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REC Ref-18/SC/0679

PARTICIPANT INFORMATION SHEET: VAC 072

A study to test a new malaria vaccine: R21 plus Matrix-M

A Phase I/IIa Sporozoite Challenge Study to assess the safety, immunogenicity and protective efficacy of adjuvanted R21, administered in different dose schedules in healthy UK volunteers.

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

What is the purpose of the study?

Malaria is a major global health problem, with approximately 214 million cases and 438,000 deaths each year. There is a great need for a safe, effective malaria vaccine as the range of malaria medicines is limited and drug resistance is increasing. Currently there is no approved malaria vaccine.

The purpose of this study is to assess two types of malaria vaccines in different combinations and at different doses. The study will enable us to assess:

1. The ability of the vaccines to prevent malaria infection.
2. The safety of the vaccines in healthy participants.
3. The response of the human immune system to the vaccines.

We will do this by giving approximately 62-66 participants three doses of vaccines over 2 to 6 months. We will allocate participants to different groups: some of these will only receive vaccinations whereas others will additionally be exposed to malaria infection by allowing malaria-infected mosquitoes to bite under carefully regulated conditions. We will follow these participants closely to observe if and when they develop malaria. If the vaccines provide some protection against malaria, participants will take longer than usual to develop malaria, or will not develop malaria at all. We will also recruit around 12-16 individuals to be control subjects – these participants won't receive any vaccinations but will be infected with malaria. Control group participants in VAC072 may also serve as controls in other trials participating in the same malaria challenge experiment carried out by the Jenner institute.

Malaria exposed volunteers who do not develop malaria infection after being challenged with malaria the first time may be invited back to be infected with malaria again in a repeat challenge experiment. This would happen approximately 5-7 months after the first challenge and would be optional. Follow-up after this second challenge will last approximately 3 months. Up to 8 individuals will be recruited to be control subjects for the repeat challenge. The purpose of this second challenge is to see how long the protection of the investigational malaria vaccine lasts. You do not need to agree to take part in the second challenge in order to take part in this study.

We will also recruit some participants to receive vaccinations only (without exposure to malaria infection) in order to test the safety and immune response induced by the vaccines.

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 to which you are otherwise entitled. If you do decide to take part, you will be given this information sheet to keep (or be sent it electronically) and be asked to sign a consent form. You are free to withdraw at any time and without giving a reason, but you may be asked to return to the clinic for follow up for safety reasons.

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

What will happen if I decide to take part?

This study involves having three vaccinations given at different times or acting as a control (no vaccinations). This will depend on which group you are in.

Group Allocation: After recruitment of the 3 volunteers in group 1a has been completed, participants will be able to choose whether they take part in a vaccine only, vaccine plus challenge or challenge only (control) group. The trial is unblinded to participants, so you will know what treatments you receive.

Groups 1a and 1b: Group 1a and 1b participants will receive the vaccinations only, without undergoing exposure to malaria infection. This is to test the safety of the vaccine and its ability to generate an immune response.

Groups 2a & 3a: Groups 2a and 3a participants will be vaccinated at different times over 2 to 6 months. This will be followed by controlled exposure to malaria infection. If participants in these groups are found to be protected from malaria, they may be invited to a repeat malaria challenge at a later time

Groups 2b & 3b: Groups 2b and 3b participants will be vaccinated at different times over 2 to 6 months. These participants will not undergo exposure to malaria infection. If volunteers in Groups 2a and 3a are no longer able to participate in the malaria challenge, with consent, they may be asked to join Groups 2b and 3b respectively. Similarly, volunteers in Groups 2b and 3b, with consent, may be asked to join Groups 2a and 3a if a volunteer from one of these groups becomes ineligible.

Groups 4a, 4b &5: Similar to Groups 1a & 1b, these groups will receive vaccinations only.

Groups 6&7: Group 6 will be challenged with malaria at the same time as groups 2 and 3 but will not be vaccinated, serving as a *control* group. Similarly, group 7 will be recruited to serve as a further unvaccinated control group for the re-challenge of groups 2a and 3b.

The groups are summarised in the table on the following page.

Length of research

If you decide to take part in this study, you will be involved in the trial for approximately 8 to 18 months, depending on which group you are in.

Participants in groups 2a and 3a who are protected from malaria following the first challenge, and who choose to take part in the second malaria challenge, will continue for approximately 8 - 13 months in total.

