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PARTICIPANT INFORMATION SHEET

BIO-006

Development of a relapsing *Plasmodium vivax* Controlled Human Malaria Infection model

Thank you for your interest in the BIO-006 malaria study. We are inviting you to take part in this research study organised by the University of Oxford to help us improve our understanding about relapsing malaria infections caused by *Plasmodium vivax*.

Before you decide to take part in any research study, it is important for you to understand why the study is being conducted and what it involves. Please read the following information carefully. You can discuss it with friends and relatives. If you would like more information, please feel free to contact us on the email address or phone number at the top of the page.

This information booklet has been reviewed by members of the Oxford Vaccine Centre's patient and public involvement (PPI) team. The PPI team make sure the information is presented in a clear and understandable way.

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STUDY OVERVIEW

Who?	Five healthy adults aged 18–45 years inclusive
Duration	7.5 months in-person Email follow up until 5 years (fortnightly month 8-12, annually year 2-5)
Study Aims	To develop a method of safely and effectively introducing relapsing malaria in healthy volunteers by Controlled Human Malaria Infection (CHMI) administered by mosquito-bite, thereby developing a new method for testing future curative and preventative therapies for relapsing malaria
Location	The malaria challenge will be administered at Radboud University Medical Center (RUMC) in Nijmegen, Netherlands. All other visits will take place at the Centre for Clinical Vaccinology and Tropical Medicine (CCVTM), University of Oxford, at Churchill Hospital.
Expenses and payment	Approximately £5,510* **Final compensation total will depend on the number of relapse infections*
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.
Benefits of participation	Volunteers will not benefit directly from participation in this study. However, it is hoped that their participation will help develop a new method of testing vaccines to prevent suffering in other people caused by relapsing malaria
Visit Schedule	

Visit	Purpose
Screening visit	To see if you are eligible to take part
2 days prior to malaria challenge	Final health checks and blood test before malaria challenge
1 day prior to malaria challenge	Travel from Oxford to Nijmegen, Netherlands
Malaria challenge day	Administration of malaria infection by mosquito bite at RUMC
1 day after malaria challenge	Return from Nijmegen to Oxford
Days 1 to Day 6	Daily phone call
Day 7 to Day 21	Daily visits at the CCTVM Oxford, including a blood test to detect malaria infection, until you are diagnosed with malaria or until Day 21 (whichever is earlier)
Day of Treatment	Treatment with Riamet (or alternative antimalaria tablet, Malarone)
Following Riamet treatment	CCTVM clinic visits on Days 1, 3 & 7. Blood tests to ensure the active infection has cleared and a general health check
Relapse follow-up period	Monitoring for relapsing malaria infections. Fortnightly visits for 6 months. On-call doctor available 24/7. Riamet treatment in event of relapse malaria infection.
Definitive malaria treatment	Approximately 6.5 months after malaria challenge Full treatment with Riamet and Primaquine to prevent future relapse infections
Last in-person visit	7.5 months after malaria challenge
Long-term follow-up	Email follow-up until 5 years. Able to contact study team at any time.

WHY ARE WE CONDUCTING THIS STUDY?

Malaria is a disease caused by a parasite infection called *Plasmodium* which is transmitted by mosquitoes. *Plasmodium vivax* is the most widespread of all the *Plasmodium* species known to cause malaria in humans with approximately 3.3. billion people living in areas at risk of infection. *P. vivax* causes significant health problems in many areas of the world (Figure 1). Between 2018-2022, more than 5 million *P. vivax* infections occurred every year.

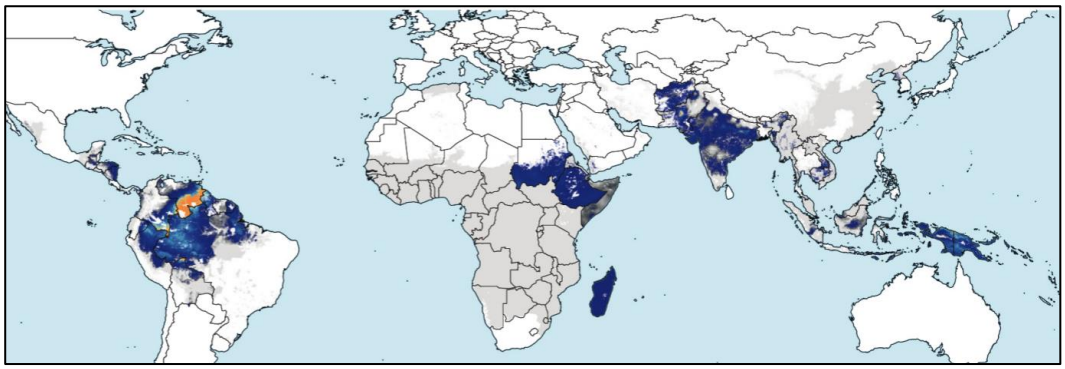


Figure 1: *P. vivax* geographical distribution

After being bitten by a mosquito carrying the malaria parasite, people usually develop symptoms of infection (such as fever, headache, and muscle aches) within 1-2 weeks. Most malaria infections can be successfully treated with tablets. However, without early effective treatment, *P. vivax* malaria can lead to severe illness and even death.

A particular feature of *P. vivax* is that, unlike other malaria species, it also produces an inactive dormant form of infection called a hypnozoite. The word hypnozoite is a name derived from the Greek word "hypnos" meaning sleep. Hypnozoites hide in the liver and can later reactivate or reawaken to cause another active malaria infection. This can occur several times over the months (or even years) after the mosquito bite which introduced the infection in the first place if left untreated. It is estimated that 80-90% of all *P. vivax* malaria cases are due to relapse infections.

We are conducting the BIO-006 study to try and find out more about relapsing malaria infections. It is a **malaria challenge study**. This means it involves deliberately infecting volunteers with malaria in a safe and controlled way. We will deliberately allow our participants to experience relapsing *P. vivax* infections over a 6-month period, each of which will be treated with tablets to clear the active infection. At the end of this period, all participants will be treated with tablets to clear any active **and** any inactive malaria parasites (hypnozoites) in the liver, to prevent any further infections occurring.

The BIO-006 study will provide us with valuable information about relapse malaria infections. It is also a proof-of-concept study, meaning that, although we have safely performed malaria challenges by mosquito bites in previous studies, we have never allowed participants to experience relapsing infections. Success would mean that we could repeat a similar study in the future (in the knowledge that it works) to test new vaccines or medications that could be used to treat or prevent relapsing malaria infections.

WHAT DOES THE STUDY INVOLVE?

We want to study relapsing malaria infections due to *Plasmodium vivax* malaria. Five healthy volunteers, who have not had malaria before, will undergo a "malaria challenge". *P. vivax* malaria will be administered by mosquito bites, on a designated day at Radboud University Medical Center (RUMC) in Nijmegen, Netherlands. This will require a short trip to the Netherlands, approximately 2 nights, with the University of Oxford study team. All other appointments will be conducted at the Centre for Clinical Vaccinology and Tropical Medicine (CCVTM) at Churchill Hospital in Oxford.

