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PARTICIPANT INFORMATION SHEET: VAC069

A study of blood-stage controlled human *Plasmodium vivax* malaria infection

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. 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. Unlike the most common malaria, *Plasmodium falciparum (P. falciparum), P. vivax* 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. In this study we will infect volunteers with *P. vivax* malaria to help us develop our understanding of *P. vivax* malaria and allow us to establish a method that will be used to test out potential future vaccines.

What are the choices for taking part in this study?

We are looking for volunteers who will be experimentally infected with malaria on up to three separate occasions, each time by receiving an injection of a tiny amount of blood containing the *P. vivax* parasites.

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. 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:

- We will be giving volunteers malaria by intravenous injection of a small amount of malaria-infected blood.
  This source or "bank" of blood is being used for the first time in this study. The blood has been thoroughly screened and tested negative for other infections but a theoretical risk of infection (other than malaria) can never be completely excluded.
- All volunteers will likely develop malaria and need to stay in the Oxford area for up to four weeks after infection for safety.
  After being given malaria, volunteers will be required to remain in Oxford and attend clinic in Oxford up to twice daily for up to four weeks. A blood test will be done at each of these visits. Further occasional follow-up visits will take place until 96 days after each challenge.

What is the purpose of the study?

The main focus of our research group is the development of malaria vaccines. Currently, the treatments and ways of preventing *P. vivax* malaria are inadequate and there is a great need for a safe and effective vaccine. At present, there are no approved vaccines for *P. vivax* malaria. Ultimately, in order to test whether a potential new vaccine works, we need to be able to "**challenge**" vaccinated volunteers with *P. vivax* malaria infection, after they have been vaccinated. We can do this by deliberately infecting vaccinated volunteers, then observing to see if they have been protected from malaria or develop symptoms more slowly compared to volunteers who did not receive the vaccine.

One way of challenging volunteers is by administering a very small transfusion of malaria infected blood, collected from a person who has been infected by mosquito bite. As we are infecting volunteers directly into the blood, this is sometimes called a **blood-stage malaria challenge**. There is a large amount of experience of safely infecting people in this way with the commonest type of malaria, *P. falciparum*. Previously, within Europe, previously there was no source or "bank" of blood that could be used to infect people with *P. vivax* malaria. In a recent study at Oxford, we created a new bank of *P. vivax* malaria infected blood.

In this study, we aim to establish that this new blood bank can be used to safely infect volunteers with *P. vivax* malaria. By doing so, we can then use the same method in future trials testing new malaria vaccines. At the same time, we also aim to understand more about the body's immune responses to malaria infection by blood-stage challenge, and about any effects of repeated challenges.

In the initial phase of this study, VAC069A which took place in January 2019, we used this blood bank for the first time. We established both that healthy volunteers can be safely infected with *P.vivax* malaria and what dose is needed to induce infection. In the next phases of the study (VAC069B-E), we will continue to make sure that this is a reliable and safe way to infect volunteers. We will do this by challenging further volunteers for the first time, as well as conducting re-challenges, with most volunteers in the study taking part in three separate challenges. We will be using the dose we have selected from the first phase in all further stages of the study.

A good vaccine will need to protect against repeated infections, so in order to test candidate vaccines, we will need to re-challenge or re-infect vaccinated volunteers. In order to carry out such studies in the future, we first need to make sure that the method of giving the infection repeatedly works and is safe for volunteers, which we will do in this study. Repeating infections can also help us better understand the body's response to malaria infection. In areas where malaria is common, we know that over time, following repeated natural infections, partially protective immune responses can develop. We aim to understand if being exposed to malaria by challenege in this study, has any effect on a subsequent challenge. We can also analyse the body's immune response, to track the changes from the first infection to the second and third. This may help to provide key information for new vaccine development., Each challenge, or infection, will be given between 5 and 9 months after the last.

For each challenge, after infecting volunteers with malaria, we will follow them closely to observe if and when they develop malaria. At the same time, we will take regular blood samples to measure the growth of the parasite and the body's immune responses to malaria infection. Once malaria has been confirmed (by detecting parasites in the blood), we will start malaria treatment to clear the infection.

As a research group we have a large amount of experience in safely infecting people by infection of blood with *P. falciparum*, but this is our first study with *P. vivax* malaria. Data from other centres outside Europe where controlled human malaria infection with *P. vivax* has been undertaken, demonstrate that this can be done safely and effectively and this was confirmed in the first phase of our study. We are aiming to build on the work done in these centres by performing detailed analysis of the growth of the parasite and immune responses to it. This will provide a new and more detailed insight than has been achieved previously.

