**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

- Known or suspected pregnancy
- Breastfeeding
- Women of childbearing potential (premenopausal females who are 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*
- Vomiting¹
- 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 females who are 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-19

Rare side effects that may be associated with ivermectin:
- Stevens-Johnson syndrome
- 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.