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PARTICIPANT INFORMATION SHEET: BIO-005

A study to assess the safety and efficacy of an experimental malaria vaccine by infecting vaccinated and unvaccinated volunteers with malaria parasites

We are inviting you to take part in a research study. You are being asked to take part because you are 18 – 45 years old and have expressed interest in taking part in research. Before you decide, it is important for you to understand why the research is being done and what it involves. Please read the following information carefully. You can discuss it with friends, relatives and your GP/doctor if you wish. Take time to decide whether you wish to take part.

- **Part 1** tells you why the study is being done.
- **Part 2** tells you what the criteria for taking part are and what will happen during the study.
- **Part 3** tells you about any possible risks and benefits.
- **Part 4** tells you more about how the study will be carried out.

You can ask us any questions at your screening visit. You can also contact us on the email address at the top of the page. This information booklet has been reviewed by four members of the Oxford Vaccine Centre's patient and public involvement (PPI) team. The PPI team make sure the information is presented clearly.

Who can take part?	Healthy adults aged 18-45 (full criteria inside)
What vaccines are being tested?	Malaria vaccines **R78C** and **RH5.1** (Group 1 only)
Total participants	Up to 24 participants
Study aims	To test if the study vaccines prevent malaria illness
Trial site	Centre for Clinical Vaccinology and Tropical Medicine (CCVTM), Churchill Hospital, Oxford, OX3 7LE
Expenses and payment	Up to £5,360 (See page 15)
Risks of participation	Short-lived (usually <7 days) post vaccine symptoms such as arm pain and fever may occur. Short-lived malaria symptoms may also occur, e.g., fever, tiredness and muscle aches. Untreated malaria infection can result in serious illness. For your safety, we will ask that you are fully contactable and provide an emergency contact. We may contact the police if we cannot reach you. It is crucial that you come for all follow-up visits and take the malaria medication. We will monitor your safety closely. A full discussion of risks starts on page 16.
Benefits of participation	Taking part in this trial will help develop a safe and effective vaccine against malaria.
Visit schedule	41 to 53 visits over approximately 3 to 10 months.

	Most study visits will last approximately 15-30 minutes. Daily and twice-daily visits will be required for a short duration of this study.

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PART 1: THE PURPOSE OF THE STUDY

Why are we conducting this study?

Malaria is a major public health problem. Malaria is a disease caused by a parasite. It is spread by the bite of an infected mosquito. There were around 263 million cases of malaria and 597,000 deaths worldwide in 2023. Most of the deaths are in children under five in Africa. It is a big problem for those who live in affected areas and for travellers.

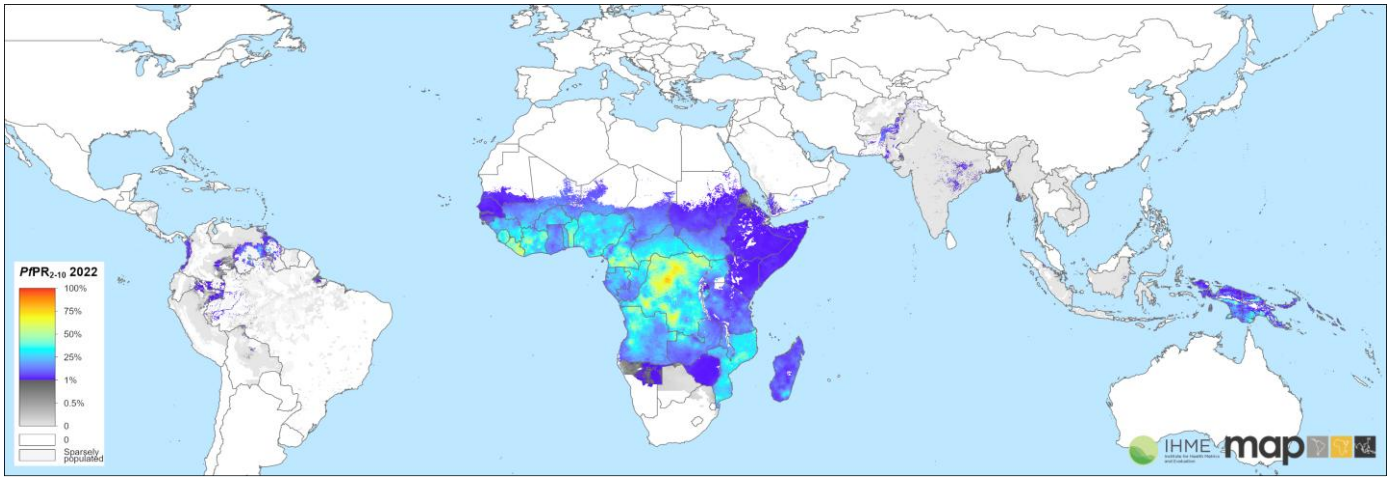


Figure 1: Map showing areas affected by malaria (Plasmodium falciparum)

