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PARTICIPANT INFORMATION SHEET: VAC079

A study to assess the safety, immunogenicity and efficacy of the malaria vaccine candidate PvDBPII in Matrix M1

A Phase I/IIa clinical trial to assess the safety, immunogenicity and efficacy of the *Plasmodium vivax* malaria vaccine candidate PvDBPII in Matrix M1 in healthy adults living in the UK

We would like to invite you to take part in a research study. Before you decide, it is important for you to understand why the research is being done and what it would involve. Please take time to read the following information carefully and discuss it with friends, relatives and your General Practitioner (GP) if you wish.

- 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.

Please ask us if there is anything that is not clear, or if you would like more information. You will be able to discuss the trial with us if you attend a screening visit, and we're happy to answer queries before this too. Take time to decide whether or not to take part.

Part 1

Why are we conducting this study?

Malaria is a major global health problem. It is a potentially fatal disease caused by a parasite (*Plasmodium* species), which is transmitted to people by mosquitoes. Each year there are more than 200 million cases and over 400,000 deaths worldwide.

Plasmodium vivax (*P. vivax*) is the second commonest type of malaria parasite and although does not cause as many deaths as the most common malaria, called *P. falciparum*, *P. vivax* malaria can still cause severe disease and even death in some cases.

This study will be one of the first to test whether a vaccine can prevent or slow *vivax* malaria infection. A safe and effective vaccine would significantly reduce the global health burden caused by *P. vivax* malaria but unfortunately, no vaccine is yet available.

What are the choices for taking part in this study?

We are looking for volunteers who will be experimentally infected with *P. vivax* malaria after receiving the PvDBPII in Matrix M1 vaccine.

Please remember taking part in this study is your choice and if you choose to take part you'll be able to withdraw at any time should you wish, although if this is after infection with malaria you will need to wait until you have been fully treated.

We would like to highlight the following key points that we think you should know before making a decision:

- **This is the first study in which this vaccine will be given to humans**
The combination of the PvDBPII vaccine with an adjuvant called Matrix-M will be given to people for the first time in this study. However, together with a different type of adjuvant, the PvDBPII vaccine has been given to 27 people in a previous small clinical trial in India. The vaccine was shown to be safe and well tolerated in this prior study.
The Matrix-M adjuvant, together with other vaccines, has been administered to over 1000 people in multiple previous trials, in which it has been demonstrated to be safe, and associated with short-lived side effects only. We expect side effects of the PvDBPII vaccine in Matrix-M, to be similar to those seen in these previous studies, but as this is the first trial of PvDBPII in Matrix-M in combination, it is possible the effects may be different or more severe.
- **The three vaccinations are given at 4 week intervals and malaria infection will take place 4 weeks after the third vaccination.**
Following each vaccination, volunteers will be required to fill in an electronic diary every day and attend clinic visits at 1,3,7 and 14 days after each vaccination
- **Volunteers will be deliberately infected with malaria by injecting a small amount of malaria-infected blood into the vein (like a small blood transfusion). This is the second time we will be using this source of malaria-infected blood.**
*The malaria-infected blood was donated by a healthy volunteer in a previous study in Oxford and has been extensively tested for blood-borne infections (other than vivax malaria), all of which were negative. We have used this malaria-infected blood in a previous study. This showed that volunteers who had not been vaccinated could be successfully infected and there were no unexpected side effects. The same method has previously been used to safely infect volunteers with *P. falciparum* malaria in studies in Oxford and around the world.*
- **All volunteers are at risk of developing malaria, even following vaccination**
We do not yet know if this vaccine can protect against malaria infection, therefore all volunteers remain at risk of getting malaria in this study.
- **After malaria infection, volunteers will be required to remain in the Oxford area for up to four weeks**
*After infection, volunteers will need to stay in the Oxford area until treatment is completed. For the first week, volunteers will be telephoned daily. From the second week volunteers will need to **attend clinic once or twice each day** (more explanation below) **for up to three weeks**. A blood test will be done at each of these visits.*

What is being studied in this trial?

The vaccine we are testing is a new vivax malaria vaccine called **PvDBPII in Matrix M1**. The PvDBPII component of the vaccine has been tested in two previous clinical trials in Oxford and in India (Phase Ia) to evaluate its safety. In these trials, the body's immune response to vaccination was also assessed and the results look promising. Now, in this study, we will assess PvDBPII in combination with an adjuvant called Matrix M1 to assess both the safety of this new vaccine combination and whether it will be effective at preventing or slowing malaria infection. This is therefore the first clinical trial testing this specific vaccine and only the third time that PvDBPII vaccines have been used in humans.

The **PvDBPII in Matrix M1** vaccine is made from part of a malaria parasite protein, called PvDBP, which the parasite uses to enter human red blood cells. In the vaccine, the protein is given together with Matrix M1 which is known as an 'adjuvant'. Adjuvants are given with most vaccines and are designed to increase the immune response to the other part of the vaccine, in this case the PvDBPII protein, so that the resulting immunity is stronger and longer lasting. Matrix M1 has been given to over 1000 individuals in clinical trials of other vaccines and has been shown to be safe, well-tolerated and effective in boosting the body's immune response.