Part of this new work will be understanding more about how malaria is transmitted from a person to a mosquito. By doing so, we wish to develop this method of infecting volunteers as a tool to also test vaccines which aim to stop the transmission of malaria, to use in future trials. The main way we will look at this is by counting how many of the parasites that we detect in the blood are in a form that can be transmitted to a mosquito – these are known as the sexual forms of the parasite. If the right mosquitoes are available, we also aim to look at this by taking samples of blood from volunteers and using these to artificialy feed mosquitoes in our lab. We can then check to see if the mosquitoes later become infected.

So, the key aims of this study are:

1. To demonstrate that infecting healthy volunteers with a new *P. vivax* infected blood bank is safe and effective.

2. To measure the growth of the *P. vivax* parasite growth in the blood over time after the first, second and third infection.

3. To analyse the body's immune responses to the first, second and third infection.

4. To see whether the *P. vivax* parasites in the blood of the infected volunteers can be taken up by mosquitoes. This is a secondary aim and will only take place if suitable laboratory-reared mosquito vectors are available

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. If you do decide to take part, **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. 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 then be asked to sign a consent form. 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 an intravenous injection of malaria infected blood as a malaria challenge up to three separate times. Volunteers recruited into Groups 12 and 13 will receive just one malaria challenge

Duration of participation

Each malaria challenge and the immediate follow-up period will last approximately three months. There will be approximately 5-9 months between each challenge. Therefore, volunteers in Groups 1-11 will be involved in the trial for approximately 2 years. As volunteers in Groups 12 and 13 are only taking part in one challenge, these participants will be involved for approximately 3 months.

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.
- Able and willing (in the Investigators' opinion) to comply with all study requirements.
- Reachable (24/7) by mobile phone during the period between malaria challenge and completion of malaria treatment
- Willing to allow the Investigators to discuss your medical history with your GP (General Practitioner)
- Practice continuous effective contraception during each of the three-month challenge periods **(women only)**.
- Willing to reside in Oxford until antimalarials have been completed at the end of each challenge.
- Answer all questions on the quiz about the trial correctly.
- You must not donate blood in the UK following participation in the study.

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 2 year 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 allow daily blood tests
- You have sickle cell anaemia, thalassemia, G6PD deficiency or any other haematological condition that might affect susceptibility to malaria infection, (e.g., red cells negative for the Duffy antigen, see page 6).
- 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 have any condition affecting your body's electrolytes, e.g. sodium or magnesium.
- You take any medications with are known to interact with malaria treatments.
- You drink on average more than 25 units of alcohol a week.
- You have injected drugs at any time in the last 5 years.
- You have hepatitis B, hepatitis C, or HIV infection.
- 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 weigh less than 50Kg (this does not apply to volunteers who took part in the first phase of the study, VAC069A)

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

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 to 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.

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. 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, re-screening 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 through being exposed to malaria, you have developed any kind of protective response against any *P.*

vivax or any other kind of 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.

STUDY GROUPS

Volunteers recruited into the study will be part of a specific study group and these are outlined in the table over the page. Over the course of the study, all volunteers, except those in Groups 12 and 13, will undergo three malaria challenges with the same strain of *Plamsodium vivax.* Volunteers in Groups 12 and 13 will undergo a single challenge only. Each time volunteers return to take part in another challenge, they will become part of a new group. For example, volunteers recruited into Group 6 for their first challenge, will become Group 7 when they take part in the second challenge and then Group 8 when they participate in the third and final challenge. VAC069A, which involved Groups 1-3, has already taken place.

Phase of Study	Study Group	Group size	Day 0 (Jan 2019)	5-9 months later	5-9 months later	5-9 months later	5-9 months later
VAC069A	**Group 1 - new volunteers**	2	1st challenge Dose: 1 vial				
	Group 2 - new volunteers	2	1st challenge Dose: 1:5 dilution				
	Group 3 - new volunteers	2	1st challenge Dose: 1:20 dilution				
VAC069B	**Group 4 - previously in Groups 1-3**	6		2nd challenge			
	Group 6 -new volunteers	3		1st challenge			
VAC069C	**Group 5 - previously in Group 4**	6			3rd challenge		
	Group 7 - previously in Group 6	3			2nd challenge		
	Group 9 -new volunteers	12			1st challenge		
VAC069D	**Group 8 -previously in Group 7**	3				3rd challenge	
	Group 10 - previously in Group 9	12				2nd challenge	
	Group 12 -new volunteers	2				Single challenge	
VAC069E	**Group 11 - previously in Group 10**	12					3rd challenge
	Group 13 - new volunteers	2					Single challenge

Table of study groups. Each challenge will take place at 5-9 month intervals.

VISITS

All visits will take place at the Centre for Clinical Vaccinology & Tropical Medicine (CCVTM) in Oxford.