There is a great need for a safe, effective malaria vaccine. This is because the number of medicines for treating malaria is limited. Commonly used medicines are also becoming less effective. Researchers around the world, including at the University of Oxford, have been working on malaria vaccines for many years.

There are now two approved vaccines for malaria recommended for children under 5 years of age in countries most affected. However, while these vaccines will save many lives, they give only partial protection. Also, multiple vaccine doses are needed to maintain protection. We are aiming to make a vaccine which is better at preventing serious illness and death and which works for longer.

This study is being done to look at two new malaria vaccines. We will test if they can prevent malaria illness. This is done using a 'blood-stage challenge model'. A '**challenge**' is when volunteers are infected with malaria parasites using malaria-infected red blood cells.

The vaccines we are testing in this study are called "**R78C**" and "**RH5.1**". They are given with an adjuvant (meaning 'to help') called "**Matrix-M**". This is a substance to improve the body's response to vaccination.

The aim is to use these vaccines and adjuvant to help the body make an immune response against the malaria parasite. This study will look at:

1. The **safety** of the R78C and RH5.1 vaccines in healthy people.
2. The **immune response** to the R78C and RH5.1 vaccines.
3. Whether R78C and RH5.1 vaccines can **prevent malaria illness**.

We will do this by recruiting participants into two groups and then exposing them to malaria:

- **Group 1**: we will give 11-13 volunteers three vaccinations. Approximately two weeks after the third vaccine, we will expose them to malaria by injecting a small number of red blood cells infected with malaria under carefully controlled conditions (this is called a **malaria challenge**). We will follow them closely to see when they develop malaria. If the R78C and RH5.1 vaccines provide any protection against malaria, then these people will take longer to develop malaria than usual. If the vaccines are very effective, they may not develop malaria at all.

- **Group 2**: We will recruit another 11 volunteers to be **control participants**, and 2 participants who will act as a **back-up** in case of any dropouts in this group. These 'control participants' won't receive any vaccinations but will be 'challenged' with malaria in the same way as Group 1. It is extremely important to have control participants. By control participants getting malaria after challenge, it proves our method of giving people malaria works. Otherwise, we may think our vaccines have worked when actually the malaria parasites in the blood cells weren't effective.

Did you know that approximately **600 people** have previously had a malaria challenge as part of a clinical trial in Oxford?
Watch this video to hear about their experiences

What are the vaccines being tested?

RH5.1 and **R78C** are both 'protein vaccines'. Protein vaccines contain small protein pieces from the parasite that causes malaria. These proteins have been chosen because they trigger a strong immune response. Protein vaccines have been used safely for decades.

RH5.1 is based on part of a malaria protein known as **RH5**. R78C is based on parts of malaria proteins known as **RIPR** and **CyRPA**. The malaria parasite uses **RH5, RIPR and CyRPA** together as a 'key' to get into red blood cells (see Figure *2* below). This is the main reason why people get sick from malaria.