In total, we aim to recruit 17 healthy volunteers to be vaccinated and then test to see whether the vaccines can protect against malaria infection. Each volunteer will receive three doses of the PvDBPII in Matrix M1 vaccine at monthly intervals. After each vaccination, we will see volunteers in clinic at regular intervals to assess for side effects and take blood samples to analyse the body's immune response to the vaccines.

Around 4 weeks after the third vaccination, we will deliberately infect volunteers with *P. vivax* malaria by injecting a tiny amount of malaria infected blood into the vein. Deliberately infecting volunteers in this way is called a **malaria challenge**. As we are infecting volunteers directly into the blood, this is sometimes called a **blood-stage malaria challenge**.

Following challenge, we will then observe volunteers closely to see if they have been protected from malaria or develop symptoms more slowly compared to volunteers who did not receive the vaccine (controls). At the same time, we will take blood daily or twice daily to measure the parasite growth in your blood and analyse the immune response. If volunteers are protected from malaria, we will analyse the immune responses to try to link these to the protective effects. If malaria infection develops (confirmed by detecting parasites in the blood), we will start malaria treatment to clear the infection.

The controls (unvaccinated volunteers) for this trial will be recruited as part of another study, called VAC069. These volunteers will not be vaccinated but will be infected with malaria at the same time and in the same way as VAC079 participants.

So, the key aims of this study are:

1. To assess the safety of the **PvDBPII in Matrix M1** vaccine in humans
2. To assess the body's immune response to the vaccine
3. To assess whether the vaccine slows or protects against malaria infection in a malaria challenge study, compared with unvaccinated control volunteers

Do I have to take part?

No. It is up to you to decide whether or not to take part. Your decision not to take part will not result in any penalty, or loss of benefits to which you are otherwise entitled. Even after consenting to take part you are free to withdraw at any time 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?

You will receive three vaccinations, followed by intravenous injection of malaria infected blood as a malaria challenge.

Duration of participation

Volunteers will be followed for approximately 1 year

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 45 years.
- 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).
- Willing to refrain from future blood donation in the UK
- Practice continuous highly effective contraception for the duration of the study (**women only**)
- Contactable (24/7) by mobile phone during the period between malaria challenge and completion of all antimalarial treatment
- Willing to take anti-malarial treatment following malaria challenge
- Willing to reside in Oxford for the duration of the malaria challenge, until antimalarials have been completed (up to 30 days after challenge)

You cannot participate in the study if:

- You have had malaria before (any species)
- You have travelled to a malaria endemic region in the last 6 months or are intending to travel to a malaria endemic area during the study period
- You take long-term antibiotics which could treat malaria (e.g. doxycycline)
- You have participated in another study in the last 30 days
- You are planning to participate in another study at the same time as this study
- You have previously received an investigational malaria vaccine
- You have received any vaccine in the last 30 days, or plan to receive any other vaccine (other than the vaccines in the study) within 30 days of receiving the study vaccines
- You have sickle cell anaemia, sickle cell trait, thalassaemia or thalassaemia trait or any other haematological condition that might affect susceptibility to malaria infection
- You have had a blood transfusion or received immunoglobulins at any time in the past
- You have problems with your immune system
- You will be taking any long-acting immune-modifying drugs at any time during the study period (e.g. infliximab).
- You have an abnormal heart rhythm
- You have a family history of congenital QT prolongation or sudden death
- Close family members have developed heart disease when aged less than 50 years
- You are pregnant, breast feeding or intend to become pregnant during the study
- You weigh less than 50kg
- You are allergic to eggs or Kathon
- You have a history of significant contact dermatitis
- You have a history of allergic disease or reactions likely to be exacerbated by any component of the vaccine, malaria infection or by the medications used to treat malaria infection
- You have had a severe allergic reaction after vaccination
- You have had your spleen removed
- You have a history of cancer
- You have a serious psychiatric condition that may affect participation in the study
- You have any serious long-term illness requiring hospital follow-up or that would make intramuscular injection unsafe
- You take medications, or have a medical condition, which means you cannot take either of the possible anti-malarial treatments
- You drink on average more than 25 units of alcohol a week (a pint of beer is two units, a small glass of wine 1 unit and a shot of spirits one unit)
- You have injected drugs at any time in the last 5 years
- You have hepatitis B, hepatitis C or HIV infection
- You are unable to stay in Oxford from the day before challenge to 30 days after challenge

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.

If we find any abnormality on examination, blood or urine tests which is clinically significant you may also be excluded from the study. In addition, if you become moderately or severely unwell on the day before or day of the malaria challenge, this will also exclude you from participating.