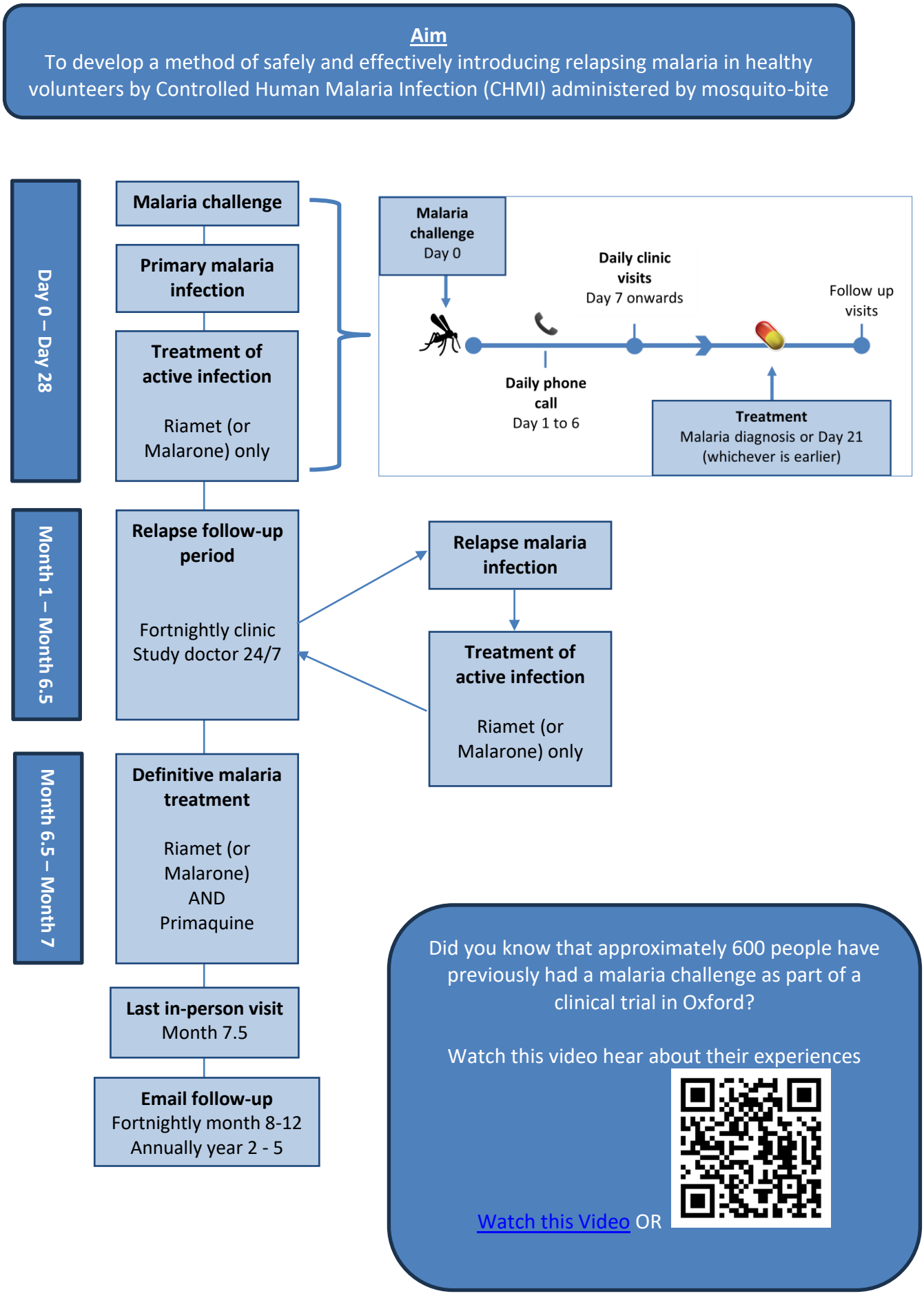
After the malaria challenge, we will return to Oxford and you can return to your usual day to day activities. However, we will monitor you very closely. We expect you to be diagnosed with malaria infection approximately between day 10-16 following the mosquito bites. We will telephone you daily for the first 6 days following the malaria challenge. From day 7 until you are diagnosed with malaria, we will see you each day at the CCVTM clinic to take a blood sample to assess the infection level. Once you are diagnosed by the study doctor, you will be treated with an effective course of malaria tablets (either Riamet or Malarone) to clear the active infection. If we do not detect any malaria infection on the daily blood tests, we will still treat you once you reach day 21 following the mosquito bites to ensure any undetected infection is treated. You may experience some early symptoms of malaria infection, such as fever and headache but we will be treating you early in the infection to minimise the duration and severity of any symptoms.

At this stage, we will deliberately not give you an additional tablet called Primaquine that is required to clear the dormant malaria infection (hypnozoites) from the liver. Instead, we will monitor you for "relapsing" *P. vivax* infections over the following 6-month period. During this 6-month period, we will keep a very close eye on you. You will be required to attend a fortnightly in-person clinic. You will also be encouraged to contact the study doctor (available 24 hours a day) should you experience any symptoms that may indicate a possible reactivated malaria infection (e.g. fever). When we see you, either at the routine clinic or because you have symptoms, we will take a blood sample. If we detect any malaria parasites, you will be treated as before to clear the active infection (with Riamet or Malarone but not Primaquine) and return to the fortnightly clinic.

At the end of the 6-month follow up period, all participants will receive a full course of both Riamet (or Malarone) *and* Primaquine treatment to clear any remaining "active" malaria parasites and any "inactive" parasites in the liver. This is to ensure you are fully treated to prevent future relapsing malaria infections from occurring. We will email you fortnightly until 1 year following the malaria challenge, and then annually until 5 years following the malaria challenge. This is to be sure that you have not experienced any unexpected recurrent infections. You will be able to contact us at any time during this period and we encourage you to contact us if you develop any symptoms of a possible relapse and/or if you seek medical attention for any unexplained symptoms.

More information about the procedures involved in the study is provided below.

Figure 2: Study Overview



STUDY PROCEDURES

Malaria challenge

A malaria challenge is where we deliberately introduce a malaria infection in volunteers in carefully controlled conditions. We monitor infection levels using blood tests and start treatment with effective malaria tablets when we detect the infection. This allows us to study malaria closely and learn more about the disease. In other studies, we use malaria challenges to test new vaccines. Challenge studies have been performed to study a wide range of infectious diseases, such as COVID-19, flu and typhoid. Malaria is particularly well-suited to this type of study because we can diagnose malaria infection quickly, we have fully effective treatments available, and there are no known consequences or long-term effects of malaria infections if they are effectively treated early.

All participants will attend a screening appointment to ensure they are eligible to undergo a malaria challenge and take part in this study. Participants will also need to attend the CCVTM research clinic 2 days before the malaria challenge (C-2 visit). During the C-2 visit, we will check that there have not been any changes to your health. We will also perform blood tests and, if you can become pregnant, a urine pregnancy test to ensure you remain eligible to undergo the malaria challenge.

In this study, we will be administering the malaria infection by mosquito bites at **Radboud University Medical Center (RUMC) in Nijmegen, Netherlands**. All other study visits will take place in Oxford.