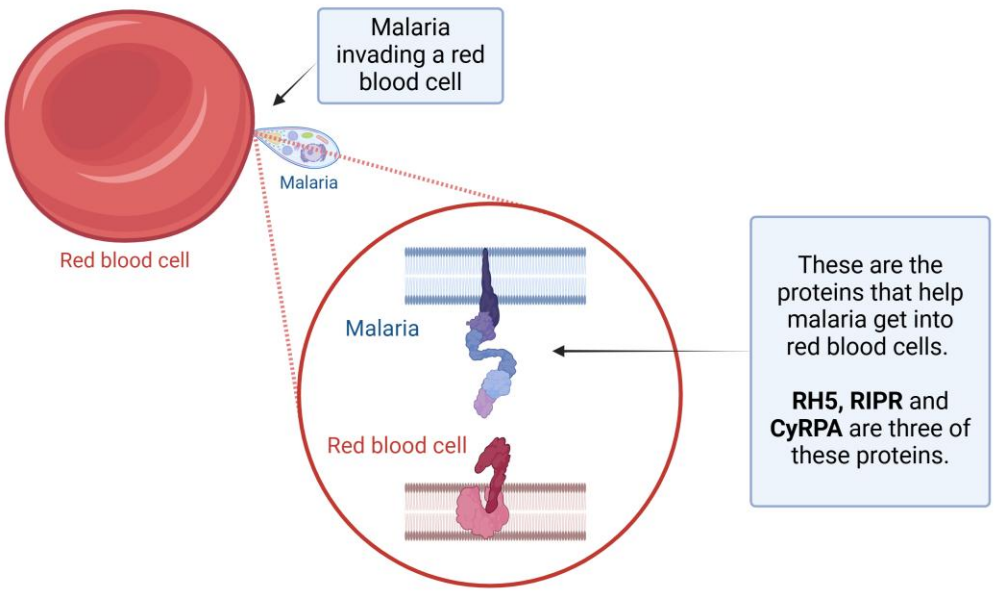


Figure 2: Illustration showing invasion of the red blood cells by malaria. Created in BioRender. Bardelli, M. (2024) BioRender.com

RH5.1 has been given to hundreds of people in previous trials in the UK, Tanzania and Burkina Faso. The vaccine was safe and well-tolerated in these trials. It also helped the body make a good immune response. Most importantly, the trial in Burkina Faso has shown that the vaccine can prevent over half of malaria cases in young children in the six months after vaccination.

R78C has been given to 25 people, either on its own or with **RH5.1**, in one trial in the UK (**VAC089**). It was safe and well-tolerated in this trial. The body's immune response to the R78C vaccine with RH5.1 looks even better than that to the RH5.1 vaccine alone. Due to these promising results, a trial in Tanzania is now being done, where adults and children will receive 3 doses of R78C and/or RH5.1.

Matrix-M has been given to tens of thousands of people in other trials. It has been shown to be safe and well tolerated. This includes trials of vaccines for malaria, COVID-19 and influenza. Matrix-M is approved for use in the UK as part of Novavax's COVID-19 vaccine.

By giving people **R78C and RH5.1/Matrix-M** we hope the body will develop an immune response that is even better than that seen against RH5.1 in previous studies. The ultimate goal is to find the best vaccine that helps the body prevent the malaria getting into the blood cells and so stop malaria illness.

Do I have to take part?

No. It is up to you to decide whether 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 asked to complete a **questionnaire** to check your understanding of the study. The purpose of this is to check your understanding of the study and not to exclude you from participating. However, you need to answer all questions correctly in order to take part. This will allow us to be sure that you fully understand what taking part will involve. If you don't answer all the questions right the first time, you will be able to complete it again after discussion with a study doctor. You will then be asked to sign a **consent form**.

You are free to withdraw from the study at any time without giving a reason. However, we may ask you to return to the clinic for safety reasons. If you have been infected with malaria and withdraw, you will still need to take anti-malaria medication.

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 take part in the study, or to withdraw from the study, will have no effect on your employment/student status at the University.

What will happen if I decide to take part?

(see also Summary box below)

You will either:

- Receive **three vaccinations** and then undergo challenge with malaria (**Group 1**)
  or
- Receive **no vaccines** and undergo challenge with malaria (**Group 2**)

We will also recruit 'back-up' participants in Group 1 and Group 2 who will either:

- Receive **three vaccinations** and **NOT** undergo challenge with malaria unless other participants drop-out **(Group 1 back-up participants)**

or

- Receive **no** vaccinations and **NOT** undergo challenge with malaria unless other participants drop-out **(Group 2 back-up participants)**

Both groups with also be given the option of undergoing a fine needle aspiration (FNA). This is an optional procedure and is explained in detail in the additional patient information sheet.

The study doctor will talk to you about which group you would be enrolled in.

Visits will take place in the **Centre for Clinical Vaccinology and Tropical Medicine (CCVTM).** This is at the Churchill Hospital in Oxford. The CCVTM clinic is wheelchair accessible, and we will try to meet all other accessibility needs wherever possible.

Length of research

- **Group 1** will be in the study for about **10 months** from the time they have the first vaccination. They will have **53 visits**.
- **Group 2** will take part in the study for about **3 months** from the time they are enrolled. They will have **41 visits**.