CONSIDERATIONS BEFORE TAKING PART IN THIS 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 to assess your understanding of the study. This is important in order for us to be confident that you fully understand what taking part will involve. You need to answer all questions correctly in order to take part in the study. If you don't answer all the questions correctly the first time, you will be able to complete the questionnaire again after discussion with the Investigator. You will be permitted two attempts at the questionnaire. If all the answers are correct, you will then be asked to sign a consent form.

After signing the consent form, you will:

- Be asked some medical questions
- Be examined by a doctor (if possible, please wear clothes to allow examination, e.g. trousers and a top)
- 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

These checks are to make sure you are eligible to participate. A urine sample is checked for glucose (to exclude diabetes), protein and blood (which can indicate kidney disease). For women, a urine pregnancy test will also be performed. 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 is necessary for the *P. vivax* malaria parasite to infect your red cells.
- Levels of an enzyme called G6PD, sickle cell anaemia and thalassaemia (disorders of the red blood cells). These conditions affect your susceptibility to malaria infection.
- Infection with hepatitis B, hepatitis C and HIV, as these conditions can affect your immune response. If you test positive to any of these, we will let you know and arrange for a repeat test. With your consent we may also report positive results to your GP and offer to refer you for further investigation/treatment. We will repeat these tests on day 96 post-malaria challenge.
- Infection with two other common viral infections called CMV and EBV. This will provide us with further information about your immune response to infection. We will only repeat testing for CMV and EBV antibodies at day 96 post-challenge, if these tests were negative at screening.

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 the screening blood results may be used in that study, where appropriate and with your consent.

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-malarial treatment you would receive and this may exclude you from participating in the challenge

Blood Donation: Under current UK regulations, **you would not be permitted to donate blood** after taking part in this trial. This is because the malaria challenge involves the injection of red blood cells from another person, which is classified as a small blood transfusion.

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. The injection, implant, the coil and most forms of hormonal contraception, including newer forms of the progesterone-only pill (containing desogestrel) will all be deemed acceptable for the trial. 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 clinician. If you are taking an oral contraceptive pill, please check with the investigators that it is acceptable for this study. 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. 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, until the start of the next menstrual period. Pregnancy tests will be carried out regularly through the study. At screening, the day of vaccination and just before anti-malarial treatment is started this will be a urinary pregnancy test. A blood pregnancy test will be performed on the day before malaria challenge at 7, 14 and 21 days after challenge (unless already diagnosed), and again before anti-malarial treatment is started.

Malaria Prophylaxis: If in future you travel to an area where malaria is common, you should not assume that the experimental vaccines you received in this study will give you any protection against malaria. Make sure you visit your GP or a travel clinic before travelling to a malaria endemic region and follow their advice on prevention measures.

VACCINATIONS

What is the vaccine that is being tested?

We are testing the vaccine; **PvDBPII in Matrix M1**. This vaccine will be given into the muscle of your upper arm.

1. **PvDBPII**

The **PvDBPII component** of the vaccine is part of a protein that the *Plasmodium vivax* parasite uses to invade human red blood cells, called Duffy Binding Protein or DBP. It has long been considered a leading candidate vaccine against *Plasmodium vivax* malaria and in recent years two DBP-based vaccines, including PvDBPII, have been developed and tested in healthy people in small safety studies. In the initial small study assessing PvDBPII conducted in India, 27 people received the vaccine in combination with an adjuvant called GLA-SE. The vaccine, given together with the GLA-SE adjuvant, was shown to be safe and well-tolerated in humans and induced a good immune response. However, the PvDBPII protein in combination with the adjuvant Matrix M1 has not yet been assessed, and will be tested for the first time in this study.

2. **Matrix M1**

Matrix-M1 is a vaccine adjuvant – a substance that helps improve the body’s immune response to a vaccine. Matrix-M1 has previously been given to over 1000 healthy volunteers in other clinical trials and has been safe and well tolerated. This includes trials of other investigational vaccines for malaria.

What dose will be used?

All volunteers will be given the same dose of PvDBPII in Matrix M1 (see table below). This is the same dose as the maximum dose given in a previous safety study of PvDBPII, which was shown to be well tolerated and resulted in a good immune response.

Based on previous studies, the optimal dose of the adjuvant Matrix-M1 is 50µg (micrograms). This is the dose that we will be using in this trial, in combination with the PvDBPII protein. The vaccination groups are summarised in the table below.

Group	Group size	D0	D28	D56	D70-84
Group 1	15(+2)	PvDBPII 50ug Matrix M1 50ug	PvDBPII 50ug Matrix M1 50ug	PvDBPII 50ug Matrix M1 50ug	CHMI

VAC079 study groups and vaccination dose schedule

A similar number of non-vaccinated control volunteers, recruited as part of another study, will be challenged alongside Group 1 VAC079 volunteers, to allow comparison and understand the effect of the vaccine.

VISITS

Over approximately 1 year, you will attend a maximum of 65 visits. This will include 3 vaccinations, malaria challenge and follow-up visits. All visits will take place at the Centre for Clinical Vaccinology & Tropical Medicine (CCVTM) in Oxford. At each visit we will check your temperature, pulse and blood pressure readings, ask you some medical questions and usually take some blood tests. You may also be examined by a doctor if needed.