There are several reasons we have decided to perform the malaria challenge at RUMC:

- The University of Oxford does not have an insectary facility suitable for the mosquito-bite malaria challenge required for this study
- RUMC is a world-leading malaria and mosquito research centre with extensive experience in conducting mosquito-bite malaria challenge studies.
- The mosquitoes for the malaria challenge will be produced and infected with *P. vivax* malaria at the RUMC insectary, so we will be able to ensure the mosquitoes are in the best possible condition for the malaria challenge without needing to be sent by international courier to the UK.

Travel arrangements

The malaria challenge therefore involves travelling to Nijmegen, Netherlands for approximately 2 nights. Travel, accommodation and food will be organised and paid for by the study team. You will receive reimbursement for the inconvenience and time associated with this trip (see *Expenses, payments and number of study visits* section for more details). The University of Oxford study team will also be accompanying participants at each stage of the journey and throughout the malaria challenge. The study team will be responsible for organising the logistics as well as ensuring your safety and well-being. We will communicate all the necessary information regarding travel with you. However, there are a few important points to consider at this stage.

1. Itinerary

We will travel from Oxford to Nijmegen the day before the malaria challenge. The study team will organise transport from Oxford to Heathrow airport, a flight/train from Heathrow to Amsterdam Schipol airport (approximately 1 hour), and a train from Schipol to Nijmegen (approximately 1.5 hour). Hotel accommodation will be arranged. You will be provided with your private room for 2 nights. The day of

malaria challenge will involve spending most of the day at the RUMC insectary. The following day we will travel back to Oxford by taking a return flight from Schipol airport to Heathrow. In total we therefore expect you to be away for 2 nights (3 days). While in Nijmegen, there will not be an opportunity to extend your travel or participate in activities beyond the scope of the malaria challenge. You must follow the instructions of the study team.

2. Passport/visa requirements

You require to have the necessary passport and/or visa requirements to visit the Netherlands. If you a UK passport holder, your passport must be:

- issued less than 10 years before the date you enter the Netherlands (check the 'date of issue')
- valid for at least 3 months after the day we plan to leave the Netherlands (check the 'expiry date')

If you are not a British or EU citizen, the study team will request to check your visa status to ensure you are able to travel to the Netherlands.

3. Individual travel insurance and UK Global Health Insurance Card (GHIC)

You are encouraged to have personal travel insurance. This should cover your personal belongings, travel arrangements and emergency medical expenses. Please share the insurance certificate, policy document and receipt/invoice with the study team who will arrange reimbursement for the expense of a single trip travel insurance. Please note that any sickness related to study procedures will be covered by the study team's clinical trial insurance policy. The study team will also be responsible for organising alternative travel in the event of cancellation. The UK Global Health Insurance Card (GHIC) allows eligible individuals to receive state healthcare in the European Economic Area (EEA). If you have an existing European Health Insurance Card, you can use this until it expires. To apply and for further information, please go to: https://www.nhs.uk/using-the-nhs/healthcare-abroad/apply-for-a-free-uk-global-health-insurance-card-ghic/

Mosquito bites

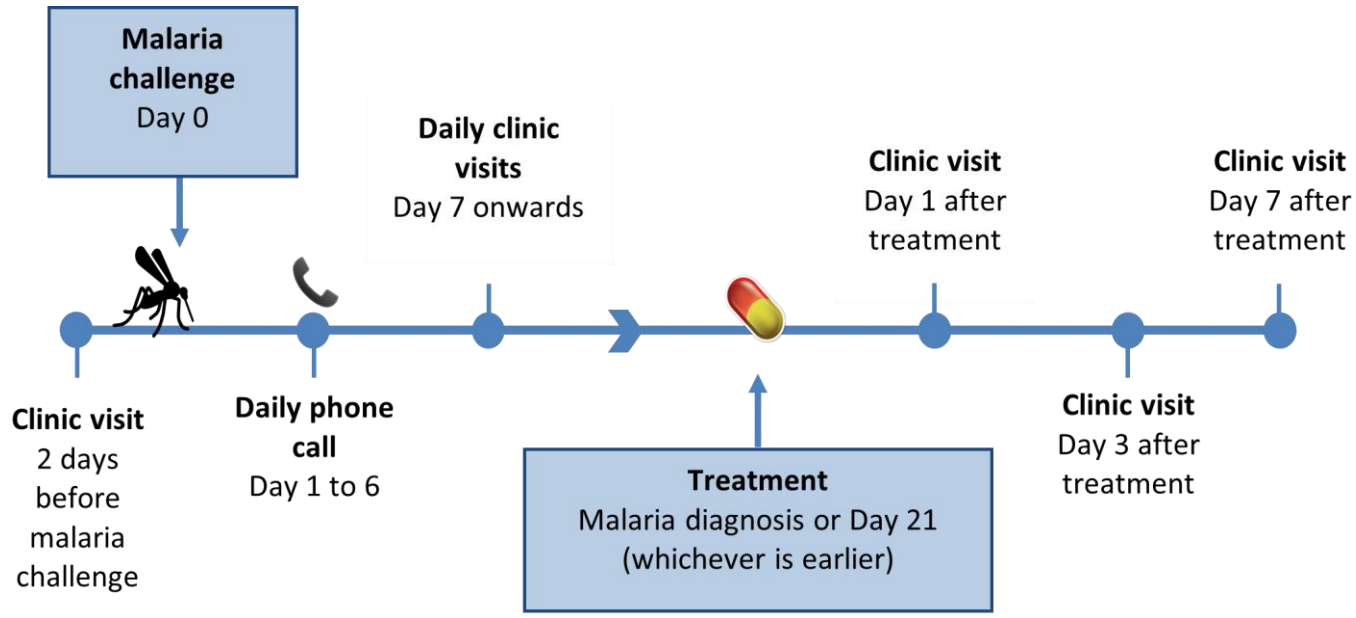
The malaria challenge will be performed at the RUMC insectary with the University of Oxford study team. You will be bitten by up to five mosquitoes carrying the malaria infection. The mosquitoes will be in a container with a gauze screen over the top. This container will be placed on the skin of the forearm, as most participants prefer this site. However, if you prefer another site then we can try putting the container there. It will need to stay in place for between five and fifteen minutes to allow the mosquitoes to feed. Once they have fed, the container will be removed, and the mosquitoes examined for signs of blood and parasites. If this examination reveals that you have not received the required number of infected bites, then additional mosquitoes will be allowed to bite until you have received 5 infected bites. This process can take most of the morning or afternoon.

The mosquitoes may not bite well if you have used perfume, aftershave, or a perfumed soap or cream on the skin where they are going to bite. We ask that you don't use any of these items, nor should you shower or bathe on the morning of the challenge. We will give you a medic alert card to keep on your person during the whole study period (explaining you have been infected with malaria and including emergency contact details of the study team), a thermometer so that you can take your temperature at home, and, if necessary, a phone.

Primary malaria infection

The malaria challenge follow-up visits are very important. Once we return from the Netherlands, we will phone you once a day until day 6. From day 7 (C+7) onwards we will see you daily at the CCVTM clinic in Oxford. At these appointments (approximately 30 mins), we will take a small sample of blood (2mL) to see if there are any detectable malaria parasites in your blood. This will continue until 21 days after malaria challenge or until you are diagnosed with primary malaria infection (whichever happens sooner). You should assume you need to attend clinic at least once a day from day 7 to day 21 unless we inform you otherwise.