Summary box

	Vaccination?	Malaria challenge?	FNA	Duration	Number of visits
Group 1	Yes, three doses	Yes*	Yes (optional)	10 months	53
Group 2	No	Yes*	Yes (optional)	3 months	41

*two 'back-up' participants

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

Am I eligible to be involved in the trial?

In order to take part in the study you must be:

- A healthy adult aged between 18 and 45 years.
- Prepared to reside in the Oxford area for the duration of the challenge study.
- Able and willing to meet all study requirements.
- Willing to allow the study doctors to discuss your medical history with your GP.
- Willing to agree to never donate blood. The reason for this is explained below.
- Willing to meet the contraception requirements below.
- Able to be contacted by mobile phone 24 hours a day after you have been given the malaria challenge until you have completed malaria medication.

You cannot take part in this study if:

- You have had malaria before.
- You have previously received a malaria vaccine.
- You have travelled or are intending to travel to an area with malaria in the last 6 months or during the study period.
- You have received any blood products in the last three months. This includes a blood transfusion or immunoglobulins.
- You have had any other vaccine in the past 30 days. Or, you plan to have any other vaccine within 30 days of receiving the study vaccines. This is **apart from** COVID-19 and flu vaccinations which have a shorter exclusion period.
- You plan to have any other vaccine in the two weeks before the challenge until after completing anti-malaria medication (2-4 weeks after the challenge).
- You are taking part or planning to take part in another study using an experimental treatment.
- You have any problems with your immune system. This includes taking any medication that supresses your immune system.
- You have a history of allergies or reactions likely to be worsened by any part of the study vaccine, by malaria infection or by the medications used to treat malaria.
- You have previously had a severe allergic reaction to any trigger.
- You are pregnant, breast feeding or intend to become pregnant during the study.
- You have a history of cancer that is exclusionary based on the doctor's assessment.
- You have a history of a serious mental health condition that may affect your taking part in the study.
- You have any other serious long-term illnesses requiring hospital follow-up.
- You drink alcohol in a way that is harmful, or you are dependent on alcohol.
- 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 (BMI calculator).
- 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 (we will calculate this risk during your screening visit).
- You have an abnormal heart rhythm, or are taking certain medications which may affect the heart rhythm
- You have a family history of a particular heart rhythm called "QT prolongation" or sudden death; or a close family member who developed heart disease when aged less than 50 years.
- You are unable to take the study anti-malaria medication for any reason.
- You have certain specific blood conditions or any other blood condition that might affect susceptibility to malaria infection.
- You are unable to stay in the Oxford area from the day of challenge to up to 4 weeks following the malaria challenge.
- There are any other reasons that the study doctors think you should not join the study.

Mild conditions do not automatically stop you joining the study. An example could be childhood asthma which is well controlled. Additionally, regular medication and intake of supplements does not exclude you from taking part in this study but would need to be discussed with the study team. *If you have any questions about the eligibility criteria, you can contact the study team who will be able to advise you.*

If enrolled in the study, we may need to delay study vaccination if:

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

Is there anything else to think about?

Blood Donation

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

Medications

You should not take any medication other than those assessed as safe to take during a malaria challenge by the doctor at screening. This also applies for medications bought over-the-counter as well as certain supplements and vitamins.

Your health and well-being are much more important than the study. If you need any medication, then you should take it. However, it is very important that you let us know **before** you start on any medication. For example, any antibiotics that you take within 4 weeks of the planned challenge may affect the malaria parasite. **You should ask the prescribing doctor to discuss with a study doctor before you start the medication.** The study doctor may be able to advise an appropriate antibiotic that will treat you but won't interfere with the study.

Some other medications can interfere with the malaria medication you would receive. These include those used to treat infections, mental health conditions, and some heart issues. If you begin taking any new medication, please inform the study team immediately. This is especially important during the challenge period as some medications could reduce the effectiveness of the malaria medication or increase the risk

of side effects from the medication.

Pregnancy and Contraception

If you are able to become pregnant then you would need to be established on an effective method of contraception prior to the start of the study. This will be required to continue for the duration of the study. The possible effects of the study vaccines on an unborn baby are unknown. Also, malaria infection is more dangerous during pregnancy. Condoms alone are not considered effective enough.