Vaccinations

On each vaccination day, we will assess you to check for any new medical problems since your last visit and make sure that you are still happy to go ahead. We will also take some blood tests. All women will also have a urinary pregnancy test. The vaccines will be given into the muscle of your upper arm, usually on the non-dominant side (e.g. left arm if right-handed).

After each vaccination, we will ask you to wait in the clinic for 1 hour to check there are no immediate problems. You will be assessed again before leaving and be given a thermometer and tape measure to take away. We will also show you how to use the electronic diary and ask you to record your symptoms and any redness at the vaccination site every day for 7 days after each vaccination. After these 7 days we will just ask you to record if you feel unwell or take any medications over the next 3 weeks.

At the follow-up visits, we may ask to photograph your vaccination site. You will not be identifiable in these photographs. Photographs may be shown to other professional staff, used for educational purposes or included in a scientific or academic publication.

First vaccination with PvDBPII in Matrix M1 and follow ups

After screening, your next visit will be for the first vaccination with PvDBPII in Matrix M1. We call this day 0 (D0).

First volunteers

As this is the first time that the PvDBPII/Matrix-M1 vaccine is being administered to people, for safety reasons, we will initially vaccinate one volunteer alone. We will then monitor the volunteer until at least 2 days after vaccination. If there are no safety concerns, a further 2 volunteers will be vaccinated, at least an hour apart. One week after the second and third volunteers are vaccinated, we will review all the information on the symptoms the first three volunteers experienced after vaccination. If any side effects experienced are as expected, then the remaining volunteers will be vaccinated.

You will be able to choose whether you wish to be one of the first three volunteers vaccinated.

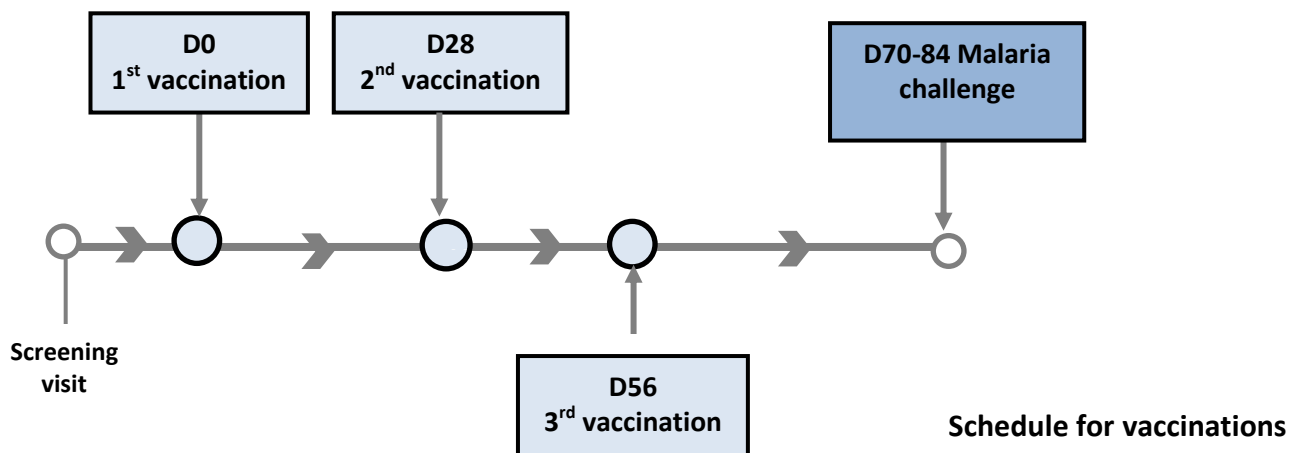
After vaccination, we will need to see you in clinic to review any symptoms you may have experienced from the vaccine. These visits will take place on days 1, 3, 7, 14 and 28 after vaccination. Between visits and up to day 28 after vaccination, you will be asked to continue recording your symptoms in the e-diary.

Second vaccination with PvDBPII in Matrix M1 and follow ups

Your next visit will be for the second vaccination with PvDBPII in Matrix M1. This will be 4 weeks after the first, on day 28 (D28). As for the first vaccination, we will then need to see you to check for any side effects of the vaccine on days 29, 31, 35, 42 and 56 and record your symptoms for 28 days.

3rd Vaccination with PvDBPII in Matrix M1 and follow ups.

Your next visit will be for the third vaccination with PvDBPII in Matrix M1. This will be 4 weeks after the second, on day 56 (D56). As for the first and second vaccinations, we will then need to see you to check for any side effects of the vaccine on days 57, 59, 63 and 70 and record your symptoms for 28 days.



C-1 visit (one day before malaria challenge)

On the day before malaria 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 the samples we will take after the challenge. These checks are to ensure you are completely healthy and can still be infected with malaria. For female participants, a blood pregnancy test will be performed. The back-up volunteers will also need to attend this visit and 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

Where did the malaria-infected blood come from?

