IRAS project ID: 228948

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NRES REF:

PARTICIPANT INFORMATION SHEET:

VAC068: Study of controlled human *Plasmodium vivax* infection.

We would like to invite you to take part in a research study. Before you make a decision, it is important you take the time to understand why the research is being done and what it would involve. Please read the following information carefully and discuss it with friends, relatives and your General Practitioner (GP) if you wish. Please ask us if there is anything that is not clear, or if you would like more information.

- Part 1 tells you the purpose of the study and what will happen to you if you take part.
- Part 2 tells you more information about the conduct of the study.

Part 1

What is the purpose of the study?

Malaria is a major global health problem, transmitted by the bite of an infected mosquito, with more than 200 million cases and over 400,000 deaths each year. There is a great need for a safe, effective malaria vaccine as other preventive measures and treatments remain inadequate. *P. vivax* is the second commonest type of malaria parasite and is very hard to grow and manipulate in the laboratory so we have a limited understanding of how it infects human red blood cells, how it grows within those cells, and of the immune responses the body makes to it. Infecting people with *P. vivax* will allow us to observe its growth and characterise any immune responses induced by analysing blood samples taken at regular intervals. As a research group we have a large amount of experience in safely infecting people with *P. falciparum*, another strain of malaria, but none to-date with *P. vivax* malaria. However, data from other centres outside Europe demonstrates that this can be done safely and effectively.

While infecting people with *P. vivax* has been performed in other studies outside Europe, detailed analysis of the growth of the parasite and immune responses to it have not been performed, so the main aim of this study is to provide new and more detailed insight than has been achieved before.

Ultimately, in order to test whether a vaccine works against the *P. vivax* parasite, we need to be able to "challenge" vaccinated volunteers with *P. vivax* following vaccination. Administering a tiny amount of blood containing *P. vivax* parasites directly into their blood is one way of doing this. We then observe to see if the volunteers develop symptoms of malaria and measure the amount of parasite growth in their blood. In order to carry out such studies we first need to obtain *P. vivax*-infected blood that we can then administer to these vaccinated volunteers. Obtaining this *P. vivax*-infected blood is a secondary aim of this study.

So, the key aims of this study are to:

1. Demonstrate that infecting 2 volunteers with *P. vivax* malaria through experimental mosquito bite infection is safe;

2. Measure the immune responses to *P. vivax* and monitor parasite growth in the blood of both infected volunteers;

3. Obtain up to 250 mL (about half a pint) of infected blood from both volunteers and freeze down the blood for use in future *P. vivax* challenge studies, in order to be able to test candidate vaccines

We will do this by exposing 2 healthy volunteers to malaria infection by allowing *P. vivax* malaria-infected mosquitoes to bite under carefully regulated conditions. We will follow participants closely to observe if and when they develop malaria and take regular blood samples to measure the growth of and immune responses to the parasite. Once malaria infection has been confirmed (by detecting parasites in the blood) in each volunteer, we will admit them to our clinical research bay at the Churchill hospital, continue to monitor them closely and take about half a pint (250 mL) of blood. We will then immediately start them on antimalarial treatment, in order to clear the infection.

Do I have to take part?

No. It is up to you to decide whether or not to take part. Your decision will not result in any penalty, or loss of medical benefits to which you are otherwise entitled. If you do decide to take part, you will be given this information sheet to keep (or be sent it electronically) and be asked to sign a consent form. You are free to withdraw at any time and without giving a reason, but you may be asked to return to the clinic for follow up for safety reasons.

The University of Oxford does not urge, influence, or encourage any employees/students of the institution to take part in this research study. Your decision to not participate in the study, or a decision on your part to withdraw from the study, will have no effect whatsoever on your employment/student status at the University.

What will happen if I decide to take part?

This study involves undergoing challenge infection with malaria through the bite of an infected mosquito, subsequent close monitoring and blood tests, including up to a half unit (about half a pint) blood donation, and then immediately receiving treatment for malaria.

"Back-up" participants

In addition to the participants to be included in the study, we will also recruit a small number of back-up participants. If you are a back-up participant, you will complete the clinic visits up to the point of challenge, but will not necessarily undergo challenge. Back-up participants will be asked to be available to take part in the study at short notice if another participant is unable to take part at the last minute. We will recruit a total of 2 back-up participants.

Length of research

If you decide to take part in this study, you will be involved in the trial for approximately 5 years. Only the first 45 days of this will involve regular clinic visits, followed by a final clinic visit at 90 days. You will then be contacted by email fortnightly for 1 year and annually until 5 years after the study begins. This is to check you have not developed any symptoms suggestive of relapse of malaria. You will be required to respond to these emails.

Am I eligible to be involved in the trial?

In order to be involved in the study you **MUST be**:

- A healthy adult aged between 18 and 50 years.

- **Blood Group O; Rhesus negative.**
- Able and willing (in the Investigators' opinion) to comply with all study requirements.
- Willing to allow the Investigators to discuss your medical history with your GP (General Practitioner)
- Practice continuous effective contraception for the first 3 months of the study **(women only)**.
- Willing to refrain from blood donation up to the last clinic visit (3 months after malaria challenge), and for at least 5 years thereafter.