Acceptable forms of contraception include:

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

Some participants may be given an anti-malaria medication called **Riamet** to treat malaria. Riamet may temporarily reduce the effectiveness of hormonal contraceptives. If you take hormonal contraceptives, you will need to use an additional form of contraception (such as condoms) while taking Riamet. This applies until the start of your next period. Free condoms are available at the Oxford Sexual Health Clinic in the Churchill Hospital and other NHS services which can be found here.

A urine pregnancy test will be done at screening and just before each study vaccination. A blood pregnancy test will also be done before malaria challenge and before starting anti-malaria medication.

If you become pregnant during the trial, we would not give you any further vaccinations and you would not proceed to the malaria challenge. However, we would like to follow you up for the rest of the study, and with your permission, until the end of your pregnancy. We would not routinely perform any further blood tests on pregnant volunteers. We would provide a letter of referral to your GP and/or specialist doctor if required who will manage your pregnancy further.

Private Insurance

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

Malaria Protection

You should not assume that the experimental vaccines you receive in this study will give you any protection against malaria. Make sure you visit your GP or a travel clinic before travelling to an area with malaria. You should follow their advice on prevention measures.

What will happen at the visits?

Screening Visit

First, we will check whether you are eligible to join the study. Following an **online pre-screening questionnaire (link)** we will contact you by telephone or email. You will have the chance to ask any more questions about the study at this point. We will also arrange for you to attend a screening appointment.

The screening appointment takes place up to 3 months before the study starts. It can last **up to two hours**. There will be a chance for a short break. The purpose of the screening visit is for you to discuss the trial with us and decide if you still wish to take part. If you do, we will ask you to complete a questionnaire to check your understanding of the study. We will also ask you to sign a consent form.

After signing the consent form:

- You will be asked some medical questions.
- A doctor will examine you.
- Blood samples will be taken for testing. These test results will need to be normal for you to take part in the study.
- A urine sample will be taken for a pregnancy test if you are able to become pregnant.
- An electrocardiogram (ECG) will be done. This checks the rhythm of the heart to make sure it is normal.
- We will also write a letter to your GP to make sure there are no other medical reasons preventing you from joining the study.

The blood tests will look at:

- Your blood count;
- Your liver and kidney function;
- Whether you have hepatitis B, hepatitis C or HIV. This is because these conditions can affect your body's response to the vaccines we are testing.
- Your cholesterol levels. This is to check your risk of heart disease in the next 10 years. You cannot take part in the trial if this risk is more than 1 in 20.

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

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

Vaccination Visits (Group 1 only)

The table below shows the vaccines that each group in the study will receive. This is for your information only.

Group	Month 0	Month 1	Month 6	Malaria challenge	FNA
1	R78C + RH5.1	R78C + RH5.1	R78C + RH5.1	Yes	Yes (optional)
2	-	-	-	Yes	Yes (optional)

Group 1 will each receive **three vaccinations** during the study. Vaccinations will be given into the muscle of the upper arm. Participants in Group 2 will not receive any vaccines and will **only** take part in the malaria challenge on the same day as Group 1.

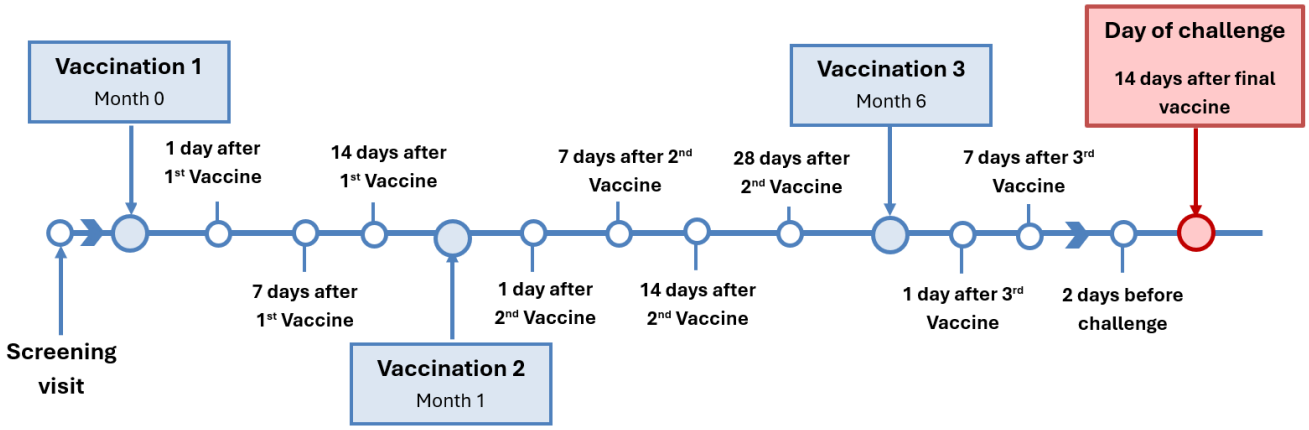
We will ask participants to wait for **60 minutes after each vaccination** to check there are no immediate problems. You may bring a book or other quiet activity to entertain yourself while you wait at the clinic during this observation period. You will be given a thermometer and tape measure to take away. We will also show you how to use the electronic diary. You will also be given a paper diary; in case you are unable to use the electronic diary. We will ask you to record your symptoms and any redness at the vaccination site (shoulder area) every day for 7 days after each vaccination. After the first 7 days, we will ask you to record only if you feel unwell or take any medications for a further 21 days.