We collected the malaria-infected blood from a volunteer who was infected with vivax malaria by mosquito bite in a recent Oxford study. The mosquitoes were originally infected by feeding on the blood of a person with malaria in Thailand. The infected mosquitoes were then shipped to the UK and were allowed to bite the UK volunteers in a controlled environment. The volunteers were observed until they developed malaria infection. Once they were diagnosed with malaria and just before treatment was started, each volunteer donated 250mL of blood, containing the *P. vivax* malaria parasites. The blood was then frozen and is being stored to use to challenge future volunteers.

The donor had a “universal” blood type (O negative), so that their blood can be safely given to everyone. Both the donors and the blood itself have also been thoroughly tested for infections which can be transmitted by blood, other than malaria, to ensure safety. All such tests have been negative.

To date, the infected blood has been given to 6 healthy volunteers in one previous study. All volunteers were successfully infected, showing that this method of infection works, and there were no unexpected side effects. As a research group, we have a large amount of experience of safely infecting people in this way with the commonest type of malaria, *P. falciparum*. For vivax malaria, the same method has also been used by another group in two published studies, which showed that blood-stage challenge was safe and effective.

What happens during the malaria challenge?

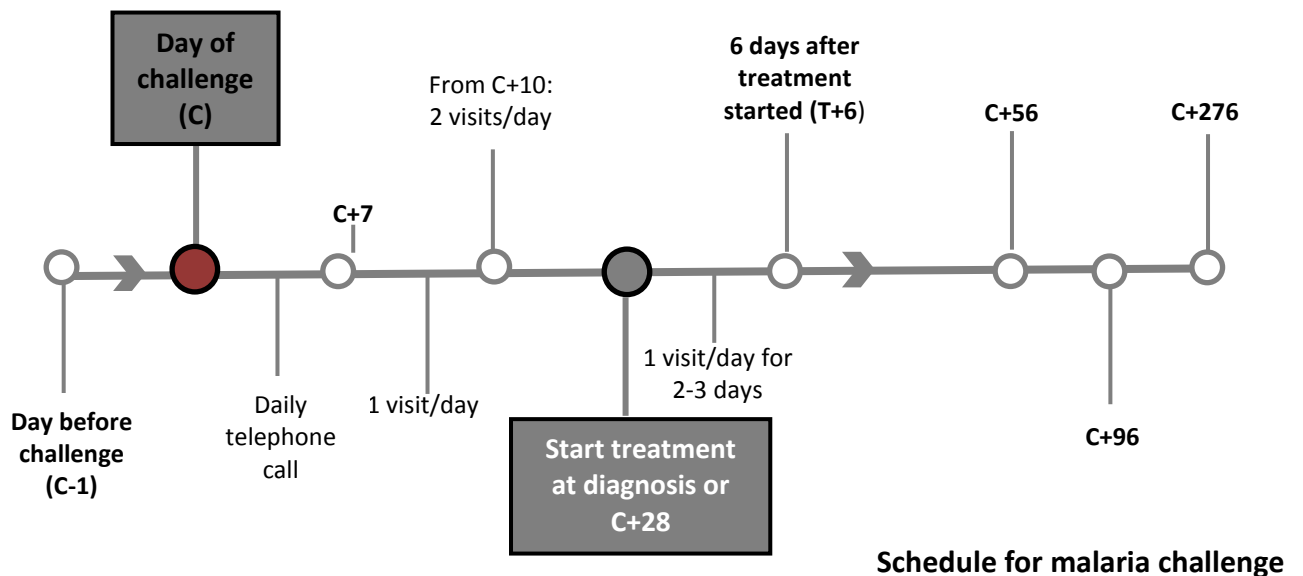
The challenge day will be between 2 and 4 weeks after your third vaccination. On the day of challenge an intravenous cannula (‘drip’) will be inserted into a vein in your arm. After this, a small amount (5 mL or 1 teaspoonful) of a solution containing red blood cells which are infected with malaria parasites will be injected into the vein. You will need to stay in CCVTM for 1 hour after being given the injection, in case you have an immediate reaction.

What happens at follow up after the malaria challenge?

The malaria challenge follow up visits are very important for your safety. After you have been challenged, it is vital that you remain in the Oxford area until completing treatment. We need to assess you by phone once a day for the first six days (from C+1 until C+6). From day seven until day nine (C+7-C9) we will need to assess you in clinic once a day, then twice daily until 28 days after challenge, or until you are diagnosed with malaria (see timeline below). If the level of parasites in your blood are very low, we may only need to see you once a day during the last week but unless you are informed otherwise, you should assume you need to attend clinic twice a day from day 10. **All these clinic visits will take place at the CCVTM at the Churchill Hospital in Oxford. It is essential that you reside in Oxford during this time** for careful monitoring and regular review by the study team. Accommodation can be arranged for you (and paid for) if you require it during this period.

