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IRAS project ID: 330788

NRES Committee South Central

Berkshire 23/SC/0364

PARTICIPANT INFORMATION SHEET: BIO-004

Understanding how the immune system responds to repeated malaria infections

We are inviting 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 involves. Please read the following information carefully. You can discuss it with friends, relatives and your GP (General Practitioner/family doctor) if you wish. Take time to decide whether or not you wish to take part.

- **Part 1** tells you about the purpose and the design of the study.
- **Part 2** tells you if you are eligible to take part and what will happen if you take part.
- **Part 3** tells you about any possible risks and benefits of taking part.
- **Part 4** gives you more information about how the study will be carried out.

Ask us if there is anything that is not clear or if you would like more information. You can ask us any questions at your screening visit. You can also contact us on the email address at the top of the page. This information booklet has been reviewed by four members of the Oxford Vaccine Centre's patient and public involvement (PPI) team. The PPI team make sure the information is presented in a way that is clear and understandable.

Who can take part?	Healthy adults aged 18–45 (full criteria inside)
Total participants	22 participants
Study aims	To understand how the body's cells that help to fight infection (T-cells) learn to tolerate repeated malaria infections
Study site	Centre for Clinical Vaccinology and Tropical Medicine (CCVTM) and Oxford Experimental Medicine Clinical Research Facility (EMCRF), Churchill Hospital, Oxford, OX3 7LE
Expenses and payment	Up to £9,325 to £9,955
Risks of participation	Untreated malaria infection can result in serious illness, therefore it is crucial that you attend all follow-up visits and take the anti-malarial treatment as advised. Short-lived post-vaccination symptoms such as arm pain and fever may occur. There is also a small risk of pain, bleeding and infection following a bone marrow test. We will monitor the safety of all participants closely. A full discussion of risks starts on page 20.
Benefits of participation	Participating in this study will not benefit you directly. It will help our research into changes in the immune response to malaria after repeated infections. A better understanding of this may help us

	develop more effective strategies to reduce the global burden of malaria disease and malaria deaths.
Visit schedule	Group 1: Average of 74 visits* (min. 53 visits to max. 95 visits) over 20 months with 2 additional optional visits Group 2: Average of 70 visits* (min. 51 visits to max. 88 visits) over 20 months **Average calculated based on previous similar studies. All participants enrolling must be aware that the actual no. of visits will vary between the minimum and maximum visits indicated above.*

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PART 1: THE PURPOSE AND DESIGN OF THE STUDY

Why are we conducting this study?

Malaria is an infectious disease caused by the *Plasmodium* parasite and is a major public health problem in many parts of the world. Malaria is spread by the bite of an infected mosquito. There are five species of the *Plasmodium* parasite that are known to cause malaria in humans. Of these five species, *Plasmodium falciparum* causes the most sickness and death globally, with an estimated 241 million cases of malaria and 619,000 deaths worldwide in 2021. *Plasmodium vivax* accounts for more than half of all malaria cases in the Americas and South-East Asia; globally, around 14 million annual cases present a significant clinical and economic burden. Most of the deaths from malaria occur in children under five living in Africa, with infants under 1 year being at the highest risk.

A significant study conducted in Tanzania showed that while the number of malaria parasites in the blood remained constant over the first few malaria infections of life, the risk of severe disease and hospitalisation decreased significantly with each infection. This study concluded that rather than killing the malaria parasite, the immune system developed the ability to 'tolerate' the presence of the parasite in the body, which reduced the damage caused during repeated infections. This was an important finding, however the way that the immune system tolerates the malaria parasite remains unknown.

In order to better understand how the immune system adapts to tolerate the malaria parasite after repeated infections, we are recruiting participants to undergo three malaria challenges. In a 'malaria challenge', study participants are injected with a small amount of malaria-infected blood under carefully regulated conditions in order to cause malaria infection. This is important as we will know the exact moment of infection and will be able to track the immune response that follows. This is difficult to do when studying infections that occur naturally.

This study will assess:

1. Changes in the immune (T-cell) response after three infections with *P. falciparum* malaria (Group 1 only)
2. Changes in the immune (T-cell) response after two infections with *P. falciparum* malaria followed by one infection with a different species of malaria, *P. vivax* (Group 2 only)
3. Changes in the bone marrow following the first malaria infection (Group 2 only) compared to the third malaria infection (Group 1 only) (we will do this by taking samples of bone marrow through a procedure called a 'bone marrow test')
4. Whether the immune (T-cell) response to vaccination is changed by repeated malaria infection – we will use the yellow fever vaccine to answer this question as this vaccine is known to stimulate a T-cell response.

While the main aim of our study is to improve malaria survival among children in areas of the world where malaria is common, there are a number of reasons why we have chosen to do this study among healthy adults in the UK. Firstly, in areas of the world where malaria is common, it would be difficult to find adults who have not had malaria before. This is an important part of our study as we want to understand the difference in the immune response to the first ever malaria infection and malaria infections that occur afterwards. Additionally, we could not conduct this type of research in infants as it would not be possible or ethical to take the amount of blood needed for the laboratory tests from young children.

It is hoped that the results of this study will help inform strategies to reduce the frequency of severe disease and death among children in parts of the world where the burden of malaria is high.

Do I have to take part?

No. It is up to you to decide whether or not to take part. Your decision will not result in any penalty, or loss of benefits or access to medical care to which you are otherwise entitled.

If you are eligible for the study, you will have the opportunity at ask the study team any questions you have to help you decide whether you want to take part. You will then be asked to complete a questionnaire to assess your understanding of the study. This will allow 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. If you don't answer all the questions right the first time, you will be able to complete it again after discussion with a study doctor. You will then be asked to sign a consent form.

You are free to withdraw from the study at any time without giving a reason. However, we would ask that you discuss this with a member of the study team before making this decision. We may also ask you to return to the clinic for follow up for safety reasons.

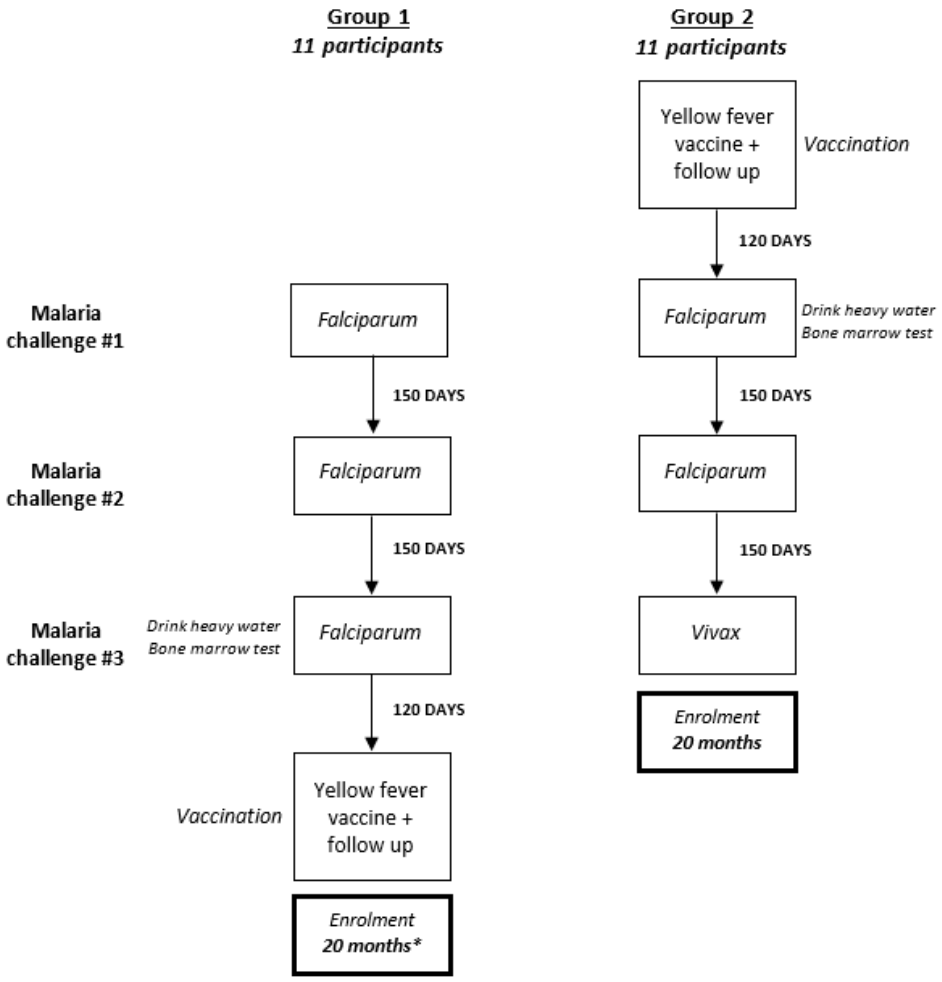
For University of Oxford staff or students: The University does not urge, influence, or encourage you to take part in this research study. Your decision to not participate in the study, or a decision on your part to withdraw from the study, will have no effect whatsoever on your employment/student status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

What will happen if I decide to take part?

If you decide to take part in the study, you could either be enrolled into Group 1 or Group 2.

In summary:

- **Group 1:** You will undergo three malaria challenges, approximately 5 months apart. After the third (and last) malaria challenge, you will be asked to drink a small amount of a substance called heavy water daily for between 2–3 weeks (more information about heavy water in Part 2 of this document). You will also undergo a bone marrow test. You will then receive the yellow fever vaccination and complete your follow-up visits. Your total study time will be around **20 months** (plus 2 later optional visits occurring 3 and 15 months later)
  or
- **Group 2:** You will receive the yellow fever vaccination first and then undergo three malaria challenges, approximately 5 months apart. After the first malaria challenge, you will be asked to drink a small amount of a substance called heavy water daily for between 2–3 weeks. You will also undergo a bone marrow test. You will then complete your follow-up visits. Your total study time will be around **20 months**.