We may ask to **photograph** your vaccination site. You can choose whether to agree to this when you sign the consent form. Your face, and other identifying features (e.g. tattoos/prominent scars), will not appear in these photographs. 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.

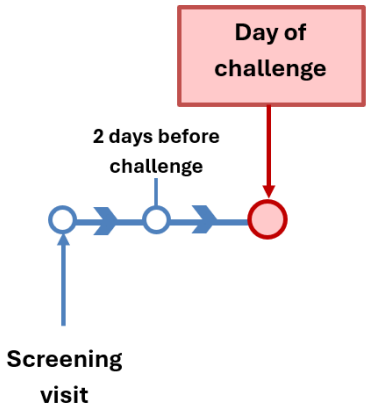
Follow-up visits

The diagram below shows the timing of post-vaccination follow-up visits up until the day of malaria challenge. Visits include a medical assessment and examination by a doctor if needed. We will also take temperature, pulse and blood pressure readings as well as blood tests. Follow up visits will be approximately 15-30 minutes in duration.

Group 1



Group 2



Group 1 back up participants

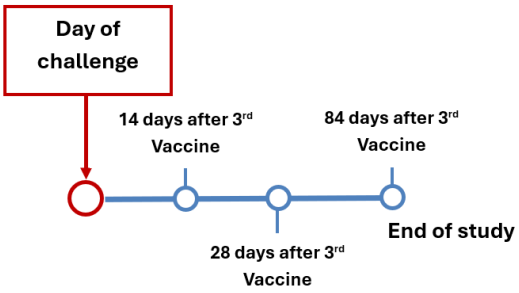


Figure 3: Diagram showing the vaccination schedule, follow-up visits and day of challenge.
Note: back-up participants in Group 1 would undergo the same vaccination schedule, would be present at the Day of Challenge (without receiving the challenge) and then would follow the Schedule in the final diagram.

The Malaria Challenge

What happens during the malaria challenge?

A challenge means that you will get infected with malaria. The best way of seeing how well new malaria vaccines work is to test whether they protect against malaria. The malaria challenge is 2 weeks after the vaccination group (Group 1) receive their final vaccination. All participants will need to attend CCVTM 2 days before challenge. We will check if there are any changes to your health. We will take blood tests and, if you are able to get pregnant, do a pregnancy test. On the day of challenge, an intravenous cannula (commonly known as a 'drip') will be inserted into a vein in your arm. A small amount of a salt solution containing red blood cells infected with malaria parasites will be injected into the vein. This will be about 5 ml or 1 teaspoonful. **You will need to stay in CCVTM for 60 minutes** after being given the injection, in case you have an immediate reaction.

What happens at follow-up after the Malaria Challenge?

The malaria challenge follow-up visits are very important for your safety. We need to assess you by phone once a day for the first 4 days. From day 5 onwards we will see you at the clinic once a day. Once your malaria parasite count in the blood rises higher, we will need to see you twice daily. This will continue until 21 days after challenge or until you are diagnosed with malaria (whichever happens sooner). From the 7th day after the malaria challenge, you should expect to **visit the clinic twice a day** until day 21, unless we tell you otherwise. All these clinic visits will take place at the CCVTM. **It is essential that you reside in Oxford during this time.** This is for careful monitoring and regular review by the study team. If finding accommodation in Oxford is difficult for you, you can discuss your options with the study team.