Each time we see you, we will assess your symptoms and a doctor will examine you, if necessary. A small amount of blood will be taken and examined under the microscope for malaria parasites. This is called a thick film and it 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). These visits will last approximately 10 minutes, although you may have to wait to be seen. The

total number of visits post challenge will vary depending on when and if you get malaria. It is important you are able to attend all the visits. We will also give you a medication diary card on which you will be asked to record all medications that you take, which you should bring with you to each visit. **If you plan to travel outside of Oxford at any time from the day before challenge to 30 days after the challenge, you should discuss your plans with a study physician before participating in this study.**



How will I be diagnosed and treated?

If you are diagnosed with malaria you will be started on a course of anti-malarial tablets. This visit will last longer than the other follow-up visits, approximately half an hour. Usually the blood test result is available after you have already left clinic, although if you wish to wait for the result after each test you are welcome to do so. If you have left and your blood test is positive for malaria we will contact you and ask you to return to the CCVTM as soon as possible to start treatment. However, if the diagnosis is made very late at night and you feel well, we will give you the option of waiting until the following morning to start treatment, if you would prefer. 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 to start treatment at short notice between day 1 – 28 post challenge.** You **must** also provide a name and 24-hour phone number for someone who will be living with 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 uncontactable we will contact this person.

The drug you will be treated with is called Riamet®. Each Riamet® tablet is a combination of 20mg artemether and 120mg lumefantrine. Each dose is 4 tablets and you will need 2 doses each day for 3 days. We will give you the first dose and ask you to take the second dose 8 hours later. The next day and the day after that, you will need to take 2 doses, 12 hours apart. We will watch you take one dose each day. Tablets should be taken with a meal or a snack.

When you start treatment, you may not feel better straight away, but most people start to feel better after about 24 hours. After starting treatment, you will need a blood test once every day until two blood tests in a row show the malaria parasites are clearing.

If you are feeling unwell and your symptoms are like malaria, but no malaria parasites are seen in your blood, we may not treat you straight away. If you are feeling ill for one or two days, we may decide to start treatment even if no parasites are seen. If you have still not developed malaria after 28 days, you will be given the malaria treatment regardless of whether or not we have seen malaria parasites in

your blood. This is to make sure any parasites which had not been detected are killed.

If there are any problems with Riamet® for any reason, we have a different anti-malarial treatment available which is called Malarone.

After starting treatment, you will be seen each day, until you have had two negative malaria tests on consecutive days. Our experience tells us that the malaria parasites should disappear from your blood within 2 or 3 days of starting the treatment.

If you become unwell with malaria then you may be admitted to the John Warin ward (the Infectious Diseases and Tropical Medicine Unit at the John Radcliffe Hospital in Oxford) as a precaution until you have recovered, but it is very unlikely that this will be necessary.

It is important to note that in clinical practice, patients with *P. vivax* malaria 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.

Follow-up after treatment

After completion of your treatment, you will next be seen in clinic 6 days after your treatment was started. You will then be seen again on days 56, 96 and 276 after challenge. At these visits a 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 range from a teaspoon to 6 tablespoons. 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)
- Human Leukocyte Antigen (HLA) type – these are protein or markers on the surface of your cells
- G6PD level (an enzyme in red blood cells)
- Duffy antigen (a protein on the surface of red blood cells)
- Genetic tests of your cells and the parasites
- Malaria parasites (for diagnosis and monitoring after challenge) – by microscopy and PCR
- Immune responses to vaccination

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

The total volume of blood taken during the study depends on the group. The amount taken at each visit will vary between around 4mL (less than a teaspoon) to a maximum of 98 mL (about 7 tablespoons). The volume of blood being taken over the course of the trial should not cause any problems in healthy people. There may be some temporary mild discomfort, such as bruising and tenderness at the site where the blood tests are taken from. You may experience faintness as a result of collecting blood. We will give you a copy of your blood tests if you request them, but will only send the results to your GP if you wish us to and will not report them to anyone without your permission.

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 will be informed. For example, a new diagnosis of anaemia might be made. Any newly diagnosed conditions will be looked after by your GP within the NHS.

Once malaria has been diagnosed and treated, with 2 consecutive blood tests confirming a falling parasite count (PCR) after treatment, the twice daily / daily blood tests after challenge will no longer be required.

2. Vaccination side effects

Once the vaccinations have been given they cannot be undone, so it is important you understand the potential risks of the vaccines before you agree to be involved in the study.

This particular vaccine has not been used in humans before but we do not expect the side effects of this vaccine to be significantly different from previous trials where different protein vaccines have been used with the same adjuvant (Matrix-M1). We expect that most symptoms will be mild, but symptoms may also be moderate or severe in how strong they are. All symptoms should resolve completely within a few days.