**Optional follow up visits at 23 and 35 months*

Participants will be recruited to Group 2 first. Once Group 2 is fully recruited, recruitment to Group 1 will begin. The study doctor will talk to you about which group you would be enrolled in at your screening appointment. Depending on the timing of your screening appointment, you may not be able to choose which group you are enrolled into. Malaria challenges for both groups will be conducted on the same day to ensure the conditions for the challenge are the same for all study. For this reason, there is little flexibility in the dates for study visits during this time.

Visits will take place in the Centre for Clinical Vaccinology and Tropical Medicine (CCVTM) and the Oxford Experimental Medicine Clinical Research Facility (EMCRF). This is at the Churchill Hospital in Oxford. The CCVTM clinic is wheelchair accessible. If you have other accessibility needs, please contact us to discuss them. We will try to meet your needs wherever possible.

What does the study schedule look like?

Group 1 participants will be in the study for around 20 months from the time they are enrolled. They will have visits ranging between 53 (minimum) to 95 (maximum) visits depending on their malaria diagnosis at each challenge*. There is also 2 optional longer-term visits at the end of the study. Enrolment will be for 35 months if participants in Group 1 attend both optional visits.

Group 2 participants will take part in the study for about 20 months from the time they are enrolled. They will have visits ranging between 51 (minimum) to 88 (maximum) depending on their malaria diagnosis at each challenge*.

**The reimbursement amount for both groups will remain the same regardless of the number of visits during the challenge period.*

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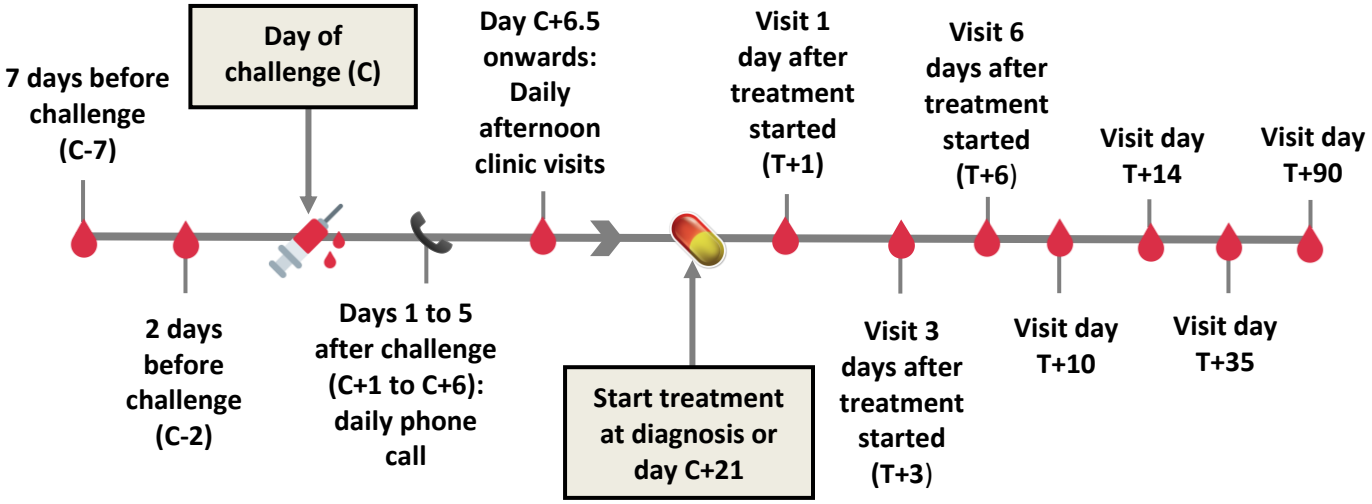
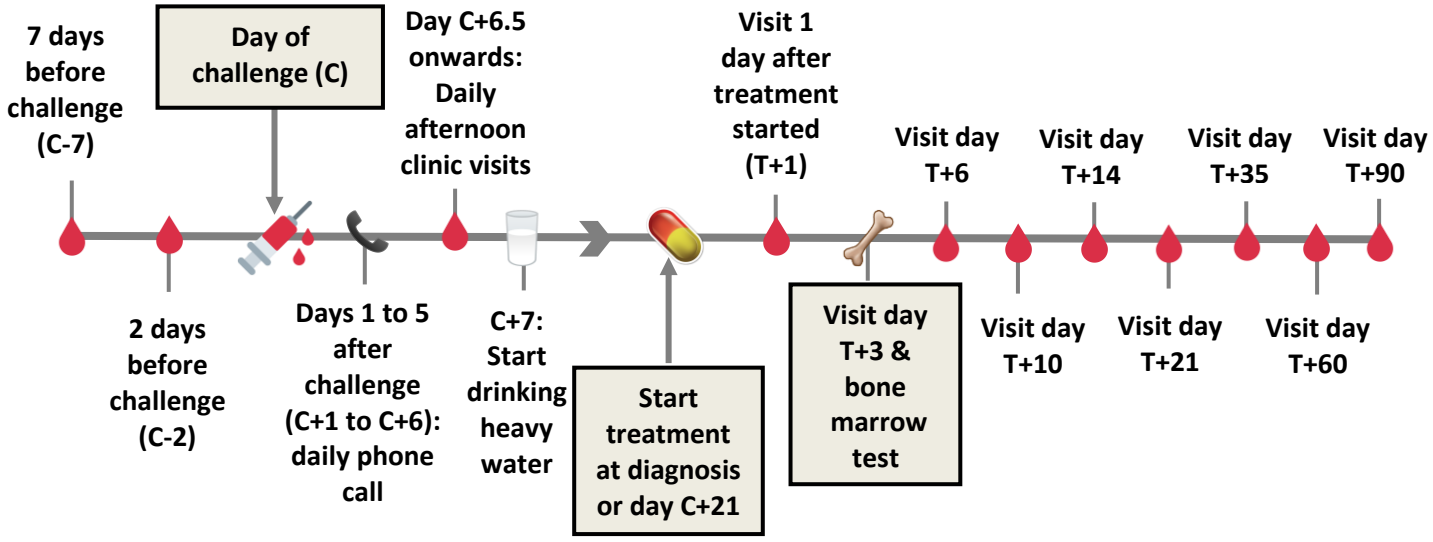
GROUP 1 STUDY SCHEDULE

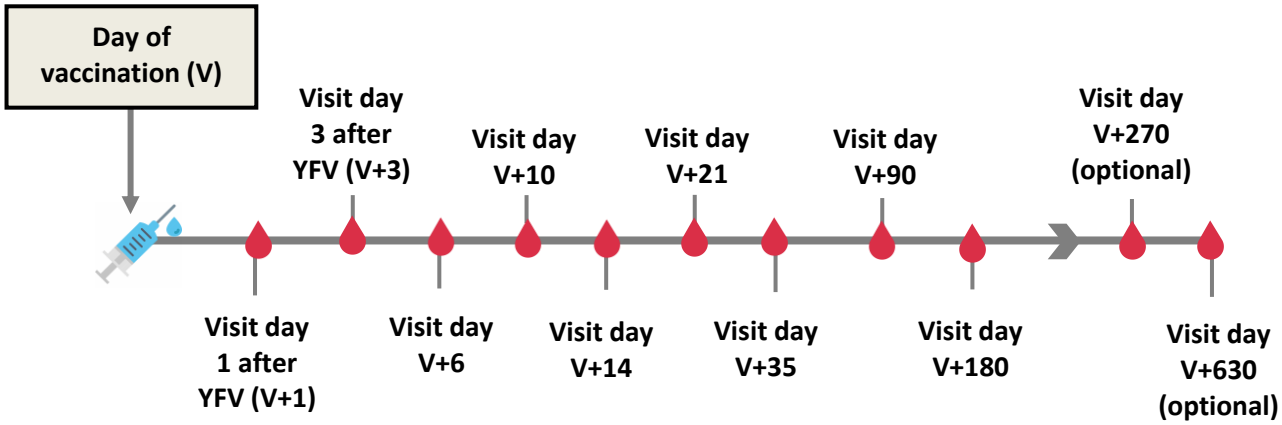
P. falciparum malaria challenge #1 and #2