Week	0	4	8
Group 1a (n=3)	10µg R21/50µg MM	10µg R21/50µg MM	10µg R21/50µg MM
Group 1b (n=7)	10µg R21/50µg MM	10µg R21/50µg MM	10µg R21/50µg MM

Week	0	4	24	28	48-56
Group 2a (n=16)	10µg R21/50µg MM	10µg R21/50µg MM	10µg R21/50µg MM	CHMI	Repeat CHMI**
Group 2b (n=2)	10µg R21/50µg MM	10µg R21/50µg MM	10µg R21/50µg MM		

Week	0	4	8	12	32 - 40
Group 3a (n=16)	10µg R21/50µg MM	10µg R21/50µg MM	10µg R21/50µg MM	CHMI	Repeat CHMI**
Group 3b (n=2)	10µg R21/50µg MM	10µg R21/50µg MM	10µg R21/50µg MM		

Week			0	0
Group 6 (n=6-8)	CONTROL GROUP	*NO VACCINATIONS*	CHMI	
Group 7 (n=6-8)	CONTROL GROUP	*NO VACCINATIONS*		CHMI

Week	0	4	24
Group 4a (n=3)	50µg R21/50µg MM	50µg R21/50µg MM	10µg R21/50µg MM
Group 4b (n=5-7)	50µg R21/50µg MM	50µg R21/50µg MM	10µg R21/50µg MM

Week	0	4	24
Group 5 (n=8-10)	10µg R21/50µg MM	10µg R21/50µg MM	2µg R21/50µg MM

Group Summary Table

*n= number of participants in group, **MM** = Matrix-M, **CHMI** = controlled human malaria infection, ****optional repeat CHMI for volunteers found to be protected against malaria in the initial CHMI.*

Am I eligible to be involved in the trial?

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

- A healthy adult aged 18 to 45 years.
- Able and willing (in the Investigator's opinion) to comply with all study requirements.
- Willing to allow the investigators to discuss your medical history with your General Practitioner and/or access your electronic medical records.
- Women only: Must practice continuous effective contraception for the duration of the study.
- Agreement to refrain from blood donation during the course of the study and
- Agreement to refrain from blood donation for at least 3 years after the end of their involvement in the study.*
- Give written informed consent to participate in the trial.
- Reachable (24/7) by mobile phone during the period between CHMI and completion of antimalarial treatment. *
- Willingness to take a curative anti-malaria regimen following CHMI. *
- For volunteers not living close to the malaria challenge follow-up site (CCVTM, Oxford) agreement to stay in a hotel room close to the trial centre during a part of the study (from at least day 6.5 post mosquito bite until anti-malarial treatment is completed).*
- Answer all questions on the informed consent quiz correctly.*

You cannot participate in this study if and of the following apply:

- You have had malaria before.
- You have travelled to a significantly malaria endemic region in the past 6 months, or are intending to travel to a significantly malaria endemic region during the study period.

- You have used antibiotics which could treat malaria in the 30 days prior to malaria*
- You have received an investigational product in the 30 days preceding enrolment, or planned receipt during the study period.
- You have received an investigational vaccine likely to impact on interpretation of the trial data as assessed by the investigator.
- You have problems with your immune system.
- You have had any immunoglobulins or blood products within 3 months prior to enrolment.
- You have a history of allergic disease or reactions likely to be exacerbated by any component of the vaccine (e.g. egg products), by malaria infection or by the medications used to treat malaria infection.
- You have sickle cell anaemia, sickle cell trait, thalassaemia or thalassaemia trait or any haematological condition that could affect susceptibility to malaria infection.
- You are pregnant, breast feeding or intend to become pregnant during the study.
- You have any medical conditions or take any medications which may affect the treatment given to treat malaria infection.*
- You have a history of cancer.
- You have a history of serious psychiatric condition that may affect participation in the study.
- You have any other serious chronic illness requiring hospital specialist supervision.
- You drink on average more than 25 standard UK units every week.
- You have injected drugs in the 5 years preceding enrolment.
- You have Hepatitis B, Hepatitis C or HIV infection
- You have close family members who have developed heart disease when aged less than 50 years.*
- You are unable to be closely followed up for the duration of the malaria challenge.*
- You have any clinically significant abnormal finding on blood tests, urinalysis or clinical examination.