Figure 3: The primary malaria infection



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 following the malaria challenge.

Once the study team confirms the diagnosis of malaria, you will be treated with a medication called **Riamet**. If you cannot take Riamet, we will use an alternative anti-malarial medication called **Malarone**. Both these tablets are effective at treating active malaria infections. However, they do not treat inactive malaria infections (i.e. dormant *P. vivax* hypnozoites). This is because we want to study relapsing malaria infections that occur from reactivating hypnozoites. We will see you in clinic on days 1, 3, and 7 after starting the malaria treatment. We will perform a health check and take blood samples to check your general health, look at the immune response and ensure the active malaria infection has cleared.

Relapsing malaria infections

During the following 6-month period we will monitor you for relapsing malaria infections. We expect you to experience approximately 2-3 relapsing malaria infections in 6 months. However, it is important to emphasise that relapsing malaria infections are unpredictable and variable.

- Relapse malaria infections may occur at any time during this period.
- Some people may develop symptoms of malaria due to a relapse infection.
- Some people may have a relapse infection without any symptoms.
- Some people may not experience any relapse malaria infections.

We will monitor you very closely. You will be required to attend a fortnightly in-person clinic from 4 weeks (28 days) following malaria challenge until 28 weeks following malaria challenge. At these visits we will check your blood for any detectable active malaria infection.

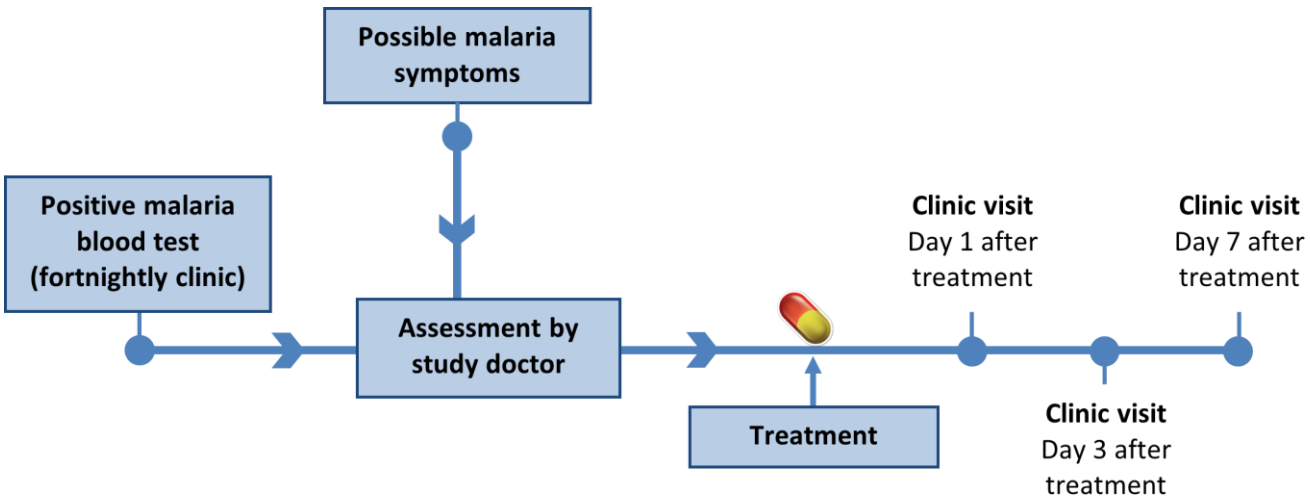
You will also be encouraged to contact the study doctor (available 24 hours a day) if you experience **any** symptoms that may indicate a possible relapse malaria infection (e.g. fever). This includes symptoms that may be due to other common illnesses (e.g. flu or cold). We would still want to see you to ensure your symptoms are not due to malaria.

Malaria symptoms may include:

Fever (≥ 38°C), feverishness, chills, shivers, sweats, headache, loss of appetite, nausea, vomiting, diarrhoea, muscle aches, joint aches, low back pain, fatigue

If you experience possible malaria symptoms, or we detect malaria parasites on the fortnightly blood test, we will ask you to attend an additional clinic visit to perform a medical assessment and blood tests. If the diagnosis of malaria is confirmed, we will start antimalarial tablets either the same day or the following day. These tablets (Riamet or Malarone) will clear the active infection as before, but not the inactive dormant hypnozoites. We will ask you to attend for extra blood tests after we have started the tablets to look at the immune response and ensure that the active infection has cleared. After these additional visits, you will go back to the routine fortnightly clinic appointments. This pathway is outlined in Figure 4.

Figure 4: Assessment and treatment of relapse malaria infection



You may experience more than one relapse malaria infection. Therefore, we may need to repeat this process on more than one occasion.

Given the unpredictable nature of relapsing malaria infections, it is important that we can start treatment at any time during this 6-month period. You will therefore be advised to remain within travelling distance of Oxford. Short trips to other locations in the UK may be possible. However, you will be required to inform the study team of any travel plans. You must also provide the name and 24-hour phone number of someone who will know where you are for the duration of the study. If you fail to attend for a clinic review and cannot be reached by phone, we will contact this person. If you cannot be located, we may need to take additional steps to ensure your safety which may involve contacting the police and media.

Definitive malaria treatment

At the end of the 6-month follow up period (day 196 following malaria challenge) we will start you on definitive malaria treatment. This is to fully treat *P. vivax* malaria and prevent further relapsing malaria infections from occurring.

You will receive a full course of both Riamet (or Malarone) ***and*** Primaquine treatment to clear any remaining "active" malaria parasites and any "inactive" parasites in the liver. Riamet is used to treat active malaria infection and is taken for three days. We will see you on day 1 following treatment and day 3 after starting Riamet treatment for a health check and blood tests. On day 3, we will start Primaquine. Primaquine is used to prevent future relapse infections by clearing hypnozoites from the liver. We will be using a high dose of primaquine (based on body weight) for 14 days. To be absolutely sure that we are effectively treating you, we will want to ensure that you take a tablet once daily for 2 weeks. Each day of this treatment, we will either contact you by telephone or ask you to attend the CCVTM clinic to take the tablet under direct observation. You will be required to attend the CCVTM clinic at least 3 times a week during this 2 week period.

You will complete Primaquine treatment approximately 7 months after the malaria challenge. Your last in-person visit will be 14 days after finishing the Primaquine treatment, approximately 7.5 months after the malaria challenge. The study doctors can commence definitive malaria treatment earlier if necessary (e.g. if you experience excessively frequent relapse infections, or if your circumstances change and you no longer wish to take part in the study).

Long-term follow-up

We will email you fortnightly until 1 year following malaria challenge, and then annually until 5 years following the malaria challenge. This is to ensure you have not experienced any unexpected relapsing malaria infections. The email will contain a link to a questionnaire asking you about any malaria symptoms, anything you have seen a doctor about, or any changes in your health. If we do not hear from you, we may contact you using an alternative method (e.g. phone or letter). If we still do not hear from you, we may contact your next of kin, GP or access your electronic health records to check if there have been any changes in your circumstance (e.g. moved away, change to health). This provides long-term safety data for the study.