You cannot participate in this study if:

- **You have had malaria before.**
- **You have travelled to a malaria endemic region in the past 6 months, or are intending to travel to a malaria endemic region during the 3-month study period.**
- You have had immunoglobulins and/or any blood products (e.g., blood transfusion), at any time in the past.
- You have used antibiotics which could treat malaria in the 30 days prior to malaria challenge.
- You have received an investigational product in the 30 days preceding enrolment, or planned receipt during the study period.
- You have previously received an investigational vaccine likely to impact on interpretation of the trial data.
- You have problems with your immune system.
- You have a reduced oxygen-carrying capacity in your blood (haemoglobin level).
- Your veins are unlikely to yield 250 mL of blood easily (as determined by the clinical Investigator).
- You have sickle cell anaemia or thalassemia, or any other haematological condition that might affect susceptibility to malaria infection.
- You are pregnant, breast feeding or intend to become pregnant during the study.
- You have a history of allergic disease or reactions likely to be exacerbated by malaria infection or by the medications used to treat malaria infection.
- You have a history of cancer.
- You have a history of a serious psychiatric condition that may affect participation in the study.
- You have any other serious chronic illnesses requiring hospital follow-up.
- You drink on average more than 42 units of alcohol a week
- You have injected drugs at any time in the last 5 years.
- You have hepatitis B, hepatitis C, syphilis, HIV or HTLV infection.
- You have an abnormal heart rhythm.
- You have a family history of congential QT prolongation or sudden death.
- Close family members have developed heart disease when aged less than 50 years.

Mild conditions, such as childhood asthma, which are well-controlled would not automatically exclude you from participating. If you are unclear whether you are eligible for the study you can contact the study team who will be able to advise you.

CONSIDERATIONS BEFORE TAKING PART IN THIS STUDY

Medications: You should not take any drugs other than vitamin pills, contraceptive pills or those medications assessed by the doctor as appropriately safe during a malaria challenge. This also applies for drugs bought over the counter. If at any time you need any medication then you should take it, however it is very important that you let us know **before** you start any treatment, as some drugs might interfere with the malaria infection and/or anti-malaria treatment you would receive.

Blood Donation: Under current UK regulations, participants will not be able to donate blood during the study or for 5 years after the last clinic visit. At this point, The National Blood Transfusion service can test your blood to see whether or not you are able to donate blood again. If you are positive for certain antibodies, you will not be

able to donate blood again in the UK. It is not possible to determine in advance whether you will still have a positive antibody test as a result of the trial after 5 years.

Private Insurance: If you have private medical or travel insurance you are advised to contact your insurance company before participating in this trial, as involvement may affect the cover provided.

Contraception and Pregnancy: Malaria infection can be particularly dangerous during pregnancy to both the mother and the foetus. For this reason, it is important that all women use adequate contraception throughout the trial. 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. Additional considerations apply while you are taking antimalarial medication - see below.

Antimalarial Medication: Volunteers will take an antimalarial medication (Riamet) for 3 days to treat malaria infection, followed by a 14-day course of a second antimalarial medication (Primaquine) to eradicate any remaining malaria parasites in the liver. Primaquine is contraindicated in pregnancy as it could potentially cause a severe anaemia in the unborn foetus, and Riamet may temporarily reduce the effectiveness of hormonal contraceptives. Therefore, women taking hormonal contraceptives will need to use an additional form of contraception (e.g. condoms) while taking Riamet and Primaquine, and until the start of the next menstrual period after Primaquine treatment. A urinary pregnancy test will be carried out at screening, before malaria challenge, and again before anti-malarial treatment is started.

VISITS

All visits except the malaria challenge itself will take place at the CCVTM in Oxford. The malaria challenge will take place at Imperial College in London.

Pre-Screening Visit: This is to take a small amount of blood to confirm that your blood group is O, Rhesus negative. This is because your blood may be used to be given in tiny amounts to vaccine trial volunteers in the future, so we need to make sure that your red blood cells don't contain proteins on the surface to which other people would respond. For this reason group O negative is "universal donor" as cells lack these proteins and so can be given to anyone else (whatever their blood group).

You will need to sign a consent form to agree to a small amount of blood being taken (about half a teaspoon) to carry out this test. If the results from these tests are favourable, you will be invited to attend for a full screening visit. Otherwise, you will not be invited to attend for screening and you will not be able to have any further involvement in the study.

Screening Visit: This takes place up to 3 months before the study starts and will last up to two hours. The purpose of the screening visit is for you to discuss the trial with us and decide if you wish to enter the study. If you decide to participate, you will be asked to complete a questionnaire assessing your understanding of the study in order for us to be confident that you fully understand what taking part will involve.

During the screening visit:

- You will be asked some medical questions;
- A doctor will examine you;
- Blood samples and a urine sample will be taken. These tests will need to be normal for you to be enrolled in the study;
- An electrocardiogram (ECG) will be done, to check the rhythm of the heart;
- All women will have a urinary pregnancy test.