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 plan to travel outside of Oxford at any time from two days before challenge to 4 weeks after the challenge, you should discuss this with a study doctor before taking part in this study.

Each time we see you, we will check your symptoms and a doctor may examine you. Your blood will be tested for malaria parasites. These visits will last **approximately 15-30 minutes**. However, you may have to wait to be seen. The total number of visits after the challenge will vary depending on when and if you get malaria. It is important you are able to attend all the visits. We will also give you a medication diary

card on which you will be asked to record all medications that you take. You should bring this with you to each visit.

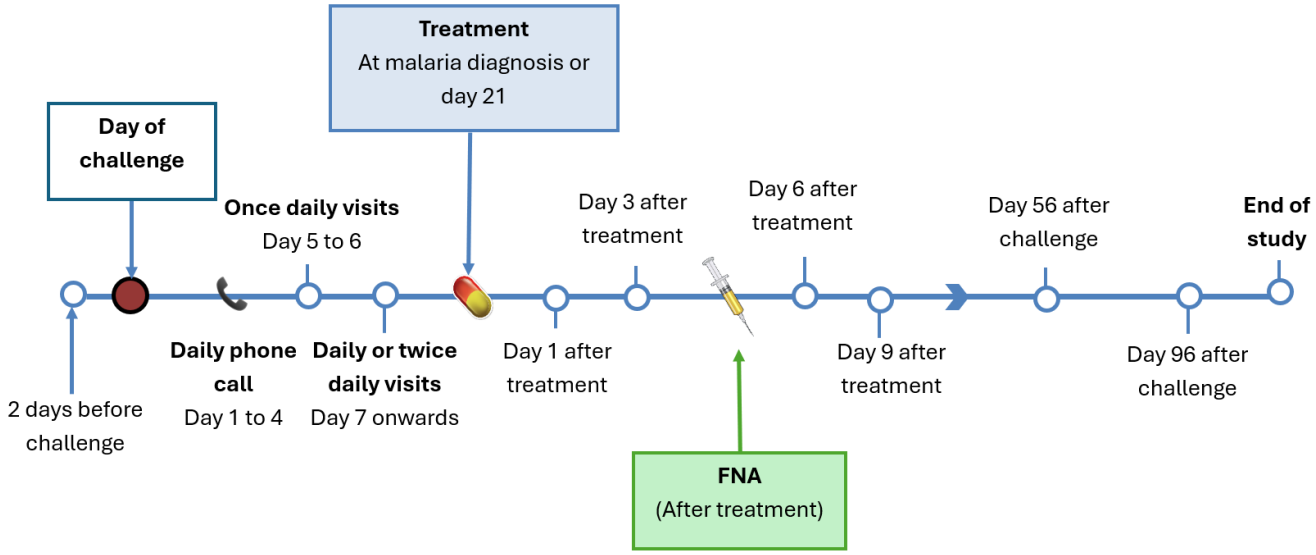


Figure 4: Diagram showing the follow-up visits after the malaria challenge

The malaria test result will be available after you have left clinic. If your blood test is positive for malaria, we will contact you and let you know we will start treatment at your next visit. It is therefore **essential that we are able to contact you at all times on your telephone. You must be available to return to the CCVTM to start treatment at short notice between day 1 – 21 post challenge**. You **must** also provide a name and 24-hour phone number for someone who will know where you are for the duration of the study. If you fail to attend a visit during the post-challenge period and are uncontactable, we will contact this person.

When you are diagnosed with malaria, you will start anti-malaria medication. This visit will last longer than the other visits. It may be **up to an hour.**

You will be treated with a medication called **Malarone**. If you cannot take Malarone (e.g. if you are allergic to it) there is another medication you can take called **Riamet**. More information on these medications is found in the next section under Treatment of Malaria. You may not feel better as soon as you start treatment. Some people feel more unwell in the first 24 hours after starting treatment. This is your body reacting to the parasites being killed by the drug. However, most people then start to feel better. You will need to come to clinic for a blood test on days 1 and 3 after starting treatment so we can check that the treatment is working.

We may not treat you straight away even if you feel unwell. This is because we look at the number of malaria parasites in your blood as well. However, if you are feeling ill for one or two days, we may decide to start treatment anyway.

If you become very unwell you may be admitted to the John Warin ward as a precaution. This is the **Infectious Diseases Unit at the John Radcliffe Hospital in Oxford**. However, it is very unlikely that this will be necessary.