**** = Not applicable for volunteers who do not undergo malaria challenge***

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

CONSIDERATIONS BEFORE TAKING PART IN THIS STUDY

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

Blood Donation: Under current UK regulations, participants will not be able to donate blood during the study or for 3 years after the end of the trial. At this point, The National Blood Transfusion service can test your blood to see whether or not you are able to donate blood again. If you are positive for certain antibodies, you will not be able to donate blood again in the UK. It is not possible to determine in advance whether you will still have a positive antibody test as a result of the trial after 3 years.

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

Contraception: It is currently unknown whether the vaccines being tested are safe during pregnancy. Also, malaria infection can be particularly dangerous during pregnancy to both the mother and the foetus. For this reason, it is important that all women use adequate contraception throughout the trial. If you were to become pregnant during the trial you must tell us immediately and you will be withdrawn from the study, although we will ask to follow you up for safety reasons.

Antimalarial Medication: Volunteers will take Riamet, an antimalarial medication, for three days to treat malaria infection. As Riamet may temporarily reduce the effectiveness of hormonal contraceptives, women taking hormonal contraceptives will need to use an additional form of contraception (e.g. condoms) while taking Riamet, and until the start of the next menstrual period after Riamet treatment. A pregnancy blood test will be carried out at screening and before malaria challenge. Additionally, urinary pregnancy tests will be carried out just prior to each

study vaccination, before malaria challenge, and again before anti-malarial treatment is started.

VACCINATIONS

What are the vaccines that are being tested?

We are testing a malaria vaccine candidate that contains two components: R21 and Matrix-M. The vaccine will be injected into the muscle of your upper arm on 3 different occasions.

R21

R21 is a protein particle, which is produced by combining a protein from Hepatitis B with the circumsporozoite protein (CSP) of the malaria parasite. CSP is a protein required by the malaria parasite to get into liver cells. We are hoping to make the body develop an immune response to this protein, in order to stop the malaria parasite from getting into liver cells.

R21 is highly similar to R21c, which has been tested in over 80 healthy volunteers (combined with Matrix-M) in phase I/IIa studies so far. The end of the R21c protein contains 4 extra amino acids (the building blocks of proteins) compared to R21. Due to a change in the manufacturing process, these extra 4 amino acids are no longer required. As the alteration from R21c to R21 is minor, it is unexpected to affect its safety and ability to generate an immune response, however this trial will seek to confirm this. Side effects from the R21c + Matrix-M vaccine were comparable to another similar vaccine RTS,S, which has already been tested in more than 10,000 babies and children. It was found to be safe and well tolerated but can cause temporary side effects as detailed in the section titled "What are the risks of taking part in the study?".

Matrix-M

Matrix-M is a vaccine component used to boost the immune response, which will be given in combination with R21 for volunteers in Groups 1-5. It has been shown to boost the immune response when given in combination with an influenza vaccination. It has also been tested clinically in combination with a different malaria vaccine. Overall, Matrix-M has been given to over 1400 healthy volunteers and has been safe and well tolerated. Volunteers may experience temporary side effects as mentioned in the section titled "What are the risks of taking part in the study?".

VISITS

Screening Visit: This takes place at your local study site (Centre for Clinical Vaccinology and Tropical Medicine (CCVTM), University of Oxford) up to 3 months before the study starts and will last up to two hours. The purpose of the screening visit is for you to discuss the trial with us and decide if you wish to enter the study. If you decide to participate, you will be asked to complete a questionnaire assessing your understanding of the study in order for us to be confident that you fully understand what taking part will involve. You will then be asked to sign a consent form and we will check that you are eligible to participate.

During the screening visit:

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

The screening blood tests will look at your blood counts (e.g. to check if you are anaemic), your liver and kidney function, and your magnesium levels. We will also test your blood to see if you are infected with hepatitis B, hepatitis C or HIV, as these conditions can affect your body's response to the vaccines we are assessing. If you test positive to any of these, we will let you know and offer to refer you for treatment.

Vaccination days and follow-up visits post-vaccination

If you are in one of the vaccine groups (**Groups 1-5**) you will receive 3 doses of the R21 and Matrix-M containing vaccines. Volunteers in Groups 6 and 7 will not receive these vaccinations. The number of visits you attend will depend on

the group you are allocated to (see table below).