P. falciparum malaria challenge #3

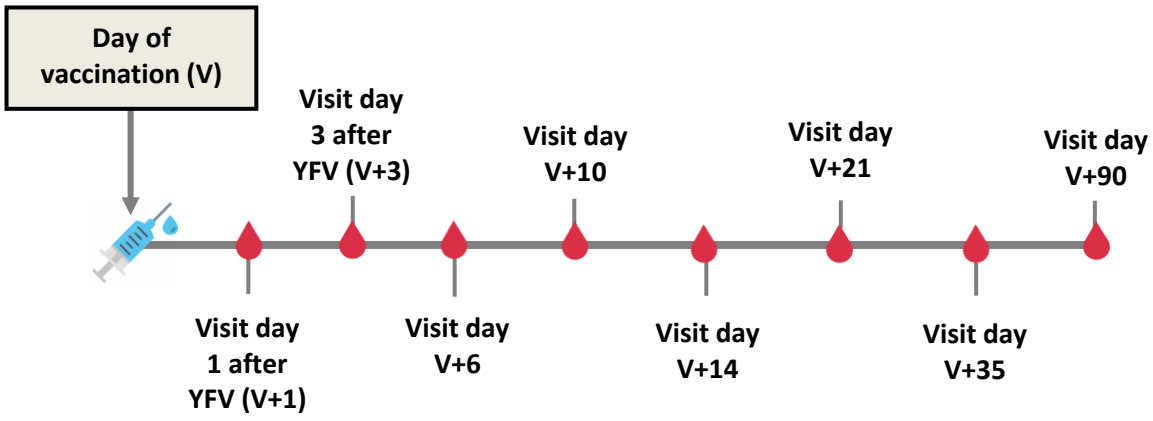


Yellow fever vaccination (YFV) visits

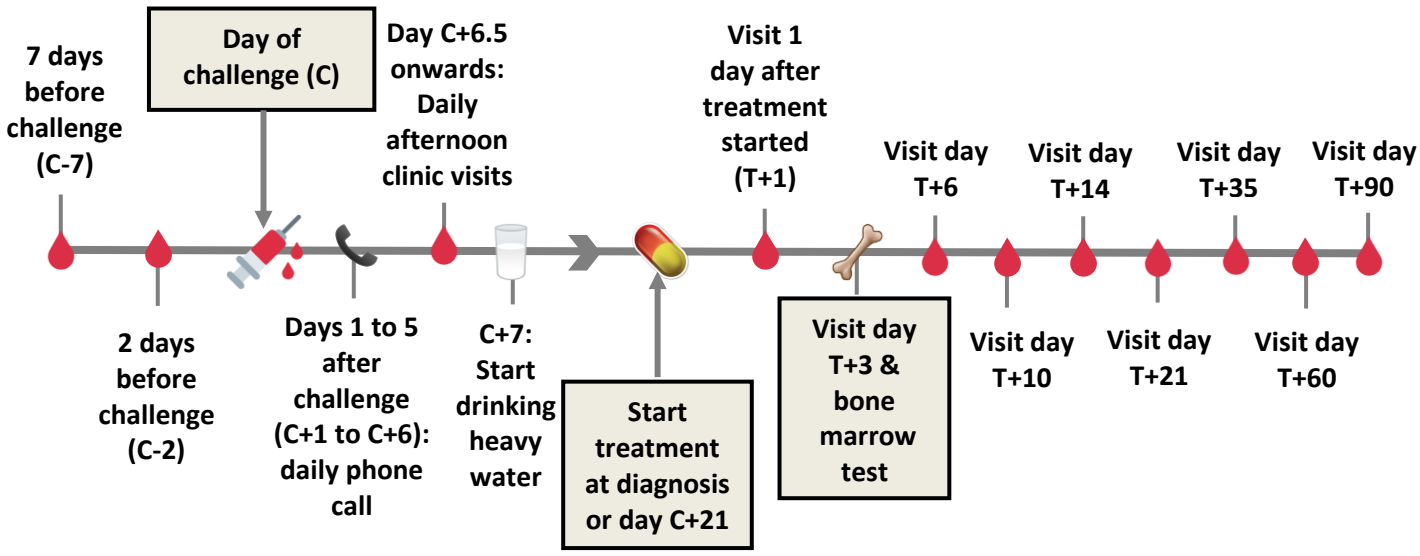


GROUP 2 STUDY SCHEDULE

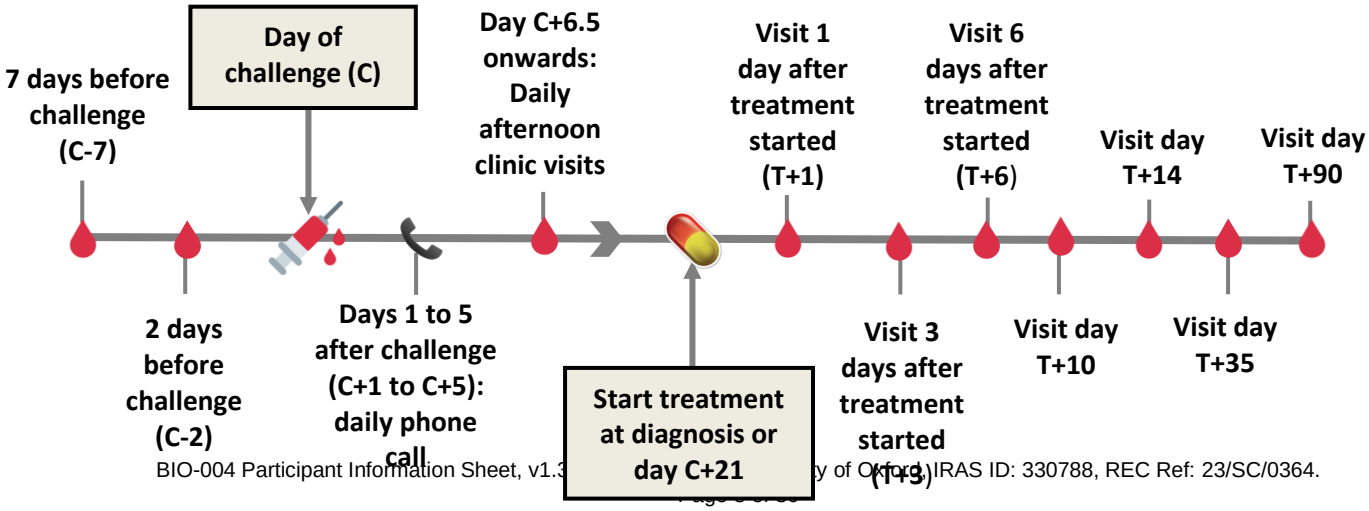
Yellow fever vaccination (YFV) visits



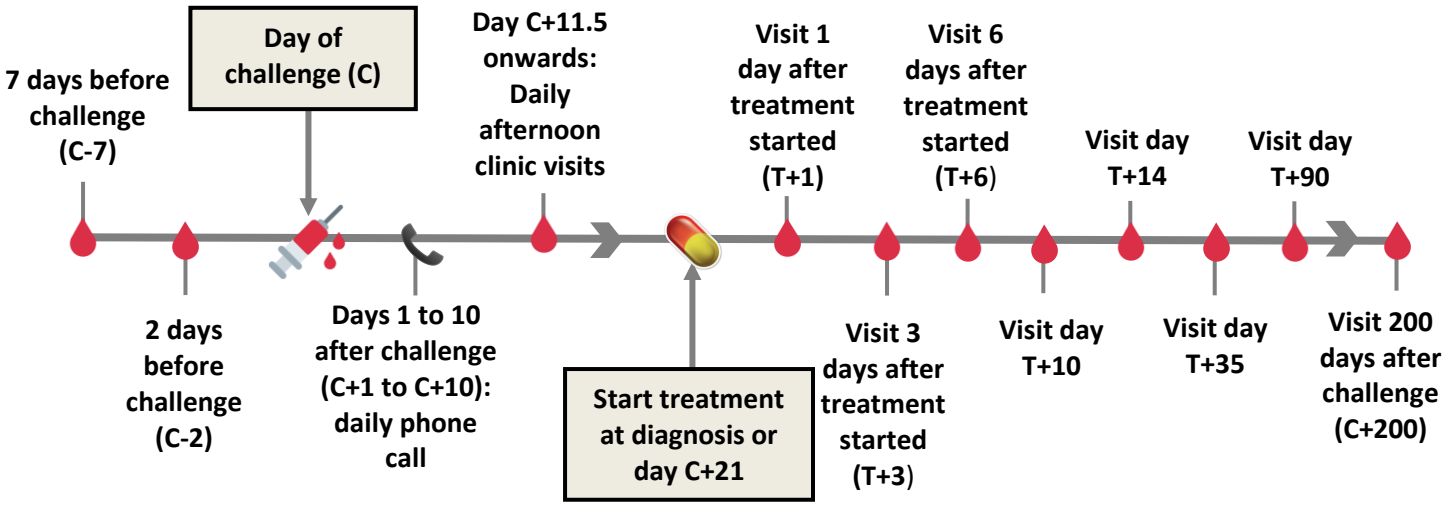
P. falciparum malaria challenge #1



P. falciparum malaria challenge #2



***P. vivax* malaria challenge #3**



What procedures are involved in the study?

Blood Tests

At most of the study visits, we will be taking at least one sample of blood from study participants. The amount of blood we will take at each appointment will vary; this may range from 2mL (less than a teaspoon of blood) to 83mL (just under 8 tablespoons of blood).

Given the frequency of blood tests, it is important that the study doctors and nurses are able to take blood from you without too much difficulty. If the study team have a lot of difficulty taking blood from you during the screening appointment, you may be deemed ineligible for the study.

Cannulation

In order to administer the malaria-infected blood to you during the malaria challenge, we will insert an intravenous cannula ('drip') into your arm on the morning of each challenge. This is a small plastic tube that allows us to inject the malaria infected blood into your vein. The intravenous cannula will usually be inserted into a vein on the inside of your elbow (the area called the antecubital fossa), however if the study team are unable to find a suitable vein in this area, we may insert it at another site such as in a vein on the back on your hand. The intravenous cannula will be removed at the end of the challenge visit before you leave the clinic.

Bone marrow test

As part of this study, we want to try and understand how malaria infection affects immune cells that live in the bone marrow. Bone marrow is the spongy material found on the inside of most bones and is where most of the cells in your blood are made. This includes white blood cells, which are an important part of your immune system. In order to examine these cells more closely, we would like to take a sample of your bone marrow through a procedure called a bone marrow aspiration and biopsy.

During this procedure, we will take a sample of bone marrow from your pelvic bone. This is the large bone between your hips. The bone is also relatively close to the skin, making it easier to get a sample of bone marrow. You will have the opportunity to discuss the procedure with the study doctor at the screening appointment. You will also have an opportunity to ask the person performing the procedure questions on the day of the procedure.