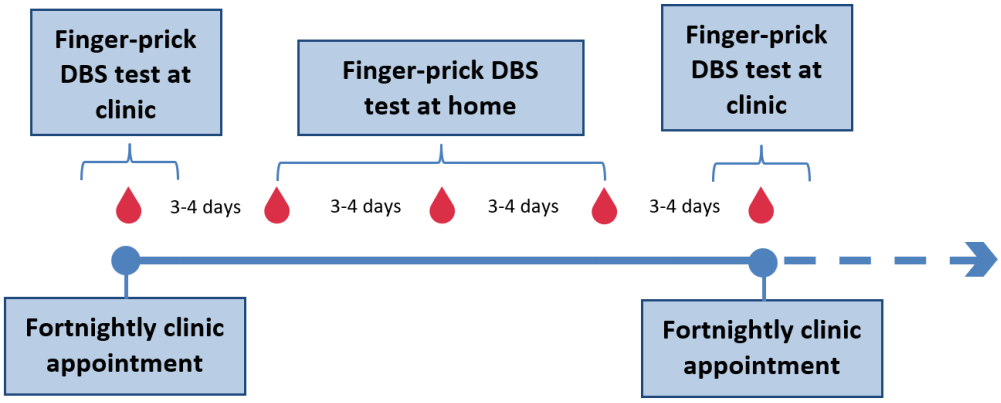
You will be able to contact us at any time during this period. We strongly encourage you to contact us at any time if you develop any symptoms of a possible relapse infection and/or if you seek medical attention for any unexplained symptoms. We may ask to see you at the CCVTM clinic for further assessment if required and if you are able to attend.

Blood tests

At most of the in-person study visits, we will be taking at least one blood sample from a vein in your arm. The amount of blood we will take at each appointment will vary. This may range from 2ml to 83ml. Given the frequency of blood tests, it is important that the study doctors and nurses can 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, we may not enrol you in the study.

Throughout the 6-month relapse follow-up period, we would also like to perform a finger-prick blood test called a "Dried Blood Spot" or "DBS" approximately twice a week. A supervised dried blood spot will also be performed at each fortnightly relapse clinic. We will ask you to take the remaining samples yourself at home (i.e. approximately one finger-prick sample every 3-4 days between clinic appointments). This is outlined in Figure 5.

Figure 5: Dried Blood Spot (DBS) fortnightly schedule during 6-month relapse follow-up period



You will be shown how to perform this simple procedure and provided with the necessary equipment. A small device containing a safety needle is used to prick the fingertip. A small drop of blood can then be dabbed on a special collection card. We will collect these cards at each clinic appointment.

Most people find the procedure very straightforward. This method of a finger-prick test is very similar to how individuals with diabetes may measure their blood sugar levels 3-4 times a day. We want to collect these Dried Blood Spot (DBS) samples as they allow us to increase the frequency of blood tests looking for *P. vivax* relapse infections without you needing to attend extra appointments. We will test these samples for malaria infection. They will give us a much more detailed, high-resolution picture of relapse malaria infections as they emerge and then disappear after treatment. We also want to see how they compare with venous blood samples (standard clinic blood tests) taken at the same time. We will therefore be performing a DBS sample when you start treatment for primary or relapsing malaria infection, and at your appointment 3 days following initiation of treatment.

It is important to note that we will not be using these DBS samples to make decisions about malaria treatment. We will analyse them at the end of the study. It is therefore very important that you attend

appointments for in-person blood tests so we can monitor infection levels in real time and treat you promptly if required.

Medical examination

At the screening visit (described below) and at the follow up appointments (if required), a qualified study doctor may perform a physical examination.

I WANT TO TAKE PART – WHAT HAPPENS NEXT?

Thank you for your interest! The first thing we will ask you to do is to complete an online pre-screening questionnaire. This questionnaire takes 3-5 minutes and will ask questions to check if you are eligible to be considered for this study. It will also ask for your permission for us to check your medical records and contact you about the study.

The pre-screening questionnaire can be accessed at Pre-screening

You can also get in touch with us if you have any questions: E-mail: info@ovg.ox.ac.uk Tel: 01865 611400.

If you are potentially eligible, we will then invite you by telephone or email to a face-to-face screening appointment at the CCVTM clinic. The purpose of the screening visit is for you to discuss the study with us and decide if you wish to take part. It also allows us to check in more detail whether you are eligible for the study. You will be asked to answer a questionnaire (like a mini quiz) to assess your understanding of the study. This allows us to be confident that you understand fully what taking part in the study will involve. You will be asked to sign a form to provide your consent to take part in the study. The screening visit can take place within 3 months before the malaria challenge. The screening visit can last up to 2 hours but there can be an opportunity for a short break.

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 can 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 performed. 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 infection, or CMV (cytomegalovirus) or EBV (Epstein-Barr virus) antibodies. This is because these viruses can affect your body's response to the malaria challenge.
- Your "Duffy antigen" status. This is a protein on the surface of your red blood cells that allows *P. vivax* malaria to infect your cells. If your blood cells do not express this protein the malaria challenge may not work and so you will not be able to take part in the study.

- Your body's ability to process the malarial drug Primaquine (CYPD26 genotype). This is to make sure that the Primaquine treatment will be effective when we give it to you.
- Levels of an enzyme called G6PDH. If your levels are normal this means it will be safe to treat you with Primaquine to clear any remaining parasites from the liver (people who have low levels of this enzyme are potentially at risk of becoming very anaemic if this treatment is given). If your levels are low you will not be able to take part in the study.
- Thalassaemia, sickle cell anaemia and other conditions that affect the blood
- Your cholesterol levels. This is to check your risk of heart disease in the next 10 years. You cannot participate in the study if your 10-year risk of heart disease is more than 5%

The urine test will look at:

- Pregnancy (if you can become pregnant)

Your samples will be coded with a unique number. You will not be identifiable to laboratory researchers. If any of your tests are not normal, we will let you know and may 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, we are required by law to notify the UK Health Security Agency of this result.

WHAT IF I DECIDE NOT TO TAKE PART IN THE STUDY?

You do not have to take part in this study. It is completely up to you. Your decision will not result in any penalty, or loss of benefits or access to medical care to which you are otherwise entitled.

You are free to withdraw from any research 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. If you decide to withdraw from the study following the malaria challenge, you must agree to take full antimalarial treatment (including Primaquine) as directed by the study team. This will be provided at the CCVTM clinic. We may also ask you to return to the clinic for follow up for safety reasons. If you are finding the Dried-Blood Spot procedure difficult, we could reduce the frequency of these samples (and otherwise keep you in the study) if required.

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.