Group	1A	1B	2A	2B	3A	3B	4A	4B & 5	6 & 7
Number of visits you will be required to attend:	14	13	44	18	42	16	20	19	31

Vaccination and follow up visits post-vaccination will take place at your local clinic site (). All women will have a urinary pregnancy test before each vaccination. We will ask all volunteers to wait for 60 minutes after each vaccination to check there are no immediate problems. You will then be given access to an electronic diary card (to record your symptoms), thermometer and tape measure to take away. We will ask you to use the diary card to record symptoms every day for 7 days after each vaccination and any other symptoms experienced for 28 days post-vaccination.

We may ask to photograph your vaccination site(s) and you can choose whether or not to agree to this when you sign the consent form. You will not be identifiable in these photographs, as only the vaccination site and your unique trial number will be visible. These photographs may be shown to other professional staff, used for educational purposes, or included in a scientific publication.

Visits may include a medical assessment, temperature, pulse and blood pressure readings, examination by a doctor if needed and blood tests. During the trial you may be asked to attend for an extra visit, for example, if a blood test needs to be repeated. You will be compensated for the time and inconvenience of any extra visits.

Clinic visit before challenge: Groups 2a, 3a, 6 and 7

Participants in groups 2a, 3a, 6 and 7 will be asked to attend clinic for a review, blood test and, for female participants, a pregnancy test, a day or two before the malaria challenge to ensure you are completely healthy and can safely be infected with malaria. This visit will take place at your local clinic site (CCVTM).

THE MALARIA CHALLENGE (Groups 2a, 3a, 6 and 7)

The best way of assessing how well new malaria vaccines work is to test whether they protect against malaria. We will do this in this trial by exposing participants to malaria under carefully controlled conditions, which involves exposure to malaria infected mosquitoes. We call this process of deliberate exposure to infection a *malaria challenge*.

What happens during the Malaria Challenge?

The challenge involves spending the whole day at **Imperial College in West London.** Transportation to and from Imperial College will be provided. You will be bitten by up to five malaria-infected mosquitoes contained in paper cups with a gauze screen over the top. The cup is placed on the skin of the forearm, as most participants prefer this site. However, if you prefer another site then we can try putting the cup there. It will need to stay in place for between five and fifteen minutes to allow the mosquitoes to feed. Once they have fed, the cup will be removed and the mosquitoes examined for signs of blood and parasites. If this examination reveals that you have not received the required number of infected bites, then additional mosquitoes will be allowed to bite until you have received 5 infected bites. This process can take up to 2 hours.

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

What happens at follow up after the Malaria Challenge?

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

Days 6-23 after Malaria Challenge

We will review you in clinic once on Day 6 following malaria challenge and then twice a day until Day 14 following challenge. From Day 15 until Day 21 after challenge, or until you have completed antimalarial treatment if you

develop malaria, we will review you in clinic once a day. You will be asked to remain local to Oxford for careful monitoring and regular review by the study team, until you have had two malaria tests showing a significant decrease in parasites after starting antimalarial treatment or completing 2 days of antimalarial treatment from Day 21 if you do not develop malaria.

For all volunteers that have been recruited either in Oxford, Southampton or London, all clinic visits will take place at the Centre for Clinical Vaccinology & Tropical Medicine (CCVTM) at the Churchill Hospital in Oxford. These volunteers will be asked to remain in Oxford for the duration of follow up after malaria challenge. If you do not normally live in or close to Oxford, or if you joined the study at the London or Southampton sites, accommodation will be provided for this time, as well as transportation to and from Oxford.

We will ask you to complete a medication diary card on which you will be asked to record all medications that you take. At each visit, which will last approximately 10 minutes, we will ask about symptoms of malaria, measure your pulse, blood pressure and temperature, and take a blood sample which will be tested for malaria parasites. The total number of visits post challenge will vary depending on when and if you get malaria. It is important you are able to attend all the visits. **If you plan to travel outside of Oxford during Days 6 to 23 post challenge, then you should discuss your plans with one of the study physicians before participating in this study.**

If you are diagnosed with malaria you will be immediately started on a course of antimalarial tablets. Usually the blood test result is available after you have left the clinic so we will contact you by telephone and ask you to return to the CCVTM, Oxford as soon as possible to start treatment. It is therefore essential that we can contact you at all times on your telephone and that you are available to return to your designated follow-up clinic to start treatment at short notice any time between Day 6 and Day 21 post challenge. You **must** also provide a name and 24-hour phone number for someone who lives near to you and who will know where you are for the duration of the study. If you fail to attend for review during the 23 days after challenge and are un-contactable we will contact this person.