You may experience any of the following short-lived side effects:

- Injection site pain (most likely mild; however there is a chance this could be moderate or severe in intensity).
- Redness, swelling, itching and warmth at the vaccine site (symptoms are likely to be mild if present; however, there is a chance this could be moderate or severe in intensity).
- A 'flu-like illness within 24 hours of vaccination which usually resolves within 48 hours. (This can include headache, muscle aches, joint aches, feverishness, tiredness, nausea and feeling generally unwell). The majority of general symptoms are likely to be mild but there is a possibility of moderate or severe symptoms occurring.

It is important to remember this vaccine is being tested in humans for the first time in this trial, so there is a chance you could experience a side effect different in nature, or more severe than those described.

Severe Reactions

With any vaccination there is a low risk of serious reactions, which may be related to the nervous system or the immune system. Severe allergic reactions to vaccines (anaphylaxis) are very rare but can be fatal. Doctors qualified in the management of anaphylaxis and appropriate equipment and medication will be present at each vaccination. Reactions in the nervous system are also extremely rare following vaccination, but can cause an illness called Guillain-Barré syndrome. Guillain-Barré syndrome is an illness in which people can develop severe weakness and may be fatal. However, these reactions have not previously been seen with the type of vaccine used in this study. If you experience unexpected symptoms, or become in any way concerned you should contact one of the Investigators (who are available 24 hours a day) using the emergency contact details that you will be given once you have been vaccinated.

3. Blood transfusion reaction

The malaria challenge in this trial involves receiving a very small number of malaria-infected red blood cells. If blood is given from one person to another there is a risk of an allergic reaction. Normally, the blood groups of the blood donor and the individual receiving the blood must be the same to avoid allergic reactions. The donor of the blood we will be using is blood group O, rhesus negative. This means the donor's blood can be given to people of the same or any other blood group, without causing an allergic reaction.

4. Transmission of blood-borne infection

The blood transfused in this study carries a much smaller risk of transmitting other infections than normal blood transfusions. Firstly, the volunteer who donated the malaria-infected blood was screened for a wide range of blood borne infections both before and after the blood was collected, all of which were negative. In addition, tests for infection have been performed on the blood bank itself. This testing was more extensive than that used by the National Blood Transfusion service. Secondly, the volume of blood injected for this study (approximately 0.025mL – 0.1mL) is more than ten thousand times smaller than the volume in a transfused unit of blood (470 mL). In addition, the blood cells have been washed and the white blood cells removed, both of which lower the risk of infection due to transfusion.

5. Malaria infection

If untreated, the malaria infection that we propose to give you could result in death. Worldwide over 1400 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 risks of taking part in this study are low provided that you return for follow-up as outlined above.

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. We hope to diagnose and treat your infection before the onset of symptoms but in previous studies most participants did experience some of the above symptoms. It is possible that you might need to take one or two days off work due to symptoms of malaria. 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 at all**.

In the unlikely event that it is necessary, you may be admitted to the Infectious Diseases ward (the John Warin ward) at the John Radcliffe Hospital, Oxford for observation and treatment. In the last 10 years, only 4 participants out of more than 400 challenged with malaria in Oxford have required hospital admission, and all have made a full recovery. There have been no long term problems in participants challenged with malaria.

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. This second individual 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 that 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 anti-malarial therapy, the police may be notified and your name may be released to the national media in order to find you.

For 5 years after your malaria infection if you develop any of the symptoms of malaria as detailed above please contact one of the study doctors or your General Practitioner and remind them that you have been involved in this study.

6. Malaria treatment

The drug you will be treated with is called Riamet. 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 show that the malaria parasites are clearing. 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 your doses of Riamet which we observe at the CCVTM. 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, or difficulty breathing, 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.

Taking some other medicines is not compatible with taking Riamet at the same time. If you cannot take Riamet or need to stop taking Riamet during the study, then there are other anti-malarial drugs that can be used effectively instead. If at the screening visit 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 for this drug to take away.

7. 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 on the emergency contact number you will be provided with immediately.

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

There may be risks, or side effects which are unknown at this time.

OTHER INFORMATION

“Back-up” participants

In addition to the participants to be included in the study, we will also recruit 2 back-up participants. If you are a back-up participant, you will receive vaccinations and clinic follow-up visits up to the point of the malaria challenge but will not necessarily undergo challenge. Back-up participants will be asked to be available to take part in the challenge at short notice if another volunteer is unable to take part at the last minute. For safety reasons, the back-up participants will be followed-up for 6 months.

Expenses and payments

You will be compensated for:

- Screening visit: £25
- Travel expenses (enrolled volunteers): £15 per visit (if travel to the trial site costs more than £15 additional reimbursement may be offered).
- Time required for visits (enrolled volunteers): £20 per hour.
- Inconvenience of blood tests: £10 per blood donation.
- Extra visits, if required: £20 per visit.
- Compensation for illness (after infection with malaria): £480.

The overall compensation will be approximately £3500, as shown in the table below. The exact number of visits and amount of blood that will be taken will depend on when you are diagnosed with malaria. 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.