ELIGIBILITY CRITERIA

To be involved in the study you must be:

- A healthy adult between 18 to 45 years of age inclusive
- Able and willing to meet all study requirements
- Willing to allow the study doctors to access your electronic medical records or discuss your medical history with your GP

- 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 full anti-malarial treatment (i.e. approximately 7 months following malaria challenge)
- Able to travel to the CCVTM clinic at Churchill Hospital, Oxford
- Able to travel to the Netherlands for malaria challenge with the necessary passport +/- visa requirements

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 travelled to an area with malaria transmission in the last 6 months, or, you are intending to travel there during the in-person study period (until month 7.5)
- 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 received a blood transfusion in the last 3 months
- You have had anaphylaxis
- 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 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 have alcohol dependency
- 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, sudden death or heart disease in an immediate family member (when they were less than 50 years old)
- You are unable to take Riamet and Malarone
- You are unable to take Primaquine
- You are unable to stay in Oxfordshire (or surrounding area) following return from the Netherlands until approximately 28 days following 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 undergoing the malaria challenge if:

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

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. E-mail: info@ovg.ox.ac.uk Tel: 01865 611400

What would I have to do?
To be enrolled in the BIO-006 study, it is essential that you agree to the following conditions:

1. If you can become pregnant, you must use effective contraception until at least 3 months after completing Primaquine treatment.

2. You must provide the name and 24-hour phone number of someone who will know where you are for the duration of the study. If you fail to attend for a clinic review and cannot be reached by phone, we will contact this person. If you cannot be located, we may need to take additional steps to ensure your safety which may involve contacting the police and media.

3. You must not donate blood during the study and for at least three years after completion of Primaquine treatment. We recommend you refer to the NHS Blood and Transplant website (https://www.blood.co.uk/) for latest guidance about who can donate blood.

4. You must agree to the travel restrictions outlined in the section below

OTHER CONSIDERATIONS

Travel restrictions

While in the Netherlands, there will not be an opportunity to extend your travel or participate in activities beyond the scope of the malaria challenge. You must follow the instructions of the study team.

Following your return from the Netherlands, you will be required to remain in Oxfordshire (or the surrounding area) until you complete treatment of the primary *P. vivax* infection (approximately 28 days following malaria challenge). This is so we can start anti-malarial treatment promptly.

After this, during the relapse follow-up period, you will be advised to remain within travelling distance of Oxford until you have completed the definitive malaria treatment (i.e. Riamet (or Malarone) *and* Primaquine). This is scheduled to finish approximately 7 months following malaria challenge. This is so that we can assess you if you experience a relapse malaria infection and commence treatment promptly. Short trips to other locations in the UK may be possible. However, you will be required to inform the study team of any travel plans. An absolute requirement is that you remain on the UK mainland within 1-2 hours of an NHS hospital. This is to ensure you can access anti-malarial treatment if required.

Following the last in-person visit, there are no further travel restrictions. However, we would be grateful if you could inform us of any plans to travel to malaria endemic countries up to 5 years following the malaria challenge. This is so that, in the unlikely event you experience a malaria infection during this

time, we can potentially assess you and help determine if it is an unexpected relapse infection (from the malaria challenge) or a "new" unrelated malaria infection from a mosquito bite.

Medications

Your health and well-being are more important than the study. If you need any medication, then you should take it. However, if it is possible, we would ask if you could let us know before you start any new treatments as some medications could impact our study findings. For example, some common antibiotics (e.g. for skin or urine infections) can treat malaria infections as well, so we may suggest an alternative antibiotic to your doctor. We will review your medications at study visits. We may not be able to enrol you in the study if you are on a certain medication which may interfere with the malaria challenge.

Pregnancy and Contraception

Malaria infection is more dangerous during pregnancy. Primaquine is also not safe to take during pregnancy. You will therefore not be able to enrol in this study if you are pregnant or planning to become pregnant any earlier than three months AFTER completing your definitive malaria treatment (i.e. approximately 10 months after malaria challenge).

If you can become pregnant, you will be asked to use a highly effective method of contraception. This will be required from when you start the study until three months after completing your definitive malaria treatment (i.e. approximately 10 months after malaria challenge). Condoms alone are not considered effective enough.

Acceptable forms of contraception include:

- Combined hormonal contraceptives. This includes the pill, or intravaginal or transdermal combined hormonal methods of contraception.
- Progesterone-only hormonal contraception e.g. oral desogestrel (mini pill), injectable depot medroxyprogesterone acetate, or subdermal implantable etonogestrel.
- 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.

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) if we use Riamet to treat your malaria infection(s). This applies until the start of your next period.

Pregnancy tests will be performed at screening and regularly throughout the study period. This may be a urine or a blood test. If you become pregnant after screening, you will not undergo the malaria challenge. If you become pregnant after the malaria challenge, we will discuss with the Data Safety and Monitoring Committee (independent infectious diseases experts) and follow the latest advice regarding treating relapsing malaria infection in pregnancy, with involvement of appropriate NHS specialists if necessary. Any participant who become pregnant will be followed up until the pregnancy outcome, with the participant's

permission. This may involve additional telephone consultations and/or performing routine follow-up visits by telephone. We will not routinely perform blood tests on such participants unless for safety reasons.

Availability for appointments

This study requires you to be able to attend regular appointments, other appointments at short notice, as well as a 2 night/3 day trip to the Netherlands. The screening appointment lasts 1-2 hours and the malaria challenge will last most of the morning or afternoon. Most other appointments generally take no more than 30 minutes.

Malaria Protection

You should not assume that, by participating in this study, you will develop any kind of protective immunity against malaria. Make sure you visit your GP or a travel clinic before travelling to a malaria endemic region and follow their advice on prevention measures.

WHAT ARE THE RISKS?

Blood Tests

At most of the in-person study visits, we will be taking at least one blood sample from a vein in your arm. We will also be performing regular finger-prick Dried-Blood Spot tests. 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, such as bruising and tenderness, at the site where the blood is taken. Some people feel faint because of having blood tests performed. We expect to take approximately 814ml over the course of the study. However, we will take additional blood tests (approximately 106ml) during each relapse malaria infection. The amount of blood taken at each visit will vary between 2ml (approx. 0.5 of a teaspoon) to a maximum of 83 ml (approx. 5.5 tablespoons). 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. 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
- 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

- Your Human Leukocyte Antigen (HLA) type – these are protein markers on the surface of cells. There are several different HLA types, like there are several blood types, and they can influence how the immune system respond to infections

Mosquito bites

Mosquito bites may cause local inflammatory reactions with redness, itching, swelling, scaling and/or tenderness. Topical antihistamine cream will be provided to help with these symptoms. Serious allergic reactions have not been seen in any malaria challenge studies to date, but could theoretically occur. We will be conducting the malaria challenge in a facility with staff appropriately trained to manage this unlikely scenario.

Transmission of other infections

The mosquitoes we are using to administer the malaria challenge were reared in controlled laboratory conditions. They were infected with malaria by feeding on human blood that contained the malaria parasite. The risk of these mosquitoes transmitting other infections is extremely low. In particular, the volunteers who provided the blood for the mosquitoes were extensively screened and tested negative for other mosquito-borne infections and other important diseases (not transmitted by mosquito) such as HIV, Hepatitis B and Hepatitis C.

Controlled Human Malaria Infection

In Oxford, approximately 600 people have safely participated in malaria challenge studies. However, it is important to emphasise that we will be administering a real malaria infection that could, untreated, be very serious. Therefore, it is important that your read the following information carefully.

The symptoms of early malaria infection include a flu-like illness, fever, chills, headache, muscle aches, diarrhoea and vomiting. In previous studies, most participants experienced 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. **The study doctors can be contacted 24 hours a day.** About 1 in 5 participants temporarily develop symptoms that prevent daily activities so it is possible that you might need to take a day or two off work. We will provide paracetamol and anti-sickness tablets which you can take as needed. Most symptoms resolve completely within 1 to 3 days.