The screening blood tests will look at your blood counts (e.g. to check if you are anaemic), your liver and kidney function, and your potential risk of heart disease (including checking your magnesium levels). We will also test your blood for the following:

- expression of a specific receptor protein (called the Duffy antigen) on your red blood cells that will allow *P. vivax* to infect your red cells
- expression of a gene called CYP2D6, which can affect your ability to respond to antimalarial treatment;
- levels of an enzyme called G6PDH. If your levels are normal this means that it will be safe to give you a second course of antimalarial treatment (with Primaquine) to eradicate any remaining parasites from the liver (people who have low levels of this enzyme are potentially at risk of becoming very anaemic if this treatment is given).
- infection with hepatitis B, hepatitis C, syphilis, HIV, or HTLV (another virus similar to HIV), as these conditions would prevent use of your blood in future human malaria challenge studies. We will repeat testing for these 1 week prior to the malaria challenge to check you have not newly acquired any of these infections since the screening visit. If you test positive to any of these, we will let you know and offer to refer you for treatment.
- infection with 2 other common viral infections called CMV and EBV. Being infected with these will not exclude you from the study, but it will provide us with further information about your immune response to infection.

Clinic visits before challenge

Primaquine test visit (after screening and up to 45 days before challenge)

If no contraindications to receiving Primaquine are discovered at the screening visit, and if the blood G6PDH levels are normal, participants will be asked to re-attend clinic to receive a test dose of Primaquine and to have blood taken at regular intervals to measure blood levels of the drug. A small amount of blood (2 mL – about a teaspoon) will be taken just before the drug is given and then at 1, 2, 4, 8 and 24 hours. This is to ensure that your body efficiently breaks down the drug into its active ingredients to allow reliable killing of the malaria parasite. If for some reason the blood tests show that you do not break down the Primaquine efficiently, you will be excluded from the study.

C-7 visit (7 days before malaria challenge)

Participants will be asked to attend clinic 7 days before malaria challenge for repeat blood testing for the above viruses (HIV, HTLV, hepatitis B and C and syphilis).

C-1 visit (one day before malaria challenge)

On the day before challenge participants will attend clinic for a review and blood test to check there have been no changes in your general health prior to challenge and to obtain some baseline samples to compare with post-challenge immune responses to the parasite. For female participants, a urinary pregnancy test will be performed, to ensure you are completely healthy and can be infected with malaria. Back-up volunteers will need to attend this visit and also must be available on the morning of the malaria challenge, in case one of the volunteers withdraws at the last minute. This means that confirmation of whether or not a back-up volunteer will be needed for the challenge will not be made until the day of challenge (one of the Investigators will call the back-up volunteer that morning to confirm either way).

THE MALARIA CHALLENGE

What happens during the Malaria Challenge?

The challenge involves spending the whole day at **Imperial College in West London**. Transportation to and from Imperial College will be provided. You will be bitten by up to five malaria-infected mosquitoes contained in paper cups with a gauze screen over the top. The cup is placed on the skin of the forearm, as most participants prefer this site. However, if you prefer another site then we can try putting the cup there. It will need to stay in place for between five and fifteen minutes to allow the mosquitoes to feed. Once they have fed, the cup will be removed and the mosquitoes examined for signs of blood and parasites. If this examination

reveals that you have not received the required number of infected bites, then additional mosquitoes will be allowed to bite until you have received 5 infected bites. This process can take up to 2 hours.

The mosquitoes may not bite well if you have used perfume, aftershave, or a perfumed soap or cream on the skin where they are going to bite. We ask that you don't use any of these items, nor should you shower or bathe on the morning of the challenge.

Before going home after being challenged with malaria we will give you a medic alert card to keep on your person during the entire 3-month post-challenge period (explaining you have been challenged with malaria and including emergency contact details of the study team), a thermometer so that you can take your temperature at home, and, if necessary, a phone.

What happens at follow up after the Malaria Challenge?

After an infected bite you will not develop malaria for at least 7 days. For this reason, you do not need to attend clinic on Days 1-5 after challenge, however one of the study team will call you each day to ensure that you are well and contactable during this time.

Day 6 up to Day 37 after Malaria Challenge (see flow timetable, page 14)

We will review you in clinic once on the late afternoon of Day 6 following malaria challenge and then twice a day (morning and late afternoon) from day 7 (it is most likely that you will develop malaria between Day 8 and Day 14 following challenge). **At an agreed point between day 8 and day 14** (depending on the level of parasites we detect in your blood and your symptoms) we will admit you to the research bay on the John Warin ward at the Churchill hospital for closer monitoring and then take up to 250 mL (about half a pint) of blood from you within 72 hours. We will then immediately start you on treatment for malaria. The admission is to monitor you closely, to be sure that you are provided with adequate symptomatic relief, that you tolerate the blood donation procedure, and that you tolerate the antimalarial treatment (sometimes people feel slightly worse within the first 24 hours of starting on the medication, before they then start to feel better). If you were to become very unwell then you would be transferred to the direct care of the NHS hospital staff, though this is highly unlikely to be necessary.