Our experience tells us that the malaria parasites should disappear from your blood within 2 or 3 days of starting the treatment. If you do develop malaria, then you will be seen each day during the treatment until the malaria parasites have significantly decreased in your blood on two consecutive days. When you finish treatment, we will give you a diary card on which to note when any ongoing symptoms of malaria stop. Once malaria has been diagnosed and treated, with 2 consecutive blood tests confirming the success of the treatment, the twice daily / daily visits and blood tests after challenge will no longer be required.

If you become unwell with malaria then you may be admitted to the Infectious Diseases ward, Oxford University Hospitals NHS Foundation Trust as a precaution until you have recovered, but it is very unlikely that this will be necessary.

If the vaccines do not work, or you are in the control group, you are most likely to develop malaria between Day 7 and Day 14 following challenge. If the vaccines protect you against malaria you may develop malaria later than Day 14, or not at all. If we do not find malaria parasites in your blood by Day 21 post challenge, then we will presume the vaccines have protected you against malaria but will give you a course of antimalarial treatment anyway to kill any undetected parasites.

Days 35 and 90 after Malaria Challenge

You will be seen in clinic on Day 35 and Day 90 post challenge. At these visits a blood sample will be taken. The appointments will last about 10 minutes and will take place at your local clinic site (i.e. Oxford, London or Southampton).

REPEAT CHALLENGE

If you are a group 2a or 3a volunteer and do not develop malaria infection in the blood after the malaria challenge this may mean that the vaccine had some effect at preventing malaria infection. However, you should still assume that you are not protected from malaria infection and take all the usual precautionary measures you would otherwise take if you travel to an area where there is malaria.

You may be invited to take part in a repeat challenge experiment. If you decide to take part in the second challenge you will be asked to attend a screening visit, which will take place up to 3 months before the repeat challenge. This screening visit will be similar to the first screening visit and you will be asked to sign a consent form for the repeat challenge. We will check that you are still eligible to participate and will conduct the same tests as at the first screening visit. Your participation in the repeat challenge is at the discretion of the researchers.

As before, a clinic visit will be conducted the day before the second challenge, and the challenge and follow up visits will be the same as for the first challenge (as described above) up to and including the visit 90 days after mosquito bite.

WHAT ARE THE RISKS OF TAKING PART IN THE STUDY?

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

1. **Blood Tests**

The total volume of blood taken during the study depends on the group. The amount taken at each visit will vary between 2.5ml (half a teaspoon) and 100ml (around 6 tablespoons). The volume of blood being taken over the course of the trial should not cause any problems in healthy people. There may be some temporary mild discomfort, such as bruising and tenderness, at the site from which blood is taken. You may experience faintness as a result of collecting blood. We will give you a copy of your blood tests if you request them and will only send the results to your GP if you wish us to.

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

- Red and white blood cells
- Liver and kidney function
- Blood borne viruses (HIV, hepatitis B & C)
- Magnesium
- HLA type
- RNA tests
- Malaria parasites (for diagnosis after challenge)
- Immune responses to vaccines and to malaria infection

2. **Vaccination Side Effects (Groups 1-5 only)**

It is likely that you will experience some symptoms at the vaccination site as well as general symptoms due to vaccination. It is important to remember this vaccine is in the early stage of development and the amount of safety data available is limited. For this reason, there is a chance you could experience a side effect that is more severe than that described below. Although the combination of R21c and Matrix-M has been tested in 80 healthy volunteers in phase I/IIa clinical trials previously, this will be the first time that R21 (rather than the slightly modified variant R21c) has been tested in humans. We can predict from past experience what the symptoms should be like with these schedules. We don't expect any new symptoms and we expect that symptoms will be mild in strength most of the time, although symptoms may also be moderate or severe. All symptoms should resolve completely within a few days.

Local Reactions:

You may experience some discomfort at the injection site as the vaccination is given. This usually gets better in 5 minutes. Later, you might experience pain resulting in some difficulty moving your arm, but this should resolve within a few days. In addition to pain, you may experience redness, swelling, or warmth at the injection site.

General reactions:

During the first 24 - 48 hours after vaccination you may experience flu-like symptoms such as muscle aches, joint aches, feverishness, chills, headache, nausea, tiredness and/or feeling generally unwell. These symptoms should usually resolve within a few days.