	Time in Trial (approximately)	Maximum No. of Clinic Visits	Maximum Volume of Blood Taken (mL)	Compensation Amount
Total	1 year	65	1517	£3500

What do I have to do?

- You **must** provide a name and 24 hour phone number for someone who lives with/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 23 days after each challenge and are un-contactable we will contact this person. If you cannot be located we will take additional steps to locate you which may involve contacting the police and national media.
- You **must** attend all the visits that are outlined above.
- Women **must** use an effective method of contraception for the duration of the study. If you are using a hormonal contraceptive, you will need to use an additional alternative method of contraception while you are taking the medication for malaria, and until the start of the next menstrual period.
- You **must not** donate blood in the UK following participation in the study.

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, but the information gained from the trial might help to prevent malaria infection and disease in those who live in areas where malaria is common and in travellers. It is hoped that the method tested in this study will allow future studies to assess possible future vaccines against *P. vivax* malaria, and ultimately contribute to the development of a safe and effective *P. vivax* malaria vaccine. At present, there is no vaccine for *P. vivax* malaria 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.

What if there is a problem?

Any complaint about the way you have been dealt with during the study or any possible harm you might suffer will be addressed. The detailed information on this is given in Part 2.

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 below.

This completes Part 1 of the Information Sheet. If this information has interested you and you are considering participation, please continue to read Part 2 below 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 may 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 anti-malaria treatment course 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.

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 616480 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. Responsible members of the University of Oxford may be given access to data for monitoring and/or audit of the study to ensure that the research is complying with applicable regulations. Any information about you that leaves the 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.

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?

All samples will be stored in an de-identified form. Your study visit blood tests will be analysed in Oxford University research laboratories. Blood tests for your general health will be carried out in the NHS laboratories at Oxford University Hospitals. 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 NHS laboratories or collaborating labs would be de-identified.

Some of your leftover blood samples will be stored indefinitely at the Oxford Vaccine Centre Biobank and may be used for further related research, including of the human body's immune response and/or vaccine research and/or your safety. Any such future research will have an appropriate ethical review. More information around the procedures for long term storage of your samples is available in the Oxford Vaccine Centre Biobank information booklet and you will be asked to sign a separate consent form for storage of your samples for future use in ethically approved research. Upon your request at any time, your remaining blood samples will be destroyed.

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.

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). We will also look at changes in the expression of your genes in response to malaria infection. Since these genetic test are not carried out to look at your general health, you would not be given the results of these tests.

What will happen to my data?

We will be using information from you and your medical records in order to undertake this study. Research is a task that we perform in the public interest. The University of Oxford, as sponsor, is the data controller. This means that we, as University of Oxford researchers, are responsible for looking after your information and using it properly. We will use the minimum personally-identifiable information possible. We will keep identifiable information about you such as contact details for a minimum of 5 years after the study has finished. The need to store this information for longer in relation to licensing of the vaccine will be subject to ongoing review. For effective vaccines that may be licensed, we may store research data securely at the University of Oxford for at least 15 years after the end of the study, subject to adjustments in clinical trials regulations. In addition to the de-identified scientific data, we will also store documents containing personal information that you provide when registering for the trial (including contact details), medical information and signed consent forms during this archiving period.

The study team will use your name and contact details, to contact you about the research study, and make sure that relevant information about the study is recorded for your care, in relation to your health during the study and to oversee the quality of the study. At the completion of the study, unless you consent otherwise (e.g. if you request to be informed of other trials), your personal details will not be used to contact you other than exceptional circumstances concerning your safety. If you consent to take part in another study carried out by the Jenner Institute, personal information and medical information including blood test results may be accessed to avoid unnecessary repetition.

Your bank details will be stored for 7 years in line with university financial policy.

Your rights to access, change, or move your personal information may be limited, as we need to manage your information in specific ways in order for the research to be reliable and accurate. Further information about your rights with respect to your personal data is available at:

<http://www.admin.ox.ac.uk/councilsec/compliance/gdpr/individualrights/>

What happens when the research study stops?

If you have any queries or concerns once the study is over, please do not hesitate to get in touch with us.

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 Wellcome Trust and 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 an MD or PhD.

A description of this study will be available on www.clinicaltrials.gov. 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.

Taking part in future vaccine related research

With your consent, we would like to keep your contact details after your participation in this study is complete, so we may inform you of opportunities to participate in future vaccine related research.

Your details will be stored electronically on a secure server and only authorised individuals at the CCVTM will have access to it. We will not, under any circumstances, share your contact details with any third party institutions without your permission. Being contacted does not oblige you to agree to take part in future research and you can ask us to have your contact details removed from our database 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 Wellcome Trust and closely aligned with other ongoing clinical trials 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 South Central - Oxford A Research Ethics Committee and has been given a favourable ethical opinion. A Research Ethics Committee is an independent group of people who review research to protect participants' interests.

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

Tel: 01865 611406

CCVTM, Churchill Hospital, Old Road, Headington, Oxford, OX3 7LE