We will discharge you home once your symptoms are improving and we are sure you are tolerating the medication (likely minimum of 1 day and a maximum of 5 days following admission).

It is important to note that in clinical practice, patients with *P. vivax* would not normally present to medical services, be diagnosed or receive treatment for malaria until they had developed significant symptoms in the community that prompted them to seek medical attention. Because you will be infected in a controlled manner, it is very likely that you will receive treatment in advance of what would normally happen if you were infected naturally and seen by your doctor.

Once you have finished the initial 60-hour course of antimalarial treatment we will give you a diary on which to note when any ongoing symptoms of malaria stop. Our experience tells us that the malaria parasites should disappear from your blood within 2 or 3 days of starting the treatment. Once you have 2 consecutive negative malaria blood tests (thick blood films – see below) on 2 consecutive days, confirmed after treatment, we will then start you on a second course of treatment for 14 days. **This is important as it will eradicate any remaining parasites from your liver and so will minimise the risk of you having a relapse of malaria later on. You will be asked to remain in Oxford for careful monitoring and alternate daily review in clinic by the study team, for directly observed treatment, until you have completed this 14-day course of treatment.** On the other days you will be telephoned by one of the Investigators to remind you to take your medication.

If for some reason you do not develop malaria, you will be started on treatment at day 21 and still be required to complete the full 2 courses of treatment, in order to kill any undetected parasites.

All these clinic visits will take place at the Centre for Clinical Vaccinology & Tropical Medicine (CCVTM) at the Churchill Hospital in Oxford. We will give you a medication diary card on which you will be asked to record all medications that you take. At each visit, until you have completed the first 60-hour course of antimalarials and have had 2 negative blood tests for malaria on 2 consecutive days, we will ask about symptoms of malaria,

measure your pulse, blood pressure and temperature, and take a blood sample. This will be examined under the microscope for malaria parasites. This is called a thick film and is the standard test for diagnosing malaria infection. Your blood will also be tested for malaria parasite genetic material (DNA) using a technique called polymerase chain reaction (PCR), that can detect even the tiniest amount of parasite. Each of these visits will last about 10 minutes. The total number of visits after challenge will vary depending on when and if you get malaria. It is important you are able to attend all the visits. **You will not be permitted to travel outside Oxford from day 7 after challenge until you have completed the full 2 courses of treatment for malaria.**

Usually blood test results becomes available after you have left clinic so we will contact you by telephone and ask you to return to the CCVTM as soon as possible if we decide you need to be admitted for blood donation and to start treatment. It is therefore **essential that we are able to contact you at all times on your telephone and that you are available to return to the CCVTM at short notice any time between Day 6 and Day 21 post challenge.** You **must** also provide a name and 24-hour phone number for someone who lives near to you and who will know where you are for the duration of the study. If you fail to attend for review during the post-challenge period and are un-contactable we will contact this person.

Days 45 and 90 after Malaria Challenge

You will be seen in clinic on Day 45 and Day 90 after challenge. At these visits a final blood sample will be taken (to exclude any residual parasites, to check general health, and to characterise any ongoing immune response to the parasite). The amount of blood taken will be a minimum of two teaspoons to a maximum of 5 table-spoons. The appointments will last about 10 minutes.

What will any blood I donate be tested for?

At different time points throughout the trial, we will take blood tests that include measures of:

- Red and white blood cells
- Liver and kidney function
- Blood borne infections (HIV, hepatitis B & C, HTLV, syphilis)
- HLA type
- Blood group (A/B/O; Rhesus status) – at pre-screening
- Enzyme levels (G6PDH and CYP2D6) and Duffy antigen - at screening
- Primaquine levels – described above
- Genetic tests of your cells and the parasites
- Malaria parasites (for diagnosis and monitoring after challenge) – by microscopy and PCR
- Immune responses to malaria infection

WHAT ARE THE RISKS OF TAKING PART IN THE STUDY?

The potential risks in the study can be divided into seven categories;

1. **Blood Tests and unit blood donation**

The amount taken at each visit will vary between 2 mL (half a teaspoon) and 100 mL (around 6 tablespoons). Both volunteers will also have a larger 250 mL (about half a pint) blood donation just prior to starting antimalarial treatment. This increases the total volume of blood being taken over the course of the trial to an absolute maximum of 783 mL, which is slightly more than a regular blood donor would donate but should not cause any problems in healthy people. There may be some temporary mild discomfort, such as bruising and tenderness, at the site from which blood is taken. You may experience faintness as a result of collecting blood, this is more likely during the 250 mL blood donation, so we will perform this with you reclined in a hospital bed. If you feel faint (light headed or dizzy, hot, sweating, trembling, shaky or nauseous) remain reclined until you feel better and drink

plenty of fluid. You will be monitored closely by a nurse and doctor during this time. If bleeding recurs, you will be asked to raise your arm and pressure will be applied to the area where the blood is coming from for at least 5 minutes.

We will give you a copy of your blood tests if you request them, and will only send the results to your GP if you wish us to.