You are encouraged to take over the counter medications, such as paracetamol or ibuprofen, as soon as you experience these symptoms as they are likely to reduce the intensity of any symptoms you have.

Serious Reactions:

With any vaccination there is a risk of rare serious adverse events, such as an allergic reaction, which may be related to the nervous system or the immune system. Severe allergic reactions to vaccines (anaphylaxis) are rare but can be fatal. Reactions in the nervous system are also extremely rare but can cause an illness called Guillain-Barré syndrome. This is a condition in which people can develop severe weakness and can be fatal. These adverse events

have not previously been seen following administration of the R21c or RTS, S vaccines.

The investigators are contactable any time if you are concerned about any possible vaccine side effects.

3. Mosquito Bites (Groups 2a, 3a, 6 and 7 only)

The mosquitoes that we are using have been laboratory-reared under very careful conditions by mosquito experts. They are infected with a strain of malaria (Plasmodium falciparum) that we know can be cured by antimalarial medications. There are other diseases that may be transmitted by the bite of a mosquito. However, the strains of mosquitoes that we are using have never shown any evidence of other mosquito-transmitted diseases and therefore the chance of contracting one of these diseases is very low.

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

4. Malaria Infection (Groups 2a, 3a, 6 and 7 only)

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

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

In the unlikely event that it is necessary, you may be admitted to the Infectious Diseases ward, Oxford University Hospitals NHS Foundation Trust. In the last 10 years, only 4 participants out of more than 400 challenged with malaria in Oxford have required hospital admission. There have been no long-term problems in participants challenged with malaria.

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

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

It is important that you understand that if you fail to attend a clinic appointment after challenge, but before you

have completed a full course of antimalarial therapy, the police may be notified, and your name may be released to the national media in order to find you.

There are no known long-term side effects of contracting or being treated for malaria. For 6 months after the challenge you should contact a doctor if you develop any of the symptoms of malaria as detailed above. In this circumstance, please contact one of the study doctors or your General Practitioner and remind them that you have been involved in this study. If you have any queries or concerns once the study is over, please do not hesitate to get in touch with us.

5. Treatment of Malaria (Groups 2a, 3a, 6 and 7 only)

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

A treatment course of Riamet consists of 6 doses of 4 tablets. The first 4 tablets will be given when diagnosis is made, followed by additional doses after 8, 24, 36, 48 and 60 hours. We will need to watch you take at least three of these doses. We will continue taking blood to look for parasites until 2 consecutive blood tests show a significant decrease in number of malaria parasites. Blood tests usually become negative for malaria parasites after 24-48 hours of treatment. Tablets should be taken with a meal or snack. We will provide a light snack with the doses of Riamet that we observe at the clinic. You should avoid taking grapefruit juice while taking Riamet.

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

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

6. Treatment of Symptoms Associated with Challenge (Groups 2a, 3a, 6 and 7 only)

Provided there are no medical reasons not to, all participants will be given some medications to help with symptoms associated with malaria challenge. These are licensed, commonly used, medications. If you wish you can see the sheets from the manufacturers, provided inside the packets of these medications, prior to taking part in the study. As with all medications, these drugs can cause a severe allergic reaction in a small number of people. If you develop any concerning symptoms you should contact the trial doctor immediately on the emergency contact number, you will be provided with.

Antihistamine Cream: Antihistamine cream can help reduce the itch and redness associated with mosquito bites. Antihistamine cream is generally well tolerated. However, there is a risk of local redness, swelling or itching in the area where the cream has been applied.

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

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

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

OTHER INFORMATION

Blood Tests

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

Abnormal Results

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

Expenses and Payments

You will be compensated for:

Screening Visit:	£25
Travel expenses:	£15 per visit
Time required for visit:	£20 per hour
Inconvenience of blood tests:	£10 per blood donation
Illness compensation	£480

Group No.	Time in Trial (approx.)	Maximum No. of Visits	Compensation Amount (up to)
1a	8 months	14	£700
1b	8 months	13	£655
2a	10 months	44	£2,700
2b	10 months	18	£880
3a	6 months	42	£2,610
3b	6 months	16	£790
4a	18 months	20	£970
4b & 5	18 months	19	£925
6/7	3 months	31	£1,800

If you choose to leave the study early, or are withdrawn from the study, you will be compensated according to the length of your participation based on these figures. The visits at day 182 (groups 2a only) and day 70 (group 3a) are optional and you will be able to choose to not attend, in which case you will receive £45 less compensation than listed in the table above. You should note that compensation payments received in this trial may have an impact on your entitlement to benefits.