Before the procedure starts, you will be asked to lie on your side with your knees bent up and your clothing loosened to expose your back at the top of your pelvic bone. Your skin will be cleaned with an antiseptic solution to reduce the risk of infection. Local anaesthetic will then be injected into the skin over the back of the pelvic bone to numb the area where the sample will be taken. Once the area is numb, a needle will be passed through the skin into the bone and a sample of liquid marrow (up to 10ml) will be drawn up into the syringe. This is called a bone marrow aspirate. In addition to the liquid marrow, we would also like to take a sample of the more solid bone marrow tissue (1-2cm) to look at the structure of your bone marrow under a microscope. In order to do this, the person performing the procedure will insert a second needle into the same numbed area to take this sample. This is called a bone marrow biopsy. During the procedure, you may experience some discomfort and a "pressure-like" sensation where the needle is being inserted. This usually gets better after the procedure is finished. A video containing information about the bone marrow test can be viewed here: https://youtu.be/tI7m2y_secI .

After the procedure is complete, a small dressing will be placed over the site of the procedure. You should wait 24 hours before removing the dressing or bathing the area. You will be asked to rest in clinic for around half an hour and have refreshments after the test is finished. A member of the study team will check your dressing and explain how to look after the area where the bone marrow was taken. You will then be able to go home.

You will only be asked to undergo one bone marrow test during the study period. Group 1 participants will undergo the bone marrow test 3-7 days after commencing anti-malarial treatment after the **third** malaria challenge. Group 2 participants will undergo the bone marrow test 3-7 days after commencing anti-malarial treatment after the **first** malaria challenge.

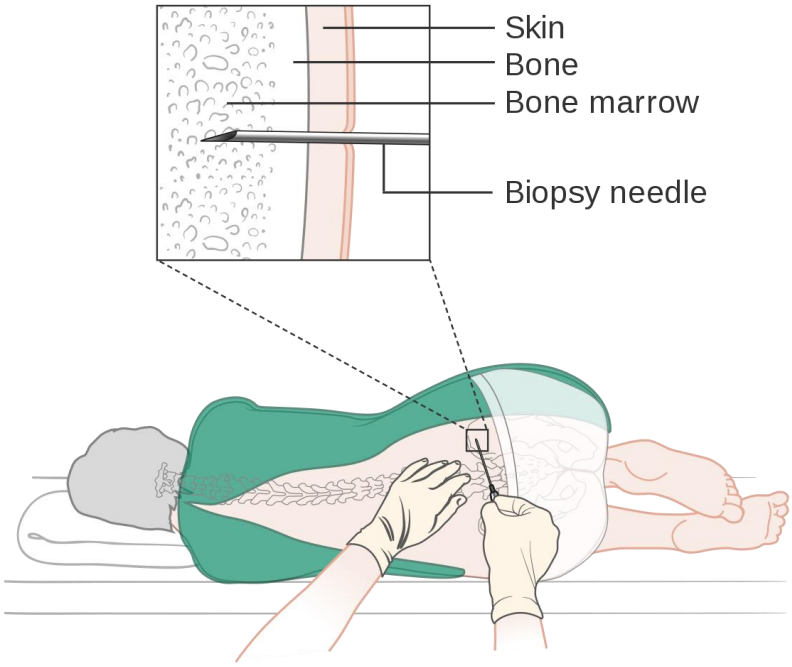


Figure 1: *Diagram showing bone marrow test procedure (Image source: Wikimedia Commons)*

You will be reminded about the procedure close to the time when we will provide you with some refresher information and give you plenty of time to ask questions. We will ask you to sign a separate consent form to agree to the procedure on the day.

PART 2: WHO CAN TAKE PART AND WHAT WILL HAPPEN?

Am I eligible to be involved in the study?

In order to be involved in the study you must be:

- A healthy adult aged 18 to 45 years
- Able and willing to meet all study requirements
- Willing to allow the Investigators to access volunteer's electronic medical records or discuss the volunteer's medical history with their GP
- **Willing to agree never to donate blood** (the reason for this is explained below)
- Able to be contacted by mobile phone 24 hours a day after you have been given the malaria infection until after you have completed the anti-malarial treatment
- Able to travel to CCVTM (Churchill Hospital)

You cannot take part in this study if:

- **You have had malaria before or previously participated in a malaria challenge study**
- **You have previously received a malaria vaccine (e.g. as part of a clinical trial)**
- **You have previously received a yellow fever vaccine or had yellow fever disease**
- **You have travelled to an area with malaria transmission in the last 6 months, or, you are intending to travel there during the study period**
- You are CMV-seronegative (i.e., you do not have antibodies to cytomegalovirus in your blood – more information on this below)
- You are Duffy antigen negative - **Group 2 only** (more information on this below)
- You have received any blood products in the last three months. This includes a blood transfusion or immunoglobulins
- You have had any other vaccine in the past 30 days or plan to have any other vaccine during the study period (except COVID-19 or flu vaccine)
- You are taking part in another study using an experimental treatment
- You have problems with your immune system. This includes taking any medication that supresses your immune system
- You have had a previous thymectomy (removal of the thymus gland) or known or suspected thymic disorder
- You have a history of allergies or reactions likely to be worsened by any part of the yellow fever vaccine (e.g. egg or chicken protein allergy), by malaria infection or by the medications used to treat malaria infection
- You have had an anaphylaxis after vaccination
- You have a confirmed or suspected bleeding disorder (e.g. haemophilia)
- You take blood thinning medications (e.g. heparin, warfarin, apixaban, edoxaban)
- You have an allergy to local anaesthetics (e.g. lidocaine)
- You have difficult intravenous access (i.e. it is not possible to take blood from you within three attempts)
- You are pregnant, breastfeeding or intend to become pregnant during the study
- You have a history of cancer (except for basal cell carcinoma of the skin and cervical carcinoma in situ - these are not exclusion criteria for the study)
- You have a history of a serious mental health condition that may affect your taking part in the study
- You have any other serious long-term illnesses requiring hospital follow-up
- You have sickle cell anaemia, thalassemia or any other blood condition that might affect susceptibility to malaria infection
- 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 recreational drugs at any time in the last 5 years
- You have Hepatitis B, Hepatitis C or HIV infection
- You weigh less than 50kg or have a BMI less than 18.0
- You have used antibiotics which could treat malaria in the 30 days prior to malaria challenge (e.g. doxycycline)
- You have taken anti-malaria medication in the 30 days prior to malaria challenge
- You have a high risk of heart disease in the next 10 years

- You have an abnormal heart rhythm
- You are taking certain medications which may affect the 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 unable to take either Riamet or Malarone for any reason
- You are unable to stay in Oxford from the day of challenge to up to 4 weeks following the malaria challenge
- There are any other reasons that the study doctors think you should not join the study

If enrolled in the study, you may be temporarily excluded from receiving the yellow fever vaccine or undergoing the malaria challenge if:

- You are feeling unwell on the day of your vaccination or challenge appointment.
- You have a fever (temperature >37.5°C).

In order to be eligible for the study, **you need to have previously had an infection with a virus called cytomegalovirus (CMV). If we can detect antibodies in your blood against CMV this means you have previously been infected**. CMV is a common virus which typically causes a mild illness with flu-like symptoms. Approximately 50–60% of adults in the UK have had CMV infection and carry antibodies against this virus in their blood. CMV antibodies can affect the way in which your immune system responds to infections such as malaria. It is important that everyone that participates in the study has these antibodies so that we can interpret any changes in the immune response to the repeated malaria challenges correctly. We will do a blood test to check whether you have CMV antibodies at your pre-screening appointment. If your blood test shows that you have CMV antibodies, we will then invite you to the full screening appointment. If you do not have CMV antibodies then you will not be eligible to continue in the study and you will be reimbursed for this single visit.

At the pre-screening visit, you will also be tested for a protein in your blood called the **Duffy antigen**. This protein is usually found on the surface of red blood cells and is important for allowing *P. vivax* malaria to enter these cells and cause infection. People who do not have this protein in their blood are naturally more resistant to *P. vivax* malaria. Because it is important that you develop malaria infection after the challenge, **you will not be able to join Group 2** if you do not have this protein in your blood. The doctor will discuss whether joining Group 1 is possible for you.

Mild conditions do not automatically stop you joining the study. An example could be childhood asthma which is well controlled. If you are unclear whether you are eligible, you can contact the study team who will be able to advise you.

What will happen at the study visits?

Pre-screening visit

Firstly, you will be asked to complete the online pre-screening questionnaire. If you only complete the online screening your data will be kept beyond the end of the study. We will contact you by telephone or email to invite you to a face-to-face pre-screening visit. At this appointment, we will ask you to sign a consent form to allow us to take around a teaspoon of blood (5mL) to check for antibodies against CMV and a smaller tube with less than a teaspoon of blood (2mL) to test for Duffy antigen. Your samples will be coded (pseudonymised) with a unique number. You will not be identifiable to laboratory researchers and these samples will be destroyed at the end of pre-screening. We will not ask you to consent to study participation at this appointment.

Screening Visit

After confirming that you have antibodies to CMV and your Duffy antigen status, we will then invite you to attend a screening visit to check whether you are eligible to join the study. The screening visit can take

place up to 3 months before the study starts. The screening visit can last up to two and a half hours, however, there will be an opportunity for a short break. The purpose of the screening visit is for you to discuss the study with us and decide if you still wish to take part. If you do, we will ask you to complete a questionnaire to assess your understanding of the study. We will also ask you to sign a consent form. You will have an opportunity to ask any more questions about the study at this point.

After signing the consent form:

- You will be asked some medical questions.
- A doctor will examine you.
- Blood samples and a urine sample (for individuals who are able to get pregnant) will be taken for testing. These test results will need to be normal for you to be enrolled in the study.
- An electrocardiogram (ECG) will be done. This checks the rhythm of the heart to make sure it is normal.