2. Mosquito Bites

After malaria challenge you will have mosquito bites on your arm which can become red and itchy for several days. Some people develop quite pronounced local reactions to mosquito bites with itching, swelling, redness and discomfort. We will give you antihistamine cream to apply to the bite sites as required to help relieve symptoms.

3. Infections transmitted by mosquito bite

The mosquitoes that we are using have been laboratory-reared under very careful conditions by mosquito experts. They are infected with a species of malaria parasite (*Plasmodium vivax*) that we know can be treated by antimalarial medications. There are other diseases that may be transmitted by the bite of a mosquito, however, the strains of mosquitoes that we are using have never shown any evidence of other mosquito-transmitted diseases and therefore the chance of contracting one of these diseases we believe to be extremely low. However, as a precaution, because the mosquitoes are infected with *P. vivax* by feeding on the blood of a malaria-infected patient in Thailand, before we use the mosquitoes we check a sample of the patient's blood for a number of potentially mosquito-borne infections. These include the viruses Chikungunya, Dengue, Zika, Japanese B encephalitis and the worm infection, filariasis, although there is no evidence that the species of mosquito we use is able to transmit any of these infections. In addition we also test the patient's blood for the presence of any blood-borne infections including HIV, hepatitis B and C, HTLV, and syphilis, although once again there is no evidence that any of these can be transmitted by the mosquito. We also test for the presence of other malaria parasites. To be absolutely safe, if any of these infections are found to be present we discard the mosquito batch and acquire a fresh batch (that have been fed on a different patient) and repeat the entire testing process. Only if the blood is clear for ALL these infections do we use the mosquito batch for administering you the malaria challenge.

4. Malaria Infection

The risks of taking part in this study are very low provided that you return for follow-up as outlined above. **If untreated, the malaria infection that we propose to give you could result in death, although this particular type of malaria is rarely fatal.** Worldwide over 1300 people have been deliberately infected with malaria and all have made a complete recovery. In Oxford more than 400 people have been infected with malaria.

The early symptoms of malaria include a flu-like illness, fever, chills, headache, muscle aches, diarrhoea and vomiting. If you develop any of these then you **must let one of the study physicians know immediately.** Study doctors can be contacted 24 hours a day. About one-fifth of participants temporarily develop symptoms graded as severe (i.e. symptoms that prevent daily activities). It is possible that you might need to take one or more days off work due to symptoms of malaria, and when you are admitted for blood donation. We will prescribe pain-killers, such as paracetamol, and anti-sickness tablets, which you can take as required. Symptoms can start or persist after treatment has started, but usually last no more than 1 to 3 days. If malaria is not treated appropriately, possible complications include jaundice, kidney failure, fluid on the lung, low blood sugar and collapse. Seizures, altered consciousness, coma and even death may occur. It is for this reason **it is crucial that you attend all the scheduled follow-up visits and contact us immediately if you have any symptoms.**

In the last 10 years, only 4 participants out of more than 400 challenged with malaria in Oxford have required hospital admission. There have been no long term problems in participants challenged with malaria. **In this study, you will need to be admitted to the hospital environment temporarily for a blood donation, so you will have even closer monitoring during this period.**

There have been two unexpected serious adverse events in persons infected in malaria challenge studies in the Netherlands. The first individual experienced an episode of chest pain diagnosed as acute coronary syndrome that occurred two days after completion of malaria treatment with a full recovery. It is uncertain whether this was a form of coronary artery spasm or blockage or cardiac inflammation. More recently, a second individual was found to have an abnormal blood test suggesting cardiac inflammation. They subsequently suffered a very short episode of chest pain. They were also found to be suffering with a viral upper respiratory tract infection (common cold virus) at the time. Again, this individual made a full recovery. It is unclear at this stage whether these findings were related to the malaria vaccine the participants received, the malaria infection, malaria treatment, or some other cause. As a result of these events we will exclude people at high risk of heart disease from involvement in this study. These individuals will be identified by medical history, family history, appropriate blood tests, and performing an ECG.

In 2010 in a malaria challenge study in Oxford, a participant failed to attend for a scheduled study visit after being infected with malaria. The police were immediately informed and began a nationwide search for the individual, which involved the national media. The participant was found 17 days following challenge when he had mild malaria symptoms. He was admitted to a local hospital where he received treatment for malaria and made a full recovery. The reason for the participant's disappearance was unrelated to the malaria vaccine he received or the malaria challenge.

It is important that you understand that if you fail to attend a clinic appointment after challenge, but before you have completed a full course of antimalarial therapy, the police may be notified and your name may be released to the national media in order to find you.

There are no known long term side effects of contracting or being treated for this type of malaria (*P. vivax*), other than a very small risk of experiencing a relapse of infection. This can occur because parasites can stay dormant in the liver and then reactivate into the blood making you sick again weeks, months or even years later – this is known as relapse. This risk is minimised by giving you a 14-day course of treatment that eradicates any remaining dormant parasites from the liver. For 5 years after the challenge you should contact a doctor if you develop any of the symptoms of malaria as detailed above, and in this circumstance, please contact one of the study doctors and your General Practitioner and remind them that you have been involved in this study. We will also conduct a fortnightly email follow-up for the first year, followed by an annual email follow-up until 5 years after challenge, where we will enquire about any symptoms of relapse and any associated medical attention you may have sought in the intervening period. You will be required to respond to these emails, and if we do not hear from you we will contact you by telephone. If you have any queries or concerns once the study is over, please do not hesitate to get in touch with us.