If you are in Group 2a or 3a and undergo re-challenge 5-7 months after the initial challenge, you will attend additional visits, undergo additional blood tests, and receive additional compensation. These additional visits, blood tests and compensation will be roughly equivalent to a further £1800.

'Back-up' participants

In addition to the participants to be included in the study, we will also recruit a small number of back-up

participants. Back-up control participants will complete the clinic visit day before challenge but will not necessarily undergo challenge. These 'back-up' participants will be asked to be available to take part in the challenge part of the study at short notice if another participant is unable to take part at the last minute. We will recruit up to a total of 6 back-up control participants (two for each control group). If back-up participants do not undergo challenge, they will be compensated in addition to compensation for visits they have already attended (e.g. screening and day before challenge).

What alternatives are present?

Your alternative is not to participate in this study.

What are the possible benefits of taking part?

This study will not benefit you, but the information gained from the study might help to develop an effective malaria vaccine and prevent malaria infection and disease in those living in areas where malaria is common and in travellers to those areas. At present, there is no malaria vaccine licensed anywhere in the world. There are other malaria vaccines in various stages of development.

What if relevant new information becomes available?

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

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

If, at any time after agreeing to participate, you change your mind about being involved with this study you are free to withdraw without giving a reason. Your decision will not result in any penalty, or loss of benefits to which you are otherwise entitled. **However, if you wish to leave after malaria challenge then you must take the treatment course of Riamet (or an agreed alternative) because of the potentially very serious consequences of untreated malaria infection.** Unless you state otherwise, any blood taken whilst you have been in the study will continue to be stored and used for research as detailed above. You are free to request that your blood samples are destroyed at any time during or after the study.

What if there is a problem?

If you are harmed as a result of taking part in this study, the study doctor can advise you of further action and refer you to a doctor within the NHS for treatment, if necessary. The University of Oxford, as Sponsor, has appropriate insurance in place in the unlikely event that you suffer any harm as a direct consequence of your participation in this trial. NHS indemnity operates in respect of the clinical treatment which may be provided if you needed to be admitted to hospital.

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

Complaints statement

If you wish to complain about any aspect of the way in which you have been approached or treated during the course of this study, you should contact your local trial team (contact details at the end of this document) or you may contact the University of Oxford Clinical Trials and Research Governance (CTRG) office on 01865 616480 or the head of CTRG, email ctrg@admin.ox.ac.uk.

Will my taking part in this study be kept confidential?

All information that is collected about you during the course of the research will be coded with a study number and kept confidential. The information is available to the study team, safety monitors, ethical review committees, Sponsors, government regulatory agencies, authorised collaborators and external monitors who can ask to audit or monitor the study. Any information about you that leaves the hospital or clinic will have your name and address

removed so that you cannot be identified from it. Your information is stored electronically on a secure server and any paper notes are kept in a locked filing cabinet.

Involvement of the General Practitioner/Family doctor (GP)

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

Prevention of 'Over Volunteering'

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

You will be asked to provide a form of identification at the screening visit (passport, drivers licence or national ID card) which will be photocopied and retained for the duration of the study.

What will happen to any samples I give?

If you consent, some of your leftover blood samples will be stored at the Oxford Vaccine Centre Biobank and may be used for further studies of the human body's immune response and/or the vaccines used in this study. Any such tests will have an appropriate ethical review. Upon your request at any time, your remaining blood samples will be destroyed. Your participation in this study will not be affected by your decision whether to allow storage and future use of your leftover samples.

More information around the procedures for long term storage of your samples is available in the Oxford Vaccine Centre Biobank information booklet and you will be asked to sign a separate consent form if you agree to have your samples stored for future use in ethically approved research.

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

Will any genetic tests be done?

Yes. Some blood will be used to look at the pattern of your genes that can affect the immune system (including your 'human leukocyte antigen' [HLA] type). The immune response to vaccines is in part genetically controlled, so knowing your pattern of genes that regulate immune responses may help us to understand the responses to vaccination. We may also look at the expression of certain genes which relate specifically to the immune response to malaria. You can opt out of 'genetic tests' if you wish, without any effect on your participation in the trial.

What will happen to the results of the research study?

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

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

Who is sponsoring, organising and funding the research?