The blood tests will look at:

- Your blood count (for example, to check if you are anaemic).
- Your liver and kidney function.
- Whether you have Hepatitis B, Hepatitis C or HIV. This is because these viruses can affect your body's response to the malaria challenge.
- Your cholesterol levels. This is to check your risk of heart disease in the next 10 years. You cannot participate in the study if this is more than 1 in 20.

The urine test will look at:

- Pregnancy (if you are able to become pregnant)

If any of your tests are not normal, we will let you know and arrange for a repeat test. With your consent we may also report any abnormal results to your GP and offer to refer you for further investigation/treatment. If you test positive for Hepatitis B or C, the laboratory is required to notify the UK Health Security Agency of this result.

Some people may test positive for Hepatitis C virus because they have previously taken part in a Hepatitis C vaccine study. You may still be able to take part in our study if this applies to you. In this case, we will contact the team who ran the Hepatitis C vaccine study. We will only do this with your written consent (clause 27 of the informed consent form). A copy of this consent will be held by both ourselves and the team responsible for the Hepatitis C vaccine study, they will hold your form in the same way they described when you originally joined the study. We will check your Hepatitis C status with them before enrolling you in this malaria study.

Vaccination Visit

During the study you will be vaccinated with the yellow fever vaccine, Stamaril. We will then 'track' the immune cells made in response to this vaccine in blood tests we take after you have been vaccinated to see how they respond to malaria infection. Stamaril contains a weakened version of the yellow fever virus (17D-204 strain). It is manufactured by Sanofi Pasteur and is licenced for use in adults.

At the vaccination visit, we will check for any temporary exclusion criteria and perform a urinary pregnancy test if you are able to become pregnant. Following administration of the yellow fever vaccine, we will monitor you in clinic for 15 minutes to ensure that you do not have any reactions to the vaccine.

Follow-up visits

We will see you in clinic on days 1, 3, 6, 10, 14, 21, 35 and 90 after you have received the yellow fever vaccine. If you are Group 1, we will also see you in clinic 180 days after you receive the yellow fever vaccine. Visits include a medical assessment and examination by a doctor if needed. We will also take temperature, pulse and blood pressure readings as well as blood tests.

Longer-term follow-up visits

Group 1 will have two optional longer-term post-vaccination follow up visits at the end of the study. These will take place at 270 days and 630 days after the yellow fever vaccination (V+270 and V+630), which corresponds to 23 and 35 months after enrolment into the study. These are important study visits in which we hope to understand the long-term changes to the immune system after repeated malaria infection. You will be asked about any changes to your health at these visits. A blood sample will also be taken at each visit.

These visits are listed as optional to account for participants who may have moved out of Oxford towards the end of the study period. **If you can attend these visits, we would be grateful for your attendance** as these visits are of great scientific value to the study. If you cannot attend these visits, an end of study visit will be conducted by telephone.

The Malaria Challenge

What happens during the challenge?

Before each malaria challenge, all participants will need to attend CCVTM seven days and two days before challenge (C-7 and C-2). During the C-7 visit, baseline blood samples will be taken. During the C-2 visit, we will check if there are any changes to your health. We will take blood tests and, if you are able to get pregnant, do a pregnancy test. We will confirm with you that all of your tests are normal before the day of the challenge. If any abnormalities are found, we may ask you to attend an extra visit the day before the challenge (C-1) to ensure that you remain eligible for the challenge.

On the day of challenge, an intravenous cannula ('drip') will be inserted into a vein in your arm. A small amount of a salt solution containing red blood cells that are infected with malaria parasites will be injected into the vein. This will be about 5 ml or 1 teaspoonful. 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. The timing of the follow up visits will depend on whether you have been infected with *P. falciparum* or *P. vivax.*

After the *P. falciparum* challenge: We will assess you by phone once a day for the first five days (C+1 until C+5). From the afternoon of day 6 (C+6.5) onwards we will see you at the clinic once a day in the afternoon. At each appointment, we will take a small sample of blood (2mL) to check your malaria parasite count. This will continue until 21 days after challenge or until you are diagnosed with malaria (whichever happens sooner). On the afternoon of day 7 after the challenge (C+7.5), we will take a slightly larger sample of blood to examine your immune response to the malaria infection. After one of the *P. falciparum* challenges (either first or third, depending on group allocation), you will also be invited to clinic on the morning of day 7 after challenge (C+7) to collect your bottles of heavy water and drink one dose under observation. You should assume you need to attend clinic at least once a day from day 6 to day 21 unless we inform you otherwise. All these clinic visits will take place at the CCVTM.

After the *P. vivax* challenge: We will assess you by phone once a day for the first ten days (C+1 until C+10). From the afternoon of day 11 (C+11.5) onwards we will see you at the clinic once a day in the afternoon. At each appointment, we will take a small sample of blood (2mL) to check your malaria parasite count. This will continue until 21 days after challenge or until you are diagnosed with malaria (whichever happens sooner). On the afternoon of day 12 after the challenge (C+12.5), we will take a slightly larger sample of blood to examine your immune response to the malaria infection. You should assume you need to attend clinic once a day from day 11 to day 21 unless we inform you otherwise. All these clinic visits will take place at the CCVTM.

Each time we see you in clinic, we will assess your symptoms and a doctor may examine you. These visits will last approximately 15–30 minutes. However, you may have to wait to be seen. The total number of visits post challenge will vary depending on if and when 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. You should bring this with you to each visit. **If you plan to travel outside of Oxford at any time from two days before challenge to 4 weeks after the challenge, you should discuss your plans with a study doctor before participating in this study.**

The malaria test result will be available after you have left clinic. If your blood test shows that you have malaria, we will contact you by telephone and let you know we will start anti-malarial medication at your next visit. It is therefore **essential that we are able to contact you at all times on your telephone. You must be available to return to the CCVTM to start treatment at short notice between day 1 – 21 post *P. falciparum* challenge and between day 1 – 21 post *P. vivax* challenge** (for participants in Group 2). **It is essential that you reside in Oxford during this time** for careful monitoring and regular review by the study team. If finding accommodation in Oxford is difficult for you, you can discuss your options with the study team. You **must** also provide a name and 24-hour phone number for someone 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. If you cannot be located we will take additional steps to ensure your safety which may involve contacting the police and media.

Once the study team confirms the diagnosis of malaria, you will be started on a course of anti-malarial treatment. This visit will last longer than the other visits. It may be up to half an hour. You will be treated with a medication called **Riamet**. For this study, it is important that participants are able to take Riamet, as this medication has an effect on the immune system that is important for the laboratory tests we will be doing. If you are aware of any reason that you cannot take Riamet (e.g. you have a known allergy to this medication), you will not be eligible for the study. If something changes during the study and you cannot take Riamet (e.g. after taking Riamet for the first time, you discover that you are allergic to it) there is another anti-malarial medication you can take called Malarone. More information on these medications are found in the next section under 'Malaria treatment'. You may not feel better as soon as you start treatment.

We may not treat you in the first few days after the challenge even if you feel unwell. This is because we look at the number of malaria parasites in your blood and use this to decide whether you have reached the threshold for a diagnosis of malaria. If you are feeling ill for one or two days, we may decide to start treatment anyway, even if the number of malaria parasites in your blood has not reached the threshold. Some people feel more unwell in the first 24 hours after starting treatment. This is your body reacting to large numbers of parasites being killed by the drug inside you. However, most people then start to feel better. You will need a blood test on days 1 and 3 after starting treatment so we can check all the parasites are killed.

If you become more unwell you may be admitted to the John Warin ward to be on the safe side. This is

the Infectious Diseases Unit at the John Radcliffe Hospital in Oxford. However, it is very unlikely that this will be necessary.

If we do not find malaria parasites in your blood by day 21 post challenge we will give you a course of anti-malarial treatment anyway. This is so that any parasites that we have not detected are killed.

Drinking heavy water

During the study, you will be asked to drink a substance called heavy water starting 7 days after one of the malaria challenges and finishing 14 days after starting anti-malarial treatment. Depending on which group you are in, you will either be asked to drink heavy water following the first or third malaria challenge. Participants in Group 2 will be asked to start drinking heavy water 7 days after the **first** challenge and participants in Group 1 will begin consumption of heavy water 7 days after the **third** challenge.

Heavy water (D_2O) is very similar to normal water (H_2O). It is clear, colourless and has no taste. In contrast to normal water, which is made up of two hydrogen (H) atoms and one oxygen atom (O), heavy water contains two atoms of deuterium (D) and one oxygen atom (O). Deuterium is an "isotope" of hydrogen, meaning it has the same atomic structure but with an additional molecule making it 'heavier'. We are using heavy water in this study because it can 'label' dividing cells in the body, including cells in the immune system. This will allow us to 'track' immune cells in your blood samples to see how they respond after the malaria challenge.

On the day that you are due to start drinking heavy water (C+7), we will invite you to CCVTM for a morning visit. At this visit, you will be given the first dose of 55mL of heavy water to consume under supervision of the study team. This is because drinking large amounts (>100mL) of heavy water can sometimes make people feel dizzy or nauseous, so we want to check that you have no side effects from drinking it. We will monitor you for 15 minutes after you have finished the vial of heavy water and then check your temperature, pulse and blood pressure before you go home.

At this appointment, we will also give you all of the pre-measured doses of heavy water that you will need to drink during the study to take home with you. It is important to note that the amount of heavy water that you will be drinking during the first three days of the heavy water regimen is different to the amount you will be drinking after this. On the first three days (C+7, C+8, C+9), you will be asked to drink 55mL of heavy water four times a day. Thereafter, you will be asked to drink 40mL of heavy water twice a day up to and including T+14 (see table below). We will provide you with a diary card with the details of the heavy water regimen to help you remember how much you need to drink on each day. As everything is pre-prepared for you there is no need for you to measure anything out.