5. Treatment of Malaria

The drug you will be treated with is called Riamet. It is a licensed drug in the UK for the treatment of acute uncomplicated malaria caused by *Plasmodium vivax* (the type of malaria you will be infected with). Riamet is a combination drug consisting of 20mg artemether and 120mg lumefantrine per tablet.

A treatment course of Riamet consists of 6 doses of 4 tablets. The first 4 tablets will be given when diagnosis is made, followed by additional doses after 8, 24, 36, 48 and 60 hours. We will need to watch you take at least three of these doses. We will continue taking blood to look for parasites until 2 consecutive blood tests are negative for malaria parasites. Blood tests usually become negative for malaria parasites after 24 hours of treatment. Tablets

should be taken with a meal or snack. We will provide a light snack with the doses of Riamet that we observe at the clinic. You should avoid taking grapefruit juice while taking Riamet.

Riamet is generally well tolerated, but may cause some side effects. Side effects can include headache, dizziness, abdominal pain and loss of appetite, sleeping problems, palpitations, nausea, vomiting, diarrhoea, skin rash, cough, muscle or joint pain, and fatigue. Side effects such as dizziness may impact on the performance of skilled tasks such as driving. Riamet can have an effect on the electrical conduction in the heart (increase in the QT interval) which could potentially increase the risk for a cardiac arrhythmia as an extremely rare side effect; as a precaution we will use a different malaria treatment if we find any reason that you would be at increased risk. Severe allergic reactions could potentially occur, but the exact frequency is unknown. Signs of severe allergic reactions include rash and itching, sudden wheezing, tightness of the chest or throat, difficulty breathing, and swollen eyelids, face, lips, tongue or other part of the body. If you experience any of these symptoms you should contact the trial doctor immediately on the emergency contact number you will be provided with, or telephone 999 and ask for an ambulance if you are having difficulty breathing.

Some other medicines cannot be taken at the same time as Riamet. If you cannot take Riamet, or need to stop taking Riamet during the study, then there are other antimalarial drugs that can be used effectively instead. If at screening the doctor thinks you may not be able to take Riamet they will discuss an alternative medication with you (Malarone) and give you an information sheet from the manufacturer of this drug to take away.

After you have completed a course of Riamet you will be given a 14-day course of a drug called Primaquine – 30 mg once a day for 14 days, to eradicate any parasites that may still be residing in the liver and that could potentially result in a relapse of malaria disease. Primaquine is usually well tolerated but carries a risk of inducing severe anaemia in individuals who are G6PDH deficient, so we will screen you for this at the beginning of the study (and exclude you from the study if your levels of G6PDH are not sufficient). The commonest side effects of Primaquine are nausea and abdominal pain and it is contraindicated in pregnancy, so females will require a urinary pregnancy test prior to starting treatment. If you have any concerns while taking Primaquine you can contact the study team for advice.

6. Treatment of Symptoms Associated with Challenge

Provided there are no contraindications, all participants will be given some medications to help with symptoms associated with malaria challenge. These are licensed, commonly used, medications. If you wish you can see the sheets from the manufacturers, provided inside the packets of these medications, prior to taking part in the study. As with all medications, these drugs can cause a severe allergic reaction in a small number of people. If you develop any concerning symptoms you should contact the trial doctor immediately on the emergency contact number, you will be provided with.

Antihistamine Cream: Antihistamine cream can help reduce the itch and redness associated with mosquito bites. Antihistamine cream is generally well tolerated. There is a very small risk of local redness, swelling or itching in the area where the cream has been applied, although we have never seen this in any of our trial volunteers to date

Cyclizine: This is a tablet that can be taken as and when needed to help reduce nausea and vomiting. Cyclizine is generally well tolerated. However, side effects include skin rashes or itching, drowsiness, headache, dry mouth, nose or throat, blurred vision, palpitations, difficulty passing water, constipation, anxiety, and difficulty sleeping. It should be noted that drowsiness may affect your performance of skilled tasks such as driving.

Paracetamol: This is a tablet that can be taken 6 hourly to reduce feverishness, muscle and joint pain, back ache and headache. Paracetamol is generally well tolerated.

7. Relapse of malaria

This potential complication is described in section 4, above, and is extremely unlikely to occur if you complete your 14-day course of Primaquine, if your test Primaquine blood levels were normal, and if your CYP2D6 genetic profile (tested on blood taken at screening) predicted that you should metabolise Primaquine efficiently (you shall be excluded from the study if this is not found to be the case). However, the risk of relapse is not zero, and so if you were to experience symptoms possibly suggestive of malaria in the future you should seek medical attention without delay and also contact the study investigators on the 24-hour phone number provided. We will also maintain contact by email for 5 years. If you do experience a relapse of malaria this is treated with the exact same medications that you were given during the study (Riamet and Primaquine). This will be managed under the NHS and the advice of an infectious diseases specialist. If you are not unwell you may be able to complete a course of treatment at home but if you have significant symptoms you may require a short admission to hospital to initiate treatment, which will then be completed at home.

