout
- Known severe liver disease

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

As there is currently no human research associated with the use of favipiravir among pregnant or lactating women, it is important that women of childbearing potential, or a male with a partner of childbearing potential, must use highly effective contraceptive 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 the trial. The injection and most forms of hormonal contraception will also be deemed 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 the drug. We will ask you to record whether you experience diarrhoea, nausea, headaches, vomiting and urinary tract infections, in your daily diary and the clinical team will monitor these and follow-up with you if required. If you are randomised to Favipiravir, you will receive a phone call from the study team within one day of being randomised, to reaffirm your consent to take part, and to explain what side-effects you may experience, and how to report and record them. This detail will also be in the participant pack that you will receive. You will also receive a call from the study team on Day 3.

In addition, if you experience any **major** side-effects at any time while taking Favipiravir (major side-effects are symptoms that cause considerable limitation in your usual activity. Medication or medical attention is required), please call the 24 hour telephone line to speak to a member of the clinical team: 0800 915 0045.

Side effects that may be associated with Favipiravir:

- Diarrhoea*
- Nausea
- Headache*
- Vomiting[1]
- Urinary Tract Infections
- Raised liver enzymes
- Elevated uric acid concentrations

**side-effects also seen with COVID-19*

Emergencies

If a medical emergency related to your treatment for this study occurs while you are at home, you should initially try to contact the usual services that are open to you, such as 111, 999 or go to the accident and emergency (A&E) department at your local hospital. If you are unable to get to the hospital you should contact your GP who, with your consent, will already have been informed of your participation in the study. You have been given a PRINCIPLE participant card that you must show to the Doctor you see.

Appendix 2 - Ivermectin

Drug Information

Ivermectin is a drug that has been used to treat parasitic infections for many years in many countries. It has a license for use as a topical agent (applied to the skin) in the United Kingdom for a condition called rosacea. Oral ivermectin (i.e. taken by mouth) is approved by the United States Food and Drug Administration (FDA) and is on the World Health Organisation (WHO) Essential Medicines List for the treatment of many infections caused by parasites but is not licensed in the UK. The WHO Essential Medicines List covers the medicine needed for a basic health-care system, listing the most effective, safe and cost-effective medicines for priority illnesses. Over 2.7 billion treatments of oral ivermectin have been given as part of mass drug administration programmes for infectious diseases caused by parasites including, strongyloidiasis, onchocerciasis, lymphatic filariasis and hyperkeratotic scabies.

Ivermectin Dose and Administration

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

An oral dose of 300 μg/kg body weight for 3 days will be used in this trial.

This was shown to be safe in a recent study in Kenya as part of combination treatment for malaria. Higher doses of 400 μg/kg for 5 days have been used in studies of COVID-19.

We will ask for your weight in the screening form and confirm this with you during a phone call, so that the correct medication dose can be calculated.

We will ask you to return all unused medication in the pre-paid envelope to the trial team, via courier. We will log receipt and the number of tablets returned.

Potential COVID-19 Treatment

Several small clinical studies have found that ivermectin may help to treat COVID-19. However, we need more evidence from large clinical trials, which is why we have included the treatment in the PRINCIPLE Trial.

The use of ivermectin in PRINCIPLE has 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 meet any of the following reasons for NOT taking ivermectin. If you meet ANY of the following criteria, you will automatically be excluded from receiving ivermectin.

Exclusions: If you have any of the following conditions you should not take ivermectin:

- A known allergy to ivermectin or any of the substances in the tablets
- 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
- Ever having travelled to countries that are endemic for *Loa loa* (Angola, Cameroon, Central African Republic, Chad, Democratic Republic of Congo, Ethiopia, Equatorial, Guinea, Gabon, Republic of Congo, Nigeria and Sudan)
- Known bleeding disorder
- Known severe liver disease
- Currently taking the following drugs:
  quinidine, amiodarone, diltiazem, spironolactone, verapamil, clarithromycin, erythromycin, itraconazole, ketoconazole, cyclosporine, tacrolimus, sirolimus, indinavir, ritonavir, cobicistat, or warfarin

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

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

As there is limited human research associated with the use of ivermectin among pregnant or lactating women, 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 the trial. The injection and most forms of hormonal contraception will also be deemed 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 the drug. We will ask you to record whether you experience any of these symptoms in your daily diary and the clinical team will monitor these and follow-up with you if required. If you are randomised to ivermectin, you will receive a phone call from the study team within one day of being randomised, to reaffirm your consent to take part, and to explain what side-effects you may experience, and how to report and record them. This detail will also be in the participant pack that you will receive. You will also receive a call from the study team on Day 3.

In addition, if you experience any **major** side-effects at any time while taking ivermectin (major side-effects are symptoms that cause considerable limitation in your usual activity. Medication or medical attention is required), please call the 24 hour telephone line to speak to a member of the clinical team: 0800 915 0045.

Side effects that may be associated with ivermectin:

- Visual disturbances: such as blurred vision, difficulty reading, tunnel vision, floaters, black spots, abnormal colours or shapes. If this happens, do not drive or use any tools or machinery.
- CNS: dizziness, tremor, somnolence, vertigo, difficulty focussing, confusion, seizures, headache*
- Gastrointestinal: diarrhoea*, nausea, vomiting, abdominal pain, lack of appetite*

- Skin: rashes, which are normally mild and resolve after stopping the medication
- General: fatigue*, general malaise*, muscle pain*

*side-effects also seen with COVID

Rare side effects that may be associated with ivermectin:

- Stevens-johnson
- Toxic epidermal necrolysis
- Blood in urine, as there is a very rare risk of bleeding
- Prolonged activated partial thromboplastic time (aPTT)

Emergencies

If a medical emergency related to your treatment for this study occurs while you are at home, you should initially try to contact the usual services that are open to you, such as 111, 999 or go to the accident and emergency (A&E) department at your local hospital. If you are unable to get to the hospital you should contact your GP who, with your consent, will already have been informed of your participation in the study. You have been given a PRINCIPLE participant card that you must show to the Doctor you see.