Study timepoint	***Time of day (+/- 1 hour)***			
	9am	**1pm**	**5pm**	**9pm**
C+7 to C+9 (loading phase)	55mL	55mL	55mL	55mL
C+10 to T+14 (continuation phase)	40mL			40mL

It is very important that you do not forget to drink your heavy water doses. To help you remember, we will provide you with a leaflet and daily reminders in the form of a text message or telephone call. On days that you are scheduled to attend a clinic visit, the study team may also confirm with you that you

have consumed your doses of heavy water as planned.

Follow-up after treatment

After each malaria challenge, we will see you in clinic on days 1, 3, 6, 10, 14, 35 and 90 after starting anti-malarial treatment. There are additional follow up visits at day 21 and day 60 after treatment; Group 1 participants will be scheduled to attend these additional visits after their third malaria challenge and Group 2 participants will be scheduled to attend these visits after their first malaria challenge. We will take a blood sample at each clinic visit. This will check your general health and look at any ongoing immune response to the malaria challenge. The amount of blood taken will range from around 2–4 tablespoons (25–64mL). Each of these appointments will last about 10 minutes.

Longer-term follow-up visits

Group 2 participants will attend a longer-term follow up visit after the third malaria challenge. This will take place 200 days after the day of the third challenge (C+200). You will be asked about any changes to your health at this visit. A blood sample will be taken to look at any ongoing changes in the immune system. We will take approximately 5 tablespoons of blood at this visit (75mL).

Is there anything else to think about?

Blood Donation

If you are a blood donor, we ask that you do not donate blood during the study period due to the additional blood volume that will be taken during the study. Additionally, under current UK regulations, **you would not be permitted to ever donate blood** after taking part in this study. This is because the malaria challenge involves the injection of red blood cells from another person. Although this is a tiny amount of blood it is still classed as a small blood transfusion.

Medications

You should not take any drugs other than those assessed as safe during a malaria challenge by the study doctor at screening. This also applies for drugs bought over the counter. Of course, your health and well-being is much more important than the study. If you need any medication, then you should take it. However, it is very important that you let us know **before** you start any treatment. For example, any antibiotics that you take within 4 weeks of a planned malaria challenge may kill or weaken the parasites. You can ask the prescribing doctor to discuss with a study doctor before you start treatment. The study doctor may be able to advise an appropriate antibiotic that will treat you but won't interfere with the study.

Pregnancy and Contraception

Malaria infection is more dangerous during pregnancy. If you are able to become pregnant, you will be asked to use an effective method of contraception. This will be required from when you start the study until the end of the study. For both groups this is a total of 20 months. Condoms alone are not considered effective enough.

Acceptable forms of contraception include:

- Hormonal contraceptives. This includes the pill, mini-pill, contraceptive injection or implant or transdermal patch.
- Placement of an intrauterine device or intrauterine system. These are also known as the copper coil or hormone coil (e.g. Mirena coil).
- Vasectomy (male sterilisation) if this is your only partner.
- Complete abstinence from any sexual relationship in which you may become pregnant. Periodic abstinence and withdrawal methods are not acceptable.

It is important to note that **Riamet may temporarily reduce the effectiveness of hormonal contraceptives**. If you take hormonal contraceptives, you will need to use an additional form of contraception (such as condoms) while taking Riamet. This applies until the start of your next period.

A urine pregnancy test will be done at screening and just before vaccination. Blood and urine pregnancy tests will also be performed before malaria challenge and before anti-malarial treatment is started.

If you become pregnant during the study, you would not undergo any further malaria challenges. However, we would like to follow you up for the rest of the study and, with your permission, until the pregnancy outcome. We would not routinely perform any further blood tests on pregnant participants.

Private Insurance

If you have private medical insurance you should contact your insurance company before taking part in this study. Involvement may affect the cover provided.

Malaria Protection

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 *Plasmodium falciparum*, P*lasmodium 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.

Expenses and Payments

You will be compensated for:

- Pre-screening visit	£45
- Travel expenses	£30 per visit
- Inconvenience of blood tests:	£20 per blood donation
- Time required for visit:	£40 per hour
- Bone Marrow Visit:	£150 per visit
- Compensation for time off work:	£150 per outpatient days*

*(max. 3 days per challenge)

If you choose to leave the study early, or are withdrawn, you will be compensated according to the length of your participation. This will be calculated based on these figures. The reimbursement provided are considered to be reasonable amounts to cover the costs of participating in this research. There should not be any consequences for tax or benefit purposes.

Group No.	Time in Study (approx.)	Average No. of Clinic Visits expected (minimum – maximum visits)	Maximum Volume of Blood Taken (ml)	Compensation Amount
1	20 months (35 months incl. optional visits)	74 (53 – 95)	2025	£9,955 (incl. optional visits)
2	20 months	70 (51 - 88)	1851	£9,325

We will recruit 1–2 'back-up participants' in addition to the 22 planned participants in this group. These participants will be asked to be available to take part in the study at short notice. This is in case another participant is unavailable at the last minute. 'Back-up participants' who are not enrolled in the study will be compensated £200 in addition to compensation for visits they have attended.

What do I have to do?

- You **must** provide a name and 24 hour phone number for someone who will know where you are for the duration of the study. If you fail to attend for review during the 21 days after the *P. falciparum* or *P. vivax* challenge and are un-contactable by phone, 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 outlined in Part 1 of this information sheet (apart from the prespecified optional visits)
- If you are able to become pregnant, you **must** use effective contraception until the end of the study period.
- You **must never** donate blood in the UK following enrolment in the study.

What alternatives are present?

Your alternative is not to take part in this study.

PART 3: RISKS AND BENEFITS

What are the risks of taking part?

The potential risks are as follows:

Blood Tests

The total volume of blood taken during the study depends on the group. The maximum blood volume that we expect to draw from participants in Group 1 is 2025mL and the maximum blood volume that we expect to draw from participants Group 2 is 1851mL. The amount taken at each visit will vary between around 2mL (less than a teaspoon) to a maximum of 83 mL (just under 6 tablespoons). The volume of blood being taken over the course of the study should not cause any problems in healthy people. There may be some temporary mild discomfort. This may include bruising and tenderness at the site where the blood is taken or at the site where the intravenous cannula (drip) is inserted into your arm on the day of malaria challenge. You may feel faint as a result of collecting blood, or during insertion of the drip.

We will only send the results of your blood tests to your GP if you wish us to and will not report them to anyone without your permission.

As we carry out several medical tests throughout the trial, it is possible that we pick up previously unknown health issues (e.g. high blood pressure, abnormal blood results). If abnormal results or undiagnosed conditions are found during the study, these would be discussed with you and, if you agreed, your GP would also be informed of these results. Sometimes incidental medical findings might require your GP to carry out further investigations such as blood tests, scans or referral to specialists.

In the UK, healthcare professionals are legally obliged to report any new suspected cases of hepatitis B and hepatitis C to the UK Health Security Agency (UKHSA). If you are found to have hepatitis B or C, we will be required to send a report to the UKHSA, including your personal contact information. It's important to note that you cannot opt out of this due to UK reporting requirements.

At different time points throughout the study, we will take blood samples for the following tests:

- Your full blood count, liver and kidney function, serum cholesterol
- Blood borne infections (HIV, Hepatitis B & C, EBV, CMV)
- Test for Duffy antigen
- Thalassaemia, sickle cell anaemia and other conditions that affect the blood
- Genetic analysis of your cells (to look at genes that are expressed in response to malaria infection) and the parasites
- Malaria parasite counts
- Immune response to malaria infection

Yellow Fever Vaccination

Reactions to the yellow fever vaccine are generally mild and short-lived, and may include headache, muscle pains, low-grade fever, swelling and redness around the vaccination site. Allergic reactions to yellow fever vaccine are rare, occurring in less than 2 out of every 100,000 doses of the vaccine administered. Symptoms of an allergic reaction to the yellow fever vaccine may include rash, tongue or facial swelling or difficulty breathing. Emergency medication can be used to treat allergies and resuscitation equipment will be immediately available for the management of anaphylaxis. A clinician trained in Advanced Life Support will always be present at the time of vaccination and for the duration of your appointment.

While the yellow fever vaccine is generally safe, there are two rare, yet serious complications that you need to be aware of: neurotropic disease (YEL-AND) and viscerotropic disease (YEL-AVD).

Symptoms of YEL-AND include fever and headache which begin between 2–56 days following receipt of the vaccine, and may progress to include confusion, tiredness, inflammation of the brain (encephalitis), and inflammation of the lining of the brain (meningitis). In rare circumstances, YEL-AND may progress to two serious neurological conditions: acute disseminated encephalomyelitis (ADEM) or Guillain-Barre Syndrome (GBS). However, the majority of people diagnosed with YEL-AND do not have any complications and make a full recovery.

YEL-AVD occurs at a lower rate than YEL-AND. It has a similar presentation to yellow fever disease and tends to involve many systems in the body including the liver, kidneys and blood, leading to failure of body organs. Symptoms may include fever, feeling generally unwell, headache, and muscle pains which typically begin around 2–8 days after vaccination. Since 2001, over 100 confirmed and suspected cases of YEL-AVD have been reported worldwide. Until recently, there were only three cases ever reported in the United Kingdom, one in 1998 and 2 in 2000; all these cases survived. Since then, a further 2 cases have occurred in the UK; one in 2018 and one in 2019. Unfortunately, both these cases died. YEL-AVD has a mortality rate of over 60%.

These complications are both very rare. Approximately 8 cases of YEL-AND occur in every one million yellow fever vaccine doses administered, and 3 cases of YEL-AVD per one million yellow fever doses administered. These complications are also significantly more likely to occur in individuals with certain risk factors, such as people with a weakened immune system, people without a thymus (a gland in your chest that helps protect against infections), and people aged 60 years or above. For this reason, we have included these risk factors in our list of exclusion criteria for this study. There is still, however, a very small risk that these complications could occur.