OTHER INFORMATION

Blood Tests

We take blood tests as part of the screening visit and at the study visits in order for us to assess your general health, your immune response to the malaria challenge, to measure the parasites in your blood after challenge and for safety reasons. If you would like them, we can give you the results of your blood tests. Coded blood samples will be stored after testing, and, if you consent, may be used in future malaria research. You will be asked to consent specifically for blood to be stored and used in future research. To avoid repeated testing, if you are not enrolled into this study and apply to enter another study conducted by the Jenner Clinical Trials Group based at the CCVTM in Oxford, the screening blood results may be used in that study, where appropriate.

Abnormal Results

If abnormal results or undiagnosed conditions are found in the course of the study these will be discussed with you and, if you agree, your GP (or a hospital specialist, if more appropriate) will be informed. Any newly diagnosed conditions will be looked after within the NHS.

Expenses and Payments

You will be compensated for:

- Pre-screening (blood-typing) Visit: £25
- Screening Visit £25
- Primaquine test visit £75

Subsequent visits:

- Travel expenses: £10 per visit
- Time required for visit: £20 per hour
- Inconvenience of blood tests: £10 per blood donation
- Admission (illness) days £1440 total

Time in Trial (approx.)	Maximum No. of Visits *	Maximum Volume of Blood Taken (ml) **	Compensation Amount
3 months (with subsequent email follow-up to 5 years)	43	783	£3255***

*The exact number of visits depends on when/if you are diagnosed with malaria following challenge.

**The exact amount of blood taken will depend on when/if you are diagnosed with malaria.

***The compensation is the same for both enrolled volunteers

If you choose to leave the study early, or are withdrawn from the study, you will be compensated according to the length of your participation based on these figures. You should note that compensation payments received in this trial may have an impact on your entitlement to benefits.

If you are a back-up participant and do not undergo challenge, you will be compensated in addition to compensation for visits you have already attended (e.g,. Screening and days before challenge). Back-ups will receive £200.

What alternatives are present?

Your alternative is not to participate in this study.

What are the possible benefits of taking part?

This study will not benefit you directly. However, it is hoped that the blood bank generated from this study will allow testing of future candidate vaccines against *P. vivax*, and ultimately contribute to the development of a safe and effective *P. vivax* malaria vaccine that can prevent malaria infection and disease in those living in areas where malaria is common and in travellers to those areas. At present, there is no malaria vaccine licensed anywhere in the world.

It is important to be clear that participating in this study will not render you immune to malaria. It is crucial that you follow recommendations for malaria prophylaxis if and when you travel to a malaria-endemic region in the future.

Will my taking part in the study be kept confidential?

Yes. All the information about your participation in this study will be kept confidential. The details are included in Part 2.

This completes Part 1 of the Information Sheet. If the information in Part 1 has interested you and you are considering participation, please continue to read the additional information in Part 2 before making any decision.

Part 2

What if relevant new information becomes available?

Sometimes during the course of a trial, new information relevant to the trial becomes available. If this happens, we will tell you about it and discuss whether you want to, or should, continue in the study. If you decide to continue to take part, you will be asked to sign an updated consent form. On receiving new information, we may consider it to be in your best interests to withdraw you from the study. Your participation in this study may also be stopped at any time by the study doctor or the Sponsor for other reasons.

What will happen if I don't want to carry on with the study?

If, at any time after agreeing to participate, you change your mind about being involved with this study you are free to withdraw without giving a reason. Your decision will not result in any penalty, or loss of benefits to which you are otherwise entitled. However, **if you wish to leave after malaria challenge then you must take the treatment courses of Riamet and Primaquine because of the potentially very serious consequences of untreated malaria infection.** Unless you state otherwise, any blood taken whilst you have been in the study will continue to be stored and used for research as detailed above. Similarly, all your data collected up to the point of your withdrawal will be stored, unless you specifically request for it to be destroyed. You are free to request that your blood samples are destroyed at any time during or after the study, **EXCEPT for the half unit of blood that we take. This will be kept even if your other samples are destroyed. This is because we will have only one chance in this study to challenge volunteers with malaria, and it will be impossible to repeat this from a "back-up" volunteer at a later date.**

What if there is a problem?

If you are harmed as a result of taking part in this study, the study doctor can advise you of further action and refer you to a doctor within the NHS for treatment, if necessary. 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. NHS indemnity operates in respect of the clinical treatment which may be provided if you needed to be admitted to hospital.

The Investigators recognise the important contribution that volunteers make to medical research, and make every effort to ensure your safety and well-being. In the event of harm being suffered, while the University will cooperate with any claim, you may wish to seek independent legal advice to ensure that you are properly represented in pursuing any complaint. At any time during the study you will be entirely free to change your mind and withdraw from the study. This will not affect your subsequent medical care in any way.