The study is organised by the University of Oxford. The study is funded through financial support to Oxford

University through an award from the Wellcome Trust. 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 Research Ethics Service (RES) Committee **South Central Oxford A** Research Ethics Committee and has been given a favourable ethical opinion. The Medicines and Healthcare products Regulatory Agency (MHRA), which regulates the use of all medicines in the UK, has reviewed the study design and has granted permission to use these unlicensed vaccines in this clinical study.

Additional information regarding your privacy

Sponsor

The University of Oxford is the sponsor for this study based in the United Kingdom. We will be using information from you in order to undertake this study and will act as the data controller for this study. This means that we are responsible for looking after your information and using it properly. The University of Oxford will keep identifiable information about you for up to 15 years after the study has completed. If you agree to your samples being used in future research, your consent form will be held securely until the samples have been used up. Your bank details will be stored for 7 years in accordance with University of Oxford financial policy.

Your rights to access, change, or move your information are limited, as we need to manage your information in specific ways in order for the research to be reliable and accurate. If you withdraw from the study, we will keep the information about you that we have already obtained. To safeguard your rights, we will use the minimum personally identifiable information possible. You can find out more about how we use your information by contacting **vaccinetrials@ndm.ox.ac.uk.**

Site and Researcher

CCVTM will collect information from you for this research study in accordance with our instructions. CCVTM] will use your name, NHS number, and contact details to contact you about the research study, make sure that relevant information about the study is recorded for your care, and to oversee the quality of the study. Individuals from the University of Oxford and regulatory organisations may look at your medical and research records to check the accuracy of the research study. CCVTM will pass these details to the University of Oxford along with the information collected from you. The only people in the University of Oxford who will have access to information that identifies you will be people who need to contact you regarding your participation in the trial or audit the data collection process. The people who analyse the information will not be able to identify you and will not be able to find out your name, NHS number or contact details. CCVTM will keep identifiable information about you from this study in accordance with local NHS trust policies up to a maximum time of 15 years.

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

Contact details for further information:

Volunteer Recruitment Co-ordinator

Email: vaccinetrials@ndm.ox.ac.uk

Phone: 01865 611424

Timetable for Vaccinations and Follow up

Group																				
1A	Visit number	1	2	3	4	5	6	7	8	9	10	11	12	13	14					
	Timeline (days)	(Screening)	0	3	7	14	28	35	42	56	57	63	70	84	224					
Group																				
1B	Visit number	1	2	3	4	5	6	7	8	9	10	11	12	13						
	Timeline (days)	(Screening)	0	7	14	28	35	42	56	57	63	70	84	224						
Group																				
2A	Visit number	1	2	3	4	5	6	7	8	9	10	11	12	13	*[14]*	***Malaria Challenge and Follow up Visits (see next page)***				
	Timeline (days)	(Screening)	0	3	7	14	28	35	42	56	84	168	169	175	*182*					
Group																				
2B	Visit number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	
	Timeline (days)	(Screening)	0	3	7	14	28	35	42	56	84	168	169	175	182	196	210	231	286	
Group																				
3A	Visit number	1	2	3	4	5	6	7	8	9	10	11	*[12]*	***Malaria Challenge and Follow up Visits (see next page)***						
	Timeline (days)	(Screening)	0	3	7	14	28	35	42	56	57	63	*70*							
Group																				
3B	Visit number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16			
	Timeline (days)	(Screening)	0	3	7	14	28	35	42	56	57	63	70	84	98	119	175			
Group																				
4A	Visit number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
	Timeline (days)	(Screening)	0	3	7	14	28	35	42	56	84	168	169	175	182	196	210	231	286	336	504
Group																				
4B & 5	Visit number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
	Timeline (days)	(Screening)	0	7	14	28	35	42	56	84	168	169	175	182	196	210	231	286	336	504

GROUPs 6 and 7 will attend a screening visit and a further visit one day prior to the challenge period ** For group 2b & 3b:* These volunteers will not undergo malaria challenge, unless other participants in Groups 2a and 3a cannot take part in the challenge after they have enrolled. If these volunteers are not required for malaria challenge they will still be followed up for the same amount of time as those in the challenge groups to look at vaccine immune responses. The timetable for the challenge period (groups 2a, 3a, 6 and 7) is shown on the following page. Visits shown in square brackets "[]" are optional and you may choose to not attend.

Timetable of Visits: Malaria Challenge and post challenge period