We will use the number of malaria parasites from your blood tests to guide whether you have reached a diagnosis of malaria. However, if at any point you develop symptoms of malaria infection which are concerning, the study doctors can start treatment even if the number of malaria parasites in your blood has not reached the threshold for diagnosis. Some people feel slightly more unwell in the first 24 hours after starting malaria treatment before improving. You will need to attend clinic on day 1 and day 3 after starting treatment so we can check all the parasites have been cleared from the blood.

Temporarily abnormal blood tests are common around the time of a 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. Temporarily abnormal liver tests are also common. However, these abnormal results have all resolved on their own after a few days or weeks, with no lasting effects.

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 during the malaria challenge period (until completion of Riamet or Malarone treatment) or during any relapse malaria infections
- You should not take more than 3 grams (6 tablets) of paracetamol per day

In the unlikely event of needing hospital treatment, we would arrange admission to the Infectious Diseases Unit at the John Radcliffe Hospital. In the last 10 years, only 4 participants out of nearly 600 have required this. There have been no long-term problems in any of the participants as a result of their participation.

Over the past 20 years, there have been five unexpected serious events in participants in malaria challenge studies in the Netherlands. These events were all (at least possibly) related to the heart, although all five people fully recovered with no long-lasting effects.

- 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 *P. falciparum* malaria called NF54 to infect participants. As a result of these events, the team in the Netherlands has stopped using NF54. There have never been any heart problems or serious events following administration of other strains of *P. falciparum* malaria or of any strains of *P. vivax* malaria (including our *P. vivax* PvW1 strain).

Malaria is a potentially serious infection and untreated, it can lead to severe illness, organ failure and death. The risks of participating in this study are low if you attend the study visits. If you do not attend a clinic appointment after malaria challenge, we may have to take additional measures to locate you and ensure your safety. We will contact your nominated contact. If we still cannot locate you, the police may be notified, and your name may be released to the national media in order to find you.

Treatment of Malaria

We will be using a medication called **Riamet** to treat “active” malaria infections in this study. Riamet is a combination drug consisting of two medications called artemether and lumefantrine. Prior to starting Riamet, we will check to ensure that you do not have any contraindications to this medication. Riamet is generally well tolerated but may cause some side effects, most commonly headache, nausea, vomiting, stomach pain, dizziness, rash, fever, reduced appetite, cough, tiredness or sleep disturbance.

If you are unable to take Riamet (for example, due to a potential interaction with a medication you normally take), we will use an alternative medication called **Malarone**. Malarone is a combination drug containing two medications called atovaquone and proguanil. Four tablets will be given to you to take

once daily for 3 days. Malarone is generally well tolerated but may cause some side effects, most commonly headache, diarrhoea, nausea, vomiting, stomach pain, dizziness rash, fever, low mood, reduced appetite, cough or sleep disturbance.

If neither Riamet nor Malarone are suitable, we would be able to use an alternative licensed anti-malarial medication.

At the end of the 6-month follow-up period, we will treat you with another course of Riamet (or Malarone) and a medication called **Primaquine**. Primaquine is used to prevent future relapse infections by completely clearing "inactive" malaria parasites (hypnozoites) from the liver. Primaquine is taken once daily for 14 days. The commonest side effects of Primaquine are nausea and abdominal pain. Primaquine is also not permitted for use in pregnancy. Therefore, if you were to become pregnant during the trial you would not be able to receive Primaquine treatment until the pregnancy was complete.

Severe allergic reactions could potentially occur with these anti-malaria medicines, as can happen with any medicine, but the exact frequency is unknown. Signs of severe allergic reactions include rash and itching, sudden wheezing, tightness of the chest or throat, difficulty breathing, and swollen eyelids, face, lips, tongue or other part of the body. If you experience any of these symptoms, you should contact the trial doctor immediately on the emergency contact number you will be provided with, or telephone 999 and ask for an ambulance if you are having difficulty breathing.

You will be provided with some additional medications (paracetamol and cyclizine) 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.

- **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. 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 a lower dose than normal and has been chosen to minimise the chance of developing abnormal liver tests during malaria infection.

Ongoing relapsing malaria

We will treat you with definitive *P. vivax* malaria treatment (Riamet and Primaquine) at 6.5 months following malaria challenge to prevent ongoing relapsing malaria infections. We will be using the gold-standard treatment to eradicate any dormant *P. vivax* infection. The dose and duration of Primaquine (0.5mg/kg/day for 14 days) is recommended in current World Health Organisation malaria guidelines.

It would be unlikely for you to experience a further relapse malaria infection following this treatment. However, there is a theoretical risk that this could occur. It is important for you to be aware of this and understand the measures we have put in place to ensure your safety.

Firstly, we will make sure that your body can process Primaquine into its active form required for effective treatment. In a previous malaria challenge study conducted in the USA, involving 33 participants, 2 participants experienced relapse malaria infections following Primaquine treatment. One of these individuals experienced relapse at 9 and 18 weeks, while the second individual experienced relapse at 11, 20 and 48 weeks. After each relapse, the active infection was cleared and Primaquine treatment was completed. By the end of the study the participants had been followed up for 5 years and had not had any further relapses. It was subsequently identified that these participants had a genetic variation in a specific enzyme (called CYP2D6) which was associated with an inability to convert Primaquine into its active form. We will therefore be making sure that you do not have this genetic variation at the screening appointment.

During the 14-day Primaquine treatment course, we will ensure that you are receiving the tablets correctly. We will either see you in the CCVTM clinic for direct observation of treatment (i.e. watching you take the tablets) or contact you by telephone to ensure you have taken the tablets at home. You will be required to attend the CCVTM clinic at least 3 times a week during this period.

After you have received Primaquine treatment, we will contact you regularly by email until 5 years following the malaria challenge. We will ask about any symptoms that may suggest an unexpected relapse infection. If you feel you are developing symptoms of malaria after Primaquine treatment, you will also be able to contact the study team at any time and we will be able to advise you accordingly. We may ask for you to attend the CCVTM clinic for a clinical assessment, blood tests and treatment or we may refer you to the most appropriate healthcare services. This will depend on the logistics of your individual circumstances (e.g. location) at that time.

If any participant experiences a relapse malaria infection following Primaquine treatment, we will inform our Data Safety Monitoring Committee, an independent panel of Infectious Diseases experts. We will also be able to contact the Infectious Diseases consultant on-call at the John Radcliffe Hospital, Oxford for independent expert medical opinion.

Undetectable malaria infection

The mosquito experts at RUMC will be monitoring the malaria challenge to give the best possible chance of successfully administrating the malaria infection. However, although unlikely, it is possible that we do not detect a malaria infection on the blood tests following the malaria challenge. In this scenario, you would be treated with malaria tablets (Riamet or Malarone) at Day 21 following malaria challenge. We would still ask you attend all the follow-up visits as scheduled (including fortnightly visits) and continue with the normal study procedures as it is still possible you may experience a relapse infection.

WHAT ARE THE BENEFITS OF TAKING PART?