Complaints statement

If you wish to complain about any aspect of the way in which you have been approached or treated during the course of this study, you should contact your local trial team (contact details at the end of this document) or you may contact the University of Oxford Clinical Trials and Research Governance (CTRG) office on 01865 572224 or the head of CTRG, email ctrg@admin.ox.ac.uk.

Will my taking part in this study be kept confidential?

All information that is collected about you during the course of the research will be coded with a study number and kept confidential. The information is available to the study team, safety monitors, ethical review committees, Sponsors, government regulatory agencies, authorised collaborators and external monitors who can ask to audit or monitor the study. Any information about you that leaves the hospital or clinic will have your name and address removed so that you cannot be identified from it. Your information is stored electronically on a secure server and any paper notes are kept in a locked filing cabinet. Records are stored for at least 15 years, and in accordance with the applicable regulations.

Involvement of the General Practitioner/Family doctor (GP)

In order to enrol into this study, you will be required to sign a form documenting that you consent for us to contact your GP. This is to inform them that you are interested in being involved in the study, and to check there are no medical reasons that they are aware of that would make your participation inadvisable. Your GP may be asked to share information about your medical history and give access to any other medical records as required. The researchers will not enrol you in the trial if your GP has relevant concerns about your eligibility or safety. We will write to your GP to let them know whether or not you are finally enrolled in the study, and whether or not you completed the study, so they can update your medical records accordingly.

Prevention of 'Over Volunteering'

Volunteers participating in this study must not be concurrently receiving investigational medications or vaccines in another study at the same time. In order to check this, you will be asked to provide your National Insurance or Passport number. This will be entered on to a national database which helps prevent volunteers from taking part in too many clinical trials. More information can be found at *www.tops.org.uk*. Your national insurance or passport number is also required to allow processing of compensation payments.

What will happen to any samples I give?

The half unit of blood that you will donate at the time you are diagnosed with malaria will be frozen down and stored indefinitely in a secure facility at ThermoFisher Scientific, Bicester, Oxfordshire. We plan to use this blood to infect other volunteers in future clinical trials to assess malaria vaccines, drugs, and the biology of the *P. vivax* malaria parasite. **Once you have given consent and donated this blood, it will not be destroyed, even if you withdraw from the study. However, if you were to withdraw from the study, your link to your donation will be destroyed so that it will remain completely anonymous.**

If you consent, some of your leftover blood samples will be stored and may be used for further studies of the human body's immune response and/or your safety. Any such tests will have an appropriate ethical review. Upon your request at any time, your remaining blood samples (other than the 250 ml infected sample) will be destroyed. Your participation in this study will not be affected by your decision whether to allow storage and future use of your leftover samples. To avoid repeat testing, if you are not enrolled into this study and you apply to enter another study conducted by the Jenner Clinical Vaccine Trials Group based at the CCVTM, the results from your screening visit blood tests may be used to determine whether you are eligible for the trial you applied for.

Your study visit blood tests will be analysed in the hospital laboratories and Oxford University research laboratories. Other blood tests to look at the response of your body to the malaria challenge will be done with collaborating laboratories in the UK and in other countries. Any samples or data sent to them would be anonymous.

Will any genetic tests be done?

Yes. Some blood will be used to look at the pattern of your genes that can affect the immune system (including your 'human leukocyte antigen' [HLA] type) and the expression of the CYP2D6 gene which predicts your body's ability to metabolise Primaquine. We may also look at the expression of certain genes which relate specifically to the immune response to malaria. You can opt out of 'genetic tests' if you wish, without any effect on your participation in the trial, except for the CYP2D6 genetic test, as this is crucial to assess your eligibility for the study.

What will happen to the results of the research study?

The results of this research study may be presented at scientific meetings or conferences and published in a scientific medical journal. This may not happen until 1 or 2 years after the study is completed. If you contact the researchers in the future, you can obtain a copy of the results. You will not be identified in any report or publication.

The anonymised data from this study will be shared with the collaborating partners who are organising and funding this research work, including the MultiViVax Consortium funded by the European Commission. Data from this study may be used to file patents, licence vaccines in the future or make profits in other ways. You will not be paid for any part of this. Data from this study may be used as part of a student post-graduate degree, for example a MD or PhD.

A description of this study will be available on www.clinicaltrials.gov, as required by US law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

Who is sponsoring, organising and funding the research?

The study is organised by the University of Oxford. The study is funded by the European Commission through the MultiViVax programme. Neither your GP nor the researchers are paid for recruiting you into this study.

Who has reviewed the study?

This study has been reviewed by the National Research Ethics Service (NRES) Committee (insert REC name when known) and has been given a favourable ethical opinion.

Thank you for reading this information sheet. If you are interested in taking part in the study please contact the study team at your local study site to arrange a screening appointment.

Contact details for further information:

Volunteer Recruitment Co-ordinator, vaccinetrials@ndm.ox.ac.uk, 01865 611424

Timetable of Visits Post-Mosquito Bite (all in Oxford)