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, and to sign a consent form.

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.

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 will allow *P. vivax* 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, HIV, as these conditions can affect your immune response. If you test positive to any of these, we will let you know and offer to refer you for treatment.
- Infection with two other common viral infections called CMV and EBV. This will provide us with further information about your immune response to infection.

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.

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 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. For the first challenge only, 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

How was the "blood bank" made?

The infected blood that will be used in this study was obtained from one of two volunteers who were infected with *P. 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 both of the UK volunteers in a controlled environment. The volunteers were observed whilst they developed malaria infection and had blood tests taken regularly to measure the parasite growth. 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. Both the volunteers and the blood bank have been thoroughly tested for infections which can be transmitted by blood, other than malaria. All tests have been negative.

What happens during the malaria challenge?

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 adverse reaction.

What happens at follow up after the malaria challenge?

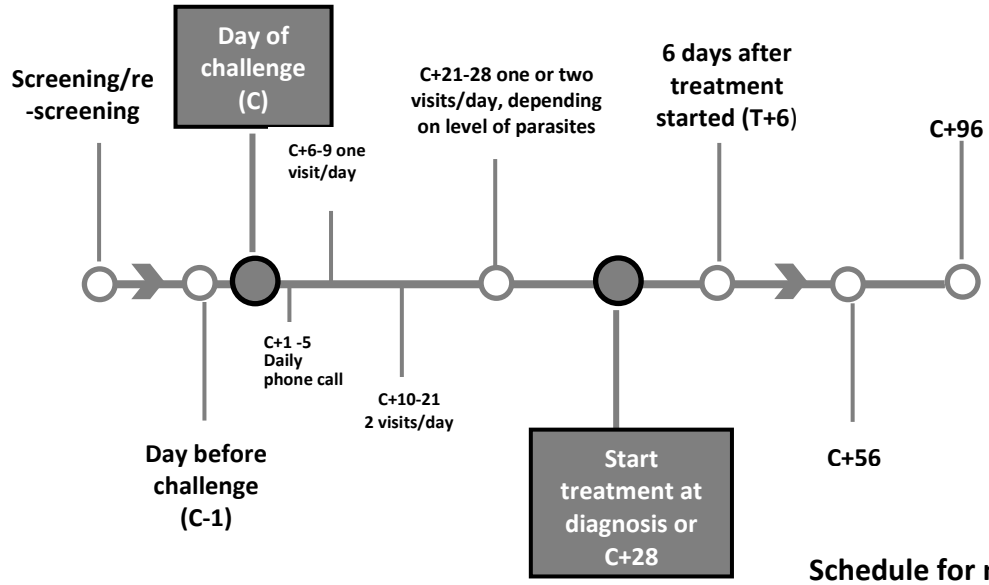
The malaria challenge follow up schedule is essential for your safety. We will telephone you once a day for the first 5 days after the malaria challenge. From day 6 until day 9 post-challenge you will attend the clinic daily for medical review and blood tests to measure the level of malaria parasite. From day 10 post-challenge (C+10) onwards you will attend the clinic twice daily for medical review and blood tests until you are diagnosed with malaria and commenced on treatment.

From day 21 after challenge (C+21), visits may be reduced to once daily if you have a very low level of parasites. Visits will go back to twice daily if the parasite level increases past a specified threshold. This pattern of clinic visits can be amended at any time if the trial doctors have any medical concerns about a volunteer. All volunteers will be treated for malaria at day 28 post-challenge (C+28) if they have not already been diagnosed and treated by that stage.

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 if you require it during this time.

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 28 days after the challenge, you should discuss your plans with a study physician before participating in this study.**



Schedule for malaria challenge

How will I be diagnosed and treated?

If you are diagnosed with malaria you will be started on a course of anti-malarial tablets. 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 un-contactable 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 have been negative for malaria parasites.

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 any problems with Riamet® for any reason, we have different anti-malarial treatments available which are called Malarone or Chloroquine.

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* 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

You will be seen in clinic 6 days after your antimalarial treatment commenced. You will then be seen again on days 56 and 96 after challenge. At these visits, blood samples will be taken to exclude any residual parasites, check your 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 tablespoons. The appointments will last about 10 minutes.

What happens during the second and third malaria challenges?