Blood Transfusion Reaction

The malaria challenge 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. The donor of the blood we will be using is blood group O negative. This means the donor's blood can be given to people with any blood group without causing an allergic reaction. However, although this is extremely unlikely to occur, we will monitor you closely for any signs of this developing. This is why we ask you to stay in the clinical facility for 1 hour after you have received the malaria challenge.

Transmission of Blood-borne Infection

The blood transfused in this study has a smaller risk of causing infection than normal blood transfusions. There are 3 reasons for this.

1. The volunteers who donated the malaria-infected blood were screened for a wide range of blood-borne diseases. This occurred both before and after the blood was collected. For the falciparum malaria donation, the blood was kept frozen for over a year while the donor was observed and retested for any evidence of infection. During this time the donor remained healthy. Repeat screenings did not reveal any infections that may have not been detected by initial tests. The malaria-infected blood was collected over 20 years ago and the donor has remained healthy since. For the vivax malaria donation, the testing performed on the blood bank was more extensive than that used by the National Blood Transfusion service. The donor has remained healthy (now over 5 years since the donation).

2. The volume of blood injected during the falciparum challenge (0.1mL) is thousands of times smaller than the volume in a transfused unit of blood (470mL). The volume of blood injected during the vivax challenge (0.5 mL) is nine hundred times smaller.
3. The blood cells have been washed and the white blood cells removed. Both of these processes lower the risk of infection due to transfusion.

The donor who provided the falciparum malaria-infected blood was known to have had infections with Epstein-Barr virus (EBV) and cytomegalovirus (CMV) in the past. Like CMV, EBV is a virus which most people are exposed to over their lifetime. It is the most common cause of 'glandular fever'. Both viruses remain within white blood cells after the initial infection.

While we will only be enrolling participants who have had CMV infection in the past, we allow participants who have not had EBV infection in the past to join the study (i.e. not having antibodies again EBV is not within the exclusion criteria). In light of this, there will be a theoretical risk of transmitting EBV from the donor to someone receiving the transfused blood who has not had EBV infection before. This risk is extremely small, however, as the white blood cells have been removed from the blood. The blood has also been tested for the presence of these viruses. These tests were negative. Furthermore, over 30 volunteers who had not had these viruses before have received the inoculum. None of them have acquired these infections.

To be on the safe side, we will test for any evidence of HIV, Hepatitis B, Hepatitis C and EBV infection after each malaria challenge to prove that transmission has not taken place.

Controlled Human Malaria Infection

Worldwide, over 2900 people have been infected with malaria as part of a challenge study. All have made a complete recovery with no long-term problems reported. In Oxford, nearly 600 people have been infected with malaria. The risks of taking part in this study are low provided that you return for all follow-up visits. **If untreated, the malaria infection that we propose to give you could result in death.**

The early symptoms of malaria include a flu-like illness, fever, chills, headache, muscle aches, diarrhoea and vomiting. In previous studies most participants did experience some of these symptoms. If you develop any severe symptoms or are otherwise concerned about your symptoms then you **should let one of the study doctors know immediately.** Study doctors can be contacted 24 hours a day. About 1 in 5 participants temporarily develop symptoms graded as severe. These are symptoms that prevent daily activities. It is possible that you might need to take one or two days off work. We will prescribe paracetamol and anti-sickness tablets. You can take these as needed (more information on this on the next page). Symptoms can start or persist after treatment has started. They usually last no more than 1 to 3 days.

If malaria is not treated appropriately, complications may occur. These include jaundice, kidney failure, fluid on the lung, low blood sugar and collapse. Seizures, drowsiness, coma and even death may occur. For this reason **it is extremely important that you attend all the scheduled follow-up visits.**

Abnormal blood tests are common after malaria infection. These may include low numbers of white cells and platelets. No bleeding or clotting problems have ever been reported after a malaria challenge. Abnormal liver tests are also common. These have only ever caused symptoms in one volunteer who had stomach pain and vomiting. These abnormal results have all got better on their own after a few weeks.

To minimise the chance of abnormal results:

- Your blood results will be closely monitored during and after the malaria challenge
- You should not drink any alcohol from the day of challenge until 1 week after treatment
- You should not take more than 3 grams (6 tablets) of paracetamol per day

If needed, you could be admitted to the Infectious Diseases Unit as described above. In the last 10 years, only 4 participants out of nearly 600 challenged with malaria in Oxford have needed this. There have been no long-term problems in any of the participants.

Over the past 20 years, there have been five unexpected serious adverse events in participants in malaria challenge studies in the Netherlands. A serious adverse event is any event that occurs resulting in serious injury, illness or death that may or may not be related to the study.

- There was one case of a possible heart attack during malaria treatment in 2002. This was in an individual with pre-existing narrowing of the blood vessels around the heart.
- There have been three cases of probable inflammation around the heart between 2007 and 2014.
- There was one case of chest pain in 2020 one day after completion of malaria treatment. No underlying cause was found.

All five people fully recovered without any long-lasting effects. It is unclear whether these events were related to the malaria vaccine the participants received, the malaria infection, malaria treatment or some other cause. These challenges in the Netherlands all used a strain of malaria called NF54. As a result of these events, the team in the Netherlands has stopped using NF54. In Oxford, for falciparum malaria challenges, we use a different strain called 3D7. There have never been any heart problems reported in challenges using the 3D7 strain of malaria. There have also never been any heart problems or serious adverse events following administration of our vivax malaria challenge agent. We will also exclude people at high risk of heart disease from this study. These individuals will be identified by medical history and family history. We will also check the cholesterol levels in your blood and perform an ECG at the screening visit.

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. They 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 received treatment for malaria and made a full recovery. The reason for the participant's disappearance was unrelated to the study. **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. Your name may be released to the national media in order to find you.**

For 6 months after the challenge, if you develop any of the symptoms of malaria as detailed above please contact one of the study doctors or your GP. You should remind them that you have been involved in this study.

Treatment of Malaria

The drug you will be treated with is called **Riamet**. It is a licensed drug in the UK for treatment of acute uncomplicated malaria caused by *P. falciparum* or *P. vivax*.

Riamet is a combination drug consisting of two medications called artemether and lumefantrine. The treatment regime will consist of 6 doses of total 80mg artemether/480mg lumefantrine (4 tablets) to clear the infection. The first dose, which will be directly observed in clinic at treatment initiation, will be followed by additional doses after 8, 24, 36, 48 and 60 hours (window period +/- 1 hour for each dose). The 24 hour

dose will also be directly observed; we will ask you to record the time that all other doses are taken at home in a post-challenge diary card.

Severe allergic reactions to Riamet could potentially occur. The exact frequency of this is unknown. Signs of severe allergic reactions include rash and itching, sudden wheezing, tightness of the chest or throat, or difficulty breathing. Swelling of eyelids, face, lips, tongue or other parts of the body can also occur. If you experience any of these symptoms you should contact the study doctor immediately. You should call 999 and ask for an ambulance if you are having difficulty breathing.

If for any reason you cannot take Riamet there are other anti-malarial drugs that can be used effectively instead. If the study doctor thinks this is the case, they will discuss with you another medication (Malarone). **Malarone** is a combination drug containing two medications called atovaquone and proguanil. If you need to take this medication, the study doctor can give you an information sheet about this medication to take away.

Treatment of Symptoms Associated with the Malaria Challenge

Unless there are reasons you cannot take them you will be given some additional medications to help with symptoms associated with malaria. These are licensed, commonly used, medications. You can ask to see the sheets from the manufacturers 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 study doctor immediately.

Cyclizine: This can be taken if 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, or blurred vision. Other side effects can include palpitations, difficulty passing urine, constipation, anxiety, or difficulty sleeping. Drowsiness may affect your performance of skilled tasks such as driving. Participants may be dispensed an alternative anti-sickness tablet to cyclizine if they are unable to take it.

Paracetamol: This can be taken as and when needed to reduce feverishness and pain. Paracetamol is generally well tolerated. However, you should not take more than 3 grams (6 tablets) of paracetamol per day. This is in order to minimise the chance of developing abnormal liver results.

Bone Marrow Test

The bone marrow test is a safe procedure, however, there are a few important risks that you should be aware of.

Local anaesthetic (such as lidocaine) is very safe and serious side effects are very rare. You may experience “stinging” from the local anaesthetic when it is being injected. You may also have some bruising where the local anaesthetic was injected, but this usually gets better within a few days. Occasionally, people can experience an allergic reaction to local anaesthetic. **If you have a known allergy to local anaesthetic, you will not be able to take part in the study.** Very rarely, local anaesthetic can cause damage to the tissue it is injected into (known as “necrosis”). Very rarely, people can experience symptoms such as dizziness, headaches, blurred vision and muscle twitching. These are very rare side effects of local anaesthetic and not likely to occur during this procedure. Only a small amount will be injected using a small needle, therefore minimising the risk of injury, and the person performing the procedure will be experienced in injecting this medication.

Sometimes people find the bone marrow test procedure very uncomfortable, despite the injection of local anaesthetic. If this is the case for you, we can provide you with a pain-relieving gas called **Entonox** (a mixture

of nitrous oxide and oxygen, more commonly known as 'gas and air') during the procedure to make it more comfortable. Entonox is delivered through a handheld mouthpiece which allows you to control how much of the gas you breathe in. It has a few side effects including drowsiness, dizziness and nausea, and can also give you a dry mouth. The effects of Entonox wear off very quickly, so, you will be able to drive home if you attended the visit by car. Entonox will only be administered by a trained individual.

Some discomfort during the bone marrow test is common, however, if you are experiencing a lot of discomfort during the procedure, please let the person performing the procedure know. **You can ask for the procedure to be stopped at any time.**

Mild pain/discomfort following the procedure is also common but typically does not last very long (usually less than 24 hours). In particular, you may feel an achiness in your back after the local anaesthetic wears off. This is usually relieved with paracetamol.