This study will not benefit you directly. However, the information gained from the study will help develop a new method of testing future curative and preventative therapies for relapsing malaria such as vaccines. As 80-90% of *P. vivax* malaria cases are thought to be due to relapsing infections, this will be an invaluable platform to develop treatments that may help in the pursuit of malaria eradication.

WHO HAS ORGANISED THE STUDY?

The study is organised by the University of Oxford. It is co-funded from the European Union Horizon Europe programme under grant agreement No. 101080744. The project also receives funding from UK Research and Innovation (UKRI) under the UK government's Horizon Europe funding guarantee (grant No. 10077974).

This study has been reviewed by the National Research Ethics Service Committee (South Central-Berkshire REC) 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.

CONTACT US

Thank you for reading this information sheet. If you are interested in taking part in the study please complete the online pre-screening questionnaire at Pre-screening or contact the study team at your local study site to arrange a screening appointment. You can also contact us with any questions about what you have read.

Contact details for further information:

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

OTHER INFORMATION ABOUT THE STUDY

Expenses, payments and number of study visits

The expected number of visits in this study is approximately 51. However, there may be slightly more or slightly less (minimum 43, maximum 87). This is because we expect most participants to be diagnosed with malaria between 10-16 days following malaria challenge and experience approximately 2-3 relapse infections, each of which is associated with 5 extra study visits.

The compensation for the screening visit is £110. We will provide reimbursement to cover the time and inconvenience of the 3-day trip to the Netherlands. This will be £450. All other study visits are reimbursed per below.

You will be compensated for:

- Travel expenses £30 per visit
- Inconvenience of blood tests: £20 per blood donation
- Time required for visit: £40 per hour
- Inconvenience of finger-prick blood test (home and clinic) £5 per test

The estimated total compensation for participation in the study (assuming 2 relapse infections and attendance at all study visits) is approximately £5,510. If you do not experience any relapse infections, the estimated compensation (assuming attendance at all study visits) is £4,870. The actual amount will depend on the total number of visits attended. 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 the above figures.

Time in Study	No. of Clinic Visits	Approximate Volume of Blood Taken	Compensation Amount
In-person follow-up approximately: 7.5 months Total follow-up (including remote/email follow-up): 5 years	Approximately 51 visits	814ml	Approximately £5,510

The reimbursement provided is considered reasonable to cover the costs of participating in this research and, as such, should not have any consequences for tax purposes. However, as the amounts detailed above include compensation for directly incurred expenses (e.g. travel) and other involvement payments, you may wish to discuss your individual circumstances with HMRC. Participants who are receiving welfare benefits are advised seek advice from their provider.

Further information is available at:

- HM Revenue and Customs (HMRC) **EIM71105 - Research volunteers, lay participants and participants in clinical trials** https://www.gov.uk/hmrc-internal-manuals/employment-income-manual/eim71105
- National Institute for Health and Care Research (NIHR) **Payment guidance for members of the public considering involvement in research** https://www.nihr.ac.uk/payment-guidance-members-public-considering-involvement-research

Back up participants

We will recruit 1–2 'back up' participants in addition to the target of 5 participants in the study. These participants will be asked to be available to take part in the study at short notice. This is in case another participant is unable to undergo the malaria challenge at the last minute. Back up participants will attend the C-2 visit and may accompany the study team and other participants to RUMC, Nijmegen. A back up participant will only undergo CHMI if required to replace a volunteer. Back up participants who are not enrolled in the study will be compensated £200 in addition to compensation for visits they have attended.

What if relevant new information becomes available?

Sometimes during a research project, new relevant 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 for other reasons.

What happens if I don't want to (or can't) 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 and blood samples that have already been collected will continue to be used for the study analysis unless you request 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 as directed by the study team (provided at the CCVTM clinic) because of the potentially very serious consequences of untreated malaria infection.** If you lose capacity to consent for ongoing participation in the study, you will be withdrawn by the Investigators. Your data and blood samples that have already been collected will continue to be used for the study analysis unless you request otherwise.

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.

If you wish to complain about any aspect of the way in which you have been approached or treated, or the way your data has been used during 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 in this study will be coded with a unique study identification number and kept confidential. Personal details will be used by the research team within the University of Oxford for identification and contacting purposes. 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)

To enrol into this study, you will be asked to provide 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 you complete 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. 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 the processing of compensation payments.

What will happen to any research samples I give?

Blood tests for your general health will be carried out in the NHS laboratories at Oxford University Hospitals. These may be processed using your identifiable details (i.e. Medical Record Number, name, date of birth, sex, NHS number). All other study samples will be stored and processed in a pseudonymised form. This means that your study number rather than your personal details will be on them. Your blood samples (including Dried Blood Spot samples) will primarily be analysed in research laboratories at the University of Oxford. They may also be analysed at other collaborating research institutions in the UK and other countries (e.g. RUMC in Nijmegen, Netherlands). Your blood samples will be handled in

accordance with the relevant national and regional guidance and the principles of the Human Tissue Act. Any samples or data sent to collaborating laboratories will be pseudonymised.

With your consent, some of your leftover cells, plasma, serum, whole blood (or their purified components) will be registered under University of Oxford Human Tissue Act licence 12217 and stored indefinitely for future immunological analysis of malaria-specific responses. This may include human DNA and RNA analysis. 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 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 only be undertaken if granted permission by an appropriate ethical review. In order to take part in this study, we require that you consent to this long-term storage and use of leftover samples. You may request that your remaining blood 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.

It is possible that in the future, we may share pseudonymised study samples or data with other collaborators to carry out further related research. We will always make sure that any such sharing for further research is done in compliance with data protection laws, and under terms that protect your privacy and the confidentiality of your data.

The pseudonymised data may be transferred to, and stored at, a destination outside the European Economic Area, in accordance with the law. If data-transferred destination country does not have equivalent data protection standards to those required in the UK, appropriate safeguards will be adopted to protect and maintain the confidentiality of your data (including using standard data protection clauses adopted by the European Commission, where relevant). If you require any information about these safeguards, you may contact data.protection@admin.ox.ac.uk.

Will the study involve genetic tests?

Yes. Some blood will be used to look at the pattern of expression of your genes responsible 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. You will not be able to be identified by the results of any of these tests however, your DNA is unique to you so the results can never be completely anonymous.

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 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. Responsible members of the University of Oxford and the funders financial team may also be given access to data in order to process, monitor and/or audit participant reimbursement payments. 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. We will store any research documents with personal information, such as consent forms, securely at the University of Oxford for 5 years after the end of the study. The need to store this information for longer will be subject to ongoing review. Anonymised research data may 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. Your information may also be shared with partners working with Oxford University (e.g. staff at RUMC). 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

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 may be taken at the screening visit. We will securely retain copies until the end of the study.

Your bank details will be stored for 7 years in line with the University of Oxford's 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 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.

If you only complete the online screening your data will not be kept beyond the end of the study.

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 necessary regulations. They will conduct a site visit to prepare and set up the study 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.

Private Medical 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.

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 the 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.

Future 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. If you agree to your details being held to be contacted regarding future research, we will retain a copy of your consent form securely until such time as your details are removed from our database. We will keep the consent form and your details separate from one another and any research data. You can ask us to have your contact details removed from our database at any time.