Re-screening visit: before each of the second and third challenges you will be invited for a re-screening visit. This visit will take place at least 2 weeks before the each of the second and third challenges and will be similar to your initial screening, but shorter, lasting up to one and a half hours. The purpose of the visit is to discuss the next challenge, to enable you to decide if you wish to continue to participate and for us to make sure you remain eligible to receive another malaria challenge. If you decide to continue with the next challenge, you will be asked to complete another questionnaire, to ensure we are confident that you still fully understand what taking part will involve, and to sign a new consent form. We will ask if there have been any changes in your medical history since your last visit and you will be examined by a doctor again. We will also repeat the same urine and blood tests as at the screening visit, with the exception that we will not repeat the blood tests for HIV, hepatitis B, hepatitis C, EBV or CMV infections. Since the disorders of red blood cells (G6PDH, sickle cell anaemia and thalassaemia) and expression of Duffy antigen (a specifc receptor on the red blood cell that allows *P. vivax* to infect the cell) that can affect your susceptibility to *P. vivax* malaria infection cannot change, we will also not re-test for these conditions. A urinary pregnancy test will be performed for women.

Will the second or third malaria challenge be any different to the first challenge?

For volunteers who took part in the first phase of the study VAC069A (Groups 1-3), the second and third challenges will be very similar to the first time but with a few key differences. These are all described in more detail above but are summarised below:

- All volunteers will receive the same dose of the inoculum
- For the first 5 days after challenge, you will not need to attend clinic routinely but you will need to ensure you are able to answer a daily telephone call. You will also need remain in the Oxford area and be contactable at all times.
- On day 6,7, 8 and 9 after challenge you only need to attend clinic once daily in the morning
- From day 10, you need to attend clinic twice daily until a maximum of day 28 after challenge. This is one week later than in VAC069A. If you have not developed malaria by day 28, we will start anti-malarial treatment
- After completing treatment, you will need to come in for a further 3 daily visits

- Instead of attending at days 45 and 90 after challenge, you will attend at days 56 and 96

For new volunteers recruited into Groups 6-11 (VAC069B-E), all the visits and other procedures in the second and third *P. vivax* malaria challenges will be exactly the same as for first, with the first visit after re-screening taking place a day before the challenge and continuing until 96 days after the challenge. You will need to remain available and fulfill the same requirements of the study, as for the first challenge.

For all volunteers: In natural malaria infections, it is known that over time, repeated infections can lead to the development of partially protective immune responses. It is therefore possible that the onset of malaria could be slower, or that the symptoms may be milder, in the second or third challenge compared to the first, leading to a later diagnosis. However, as this is the first time that repeated *P. vivax* blood-stage infections will be assessed, currently, we do not know if exposure to a previous blood-stage challenge will have any similar protective effect against another blood-stage infection. Therefore it is unknown if the timing of diagnosis or symptoms will differ in the second or third challenge compared to the first.

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)
- HLA type
- Enzyme levels (G6PDH and CYP2D6) and Duffy antigen - at screening
- 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 the following 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 149 mL (about 9 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, 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. 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 was blood group O, rhesus and Kell negative. This means the donor's blood can be given to people of the same or any other blood group.

3. Transmission of blood-borne infection

The blood transfused in this study has a smaller risk of infection than normal blood transfusions. Firstly, the volunteer who donated the malaria-infected blood was screened for a wide range of blood borne diseases both before and after the blood was collected. 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 maximum volume of blood injected for this study (0.5 mL) is nine hundred 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. We will however test for any evidence of HIV, Hepatitis B, Hepatitis C, CMV and EBV infection after each malaria infection to prove that transmission has not taken place.

4. 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. 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 (*Plasmodium falciparum*) 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 6 months after each challenge 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.

5. 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 marked reduction in 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 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 or Chloroquine) and give you an information sheet from the manufacturer for this drug to take away.

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

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, or difficulty sleeping. It should be noted that drowsiness may affect your performance of skilled tasks such as driving.

Paracetamol: Is a tablet that can be taken as and when needed 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 back-up participants. If you are a back-up participant, you will complete the clinic visits up to the point of the first challenge (2 visits), 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.

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 £10 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 vary by group, 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 Visits	Maximum Volume of Blood Taken (mL)	Estimated Compensation
Groups 1-5 (3 challenges)	2 years	149	3110	£6570
Groups 6-11 (3 challenges)	2 years	150	3132	£6855
Groups 12-13	3 months	50	1044	£2285

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 period between challenge and completion of treatment 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 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*, 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.

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.

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 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® 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 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.

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 anonymised form. 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. If you consent, 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 tests will have an appropriate ethical review. Upon your request at any time, your remaining blood samples 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. 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 if you agree to have your samples stored for future use in ethically approved research. Your participation in this study will not be affected by your decision to allow or not allow storage and future use of your leftover blood 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.

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. You can opt out of 'genetic tests' if you wish, without any effect on your participation in the trial.

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. Given the lack of long-term safety data for *P. vivax* CHMI, the need to store this information for longer be subject to ongoing review, taking into account any new information available at that time. In addition to the anonymised 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 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. 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 (Hampshire A) 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: +44 1865 611424

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