A small amount of bleeding can occur after the procedure, however, this usually stops after applying firm pressure over the dressing. In extremely rare circumstances, bleeding can continue from the site of the procedure and the blood can get trapped in the muscle around your bone causing pressure. This is called compartment syndrome and is a very rare complication of the bone marrow test. In order to reduce the risk of this complication, you will have a blood test on day 1 and day 3 after starting anti-malarial treatment to check that your platelet counts in your blood are within the acceptable range for the procedure. Platelets are important cells that help your blood clot. If your platelet count is too low, we will postpone the bone marrow test for 1-2 days and re-check your platelet count to ensure that it is within an acceptable range before performing the procedure. It is important to note that this procedure is commonly carried out in people with low platelets without complication. One study found that out of more than 13,500 bone marrow tests performed in the UK in one year, there were only 9 episodes of bleeding, so this risk is very low.

There is also a small risk of infection at the site of the bone marrow test, however, extreme care will be taken to keep the procedure sterile in order to minimise this risk, including the use of antiseptic to clean the skin and the use of sterile equipment.

In very rare circumstances, the needle used can pierce a blood vessel or an organ in your abdomen. This is an extremely rare complication of this procedure, however, the person performing the procedure will be able to recognise the signs and manage this complication if it occurs.

To minimise the risk of any complications from the bone marrow test, the procedure will only be performed by a fully trained individual. If there are any clear reasons why we should not perform to bone marrow sampling on the day, then the procedure will be delayed until these have resolved and the procedure can be safely performed. Following the procedure, every participant will have 24 hour telephone access to an on-call study doctor who can advise if there are any concerns relating to the procedure.

Heavy Water

Heavy water is a stable isotopic form of water, meaning it is <u>not</u> radioactive. Drinking small amounts of heavy water for a short period of time is considered low risk and is not associated with any short-term or long-term harmful effects. The product used in this study will be procured from a reputable supplier who will perform rigorous testing to check that it is safe for drinking. Each dose will be prepared in accordance with locally approved procedures.

Drinking more than 100mL of heavy water in one go has been reported to cause dizziness, nausea and vomiting in a very small number of people. As such, we have divided the daily amount of heavy water that we would like you to drink into smaller volumes (40–55mL each). We will never ask you to drink more than 55mL of heavy water in one go. We will also monitor you in clinic the first time that you drink heavy water to ensure that you do not experience any of these side effects.

What are the possible benefits of taking part?

This study will not directly benefit you. The information gained from the study might help us to better understand how to prevent severe disease and death among thousands of infants who live in areas where malaria is common.

PART 4: OTHER INFORMATION ABOUT THE STUDY

What if relevant new information becomes available?

Sometimes during the course of a research project, new information becomes available. If this happens, we will tell you about it. We will discuss whether you want to or should continue in the study. If you decide to continue in the study 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 without your consent for other reasons.

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

You are free to withdraw from the study at any time without giving a reason. This will not result in any penalty, or loss of benefits to which you are otherwise entitled. Your data collected and samples taken will continue to be used unless you state otherwise. You may request that your samples and data are destroyed at any time during or after the study until analysis begins. **If you wish to leave the study after malaria challenge then you must take the anti-malarial treatment prescribed because of the potentially very serious consequences of untreated malaria infection.**

Your compensation would be paid as a proportion of the total compensation according to the length of your participation.

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. If necessary, they will refer you to a doctor within the NHS for treatment. 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 study.

The Investigators recognise the important contribution that study participants make to medical research. They 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.

Complaints procedure

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 study team (contact details at the end of this document). You may also contact the University of Oxford Research Governance, Ethics and Assurance (RGEA) office on 01865 616480 or the director of RGEA, email RGEA.Complaints@admin.ox.ac.uk. The RGEA office can also be contacted if you have questions about your rights as a study participant.

Will my taking part in this study be kept confidential?

All information that is collected about you during the course of this study will be coded with a unique study identification number and kept confidential. Personal details will be stored securely and separately from the research data. Responsible members of the University and the regulatory authorities may be given access to data for monitoring and/or audit of the study. This is 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 directly identified from it. Your information will be stored electronically on a secure server and any paper notes stored securely in a secure location at the study site.

Involvement of the GP (General Practitioner/Family doctor)

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

Prevention of 'Over Volunteering'

Volunteers taking part in this study must not be 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 studies. If you are a non-UK citizen, you will need to provide your Passport number to be entered onto this database. 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 research samples I give?

All study samples will be stored in a pseudonymised form. This means that your study number rather than your personal details will be on them. Your blood and bone marrow samples will primarily be analysed in research laboratories at the University of Oxford and the University of Edinburgh. They may also be analysed at other collaborating research institutions in the UK and other countries. Your blood and bone marrow samples will be handled in accordance with the relevant national and regional guidance (e.g. Scotland and England) and the principles of the Human Tissue Act. Blood tests for your general health will be carried out in the NHS laboratories at Oxford University Hospitals. Any samples or data sent to NHS or collaborating laboratories will be pseudonymised.

With your consent, some of your leftover blood and bone marrow samples may be stored indefinitely at the University of Oxford and/or the University of Edinburgh for use in future research. These will be coded with a study number. Your informed consent form will also be stored securely (and separately from the research data and sample itself) until the samples have been depleted or destroyed in order to comply with the Human Tissue Act. The blood samples may be used for further related research, including of the human body's immune system, vaccine research and/or your safety. Any such future research will have an appropriate ethical review. You may request that your remaining blood and bone marrow samples are destroyed at any time. If you decide to withdraw your consent to storage of leftover samples, they will be disposed of at the end of this study.

Urine samples will be destroyed immediately after testing.

Will any genetic tests be done?

Yes. Some blood will be used to look at the pattern of expression of your genes that can affect the immune system (so-called 'gene expression' analysis). This type of analysis looks at how information in your genes is used to make proteins or a different type of genetic material called 'RNA'. As these tests are not done to look at your health, we would not give you these test results.

What will happen to my data?

Data protection regulations require that we state the legal basis for processing information about you. In the case of research, this is 'a task 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 information from you and your medical records in order to undertake this study. We will use the minimum personally-identifiable information possible.

Data will be collected and held by members of the Oxford Vaccine Group (OVG). It will be accessible to responsible staff at OVG and the University of Oxford who may monitor/audit the data collection process, and inspectors from the regulatory agencies responsible for research in the UK. The database servers are secure and held by the University of Oxford. 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 will be subject to ongoing review. Pseudonymised research data will be stored indefinitely.

The study team will use your name and contact details to contact you about the research study. We will also 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 end of the study, unless you consent otherwise (e.g. if you request to be informed of other studies/trials), your personal details will not be used to contact you other than for exceptional circumstances concerning your safety. If you consent to take part in another study at CCVTM, personal information and medical information including blood test results may be accessed to avoid unnecessary repetition.

A photocopy of your ID (driver's licence, passport or national ID card) and either your national insurance or passport number for TOPS database registration (see below) and payment processing will be taken at the screening visit. We will securely retain copies until the end of the study.

Your information may also be shared with partners working with Oxford University. This information will be identified only by the unique study number. You will not be directly identifiable. All data received will be kept securely by these parties in line with all regulatory requirements. If the study is paused due to safety concerns relating to the yellow fever vaccine, medications prescribed by the study team, or heavy water, we will inform the local ethics committee, the study funders (MRC) and the manufacturers of vaccine/drug/heavy water as appropriate. The data shared would be pseudonymised.

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

Data protection regulation provides you with control over your personal data and how it is used. When you agree to your information being used in research, however, some of those rights may be limited in order for the research to be reliable and accurate. Further information about your rights with respect to your personal data is available at: https://compliance.web.ox.ac.uk/individual-rights.

Involvement of the OVG Quality Assurance Team (Independent Monitors)

The OVG Quality Assurance Team act as independent monitors on behalf of the Sponsor to ensure we are complying with the clinical trial regulations. They will conduct a site visit to prepare and set up the clinical trial prior to recruitment as well as conduct monitoring visits to check the information in source documents (e.g. blood test results and GP letters). In most documents you will only be identified by a study ID number but they will see some documents which would identify you (e.g. the consent form). They will not retain any data which could identify you personally. For remote monitoring to occur they may require secure online access to electronic documents but will not download or copy them. The OVG Quality Assurance Team will comply with the University's Information Security Policies.

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. When we know the results of the study, we will send participants a summary of findings.

The anonymised data from this study will be shared with the partners who are organising and funding this research. It may be made open to the public so that others can learn from it. If data are shared publicly, they will not be linked to you personally. 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 postgraduate degree, for example an MD or PhD.

The results of this research study may be presented at scientific meetings or conferences and published in scientific or medical journals. 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.

A description of this clinical study will be available on www.isrctn.com. 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 malaria related research

With your consent, we would like to keep your contact details after your participation in this study is complete. This is so we may inform you of opportunities to take part in future malaria related research. This is entirely optional. Taking part in this study will not be affected by your decision as to whether to allow storage of your contact details beyond your participation in this study.

Your details would be stored electronically on a secure server. 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. 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 and is funded by an Experimental Medicine grant from the UK Medical Research Council (MRC). The MRC is a UK-based organization which funds biomedical and clinical research. 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 Committee South Central Berkshire 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 pre-screening appointment. You can also contact us with any questions about what you have read.

Contact details for further information:

Volunteer Recruitment Co-ordinator
E-mail: info@ovg.ox.ac.uk
Tel: 01865 611400
Oxford Vaccine Group, CCVTM, Churchill Hospital, Old Road, Headington, Oxford, OX3 7LE