Without vaccination, most people develop malaria between 7 to 12 days after malaria challenge. If the

vaccines protect you against malaria, you may develop malaria later (or not at all).

If we do not find malaria parasites in your blood by 21 days after the challenge, we will presume the study vaccines have protected you against malaria. We will still start treatment in this case, to make sure you are safe.

All challenge participants will receive antimalarial medication by day 21 days post challenge, even if they do not experience any symptoms of malaria.

Follow-up after treatment

You will next be seen in clinic **6 days** after starting treatment. We will also see you in clinic **9 days** after starting treatment. We will ask about any ongoing symptoms or side effects from treatment. You will be seen again on **days 56 and 96** after challenge. We will take a blood sample at each clinic visit. These samples will be used to check your general health and look at the immune response to the parasite. The amount of blood taken will be up to 71mL. The appointments will last about 10 minutes.

Expenses and Payments

There are no costs to you if you take part in this study.
You will be compensated for:

- Screening visit £110
- Vaccination visit £110
- Challenge visit £540
- Follow-up visit £90
- FNA (optional) £150

If you choose to leave the study early, or are withdrawn, you will be compensated according to the length of your participation. This will be calculated based on these figures. **Compensation payments received in this trial may have an impact on your entitlement to benefits.**

Group No.	Time in Trial (approx.)	Maximum No. of Clinic Visits*	Maximum Volume of Blood Taken (ml)**	Compensation Amount***
1	10 months	53	931	£5,360
1 (back-up)	9 months	17	744	£1,670
2	3 months	41	467	£4,220

*The exact number of visits depends on when/if you are diagnosed with malaria following challenge
**The exact amount of blood taken will depend on when/if you are diagnosed with malaria
*** This is the maximum compensation and will vary according to the number of visits you attend and whether you opt to have an FNA

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 both 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:

1. 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

2. 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

We will recruit a number of 'back-up participants' for Group 2 in case another participant is unavailable for the malaria challenge at the last minute. Group 2 'back-up' participants will be compensated £200 in addition to compensation for visits they have attended.

What do I have to do?

- For your health and safety during the study, you **must** provide a name and 24-hour phone number for someone who will know where you are for the duration of the study. If you fail to attend a visit during the 21 days after challenge and are uncontactable, we will contact this person. If you cannot be located, we will take additional steps to locate you which may involve contacting the police and national media.
- You **must** attend all the visits that are outlined above. In the case of unavoidable reasons for not being able to attend the visits, you must inform the study team in advance.
- You **must** complete an electronic (or paper) diary following vaccination.
- If you are able to become pregnant you **must** use effective contraception until the end of the study.
- You **must never** donate blood in the UK following enrolment in the study.

What alternatives do I have?

Your alternative is not to take part in this study.

PART 3: RISKS AND BENEFITS

What are the risks of taking part?

The potential risks are as follows.

Blood Tests

The total amount of blood taken during the study depends on the group you are in. The amount taken at each visit will be between around 2 mL (less than a teaspoon) and a maximum of 83 mL (about 7 tablespoons). The amount 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. This may include bruising and tenderness at the site where the blood is taken. This may also happen at the site where the intravenous cannula (drip) is inserted into your arm on the day of malaria challenge. You may feel faint because of collecting blood, or during insertion of the drip.

We will give you a copy of your blood test results if you ask for them. We will only send the results to your GP if you wish us to. We will not report the results to anyone without your permission. However, if you test positive for Hepatitis B or C, we are required to notify UK Health Security Agency

If abnormal results or undiagnosed conditions are found, these will be discussed with you. For example, a new diagnosis of anaemia (decreased red blood cells) might be made. If you agree, your GP will be informed. Any newly diagnosed conditions will be looked after by your GP within the NHS.

At different time points during the trial, we will take blood samples for the following tests:

- Your full blood count, liver and kidney function.
- Blood borne infections (HIV, hepatitis B & C, EBV, CMV).
- Thalassaemia, sickle cell anaemia (these are conditions which affect the red blood cells) and other conditions that affect the blood.

- Genetic analysis of your cells (to look at patterns of genes that can affect the immune system) and of the parasites.
- Malaria parasite levels.
- Immune responses to vaccination. This may include production of specific antibodies called monoclonal antibodies.

Vaccination Side Effects (Group 1 only)

Once the vaccinations have been given, they cannot be undone. It is therefore important you understand the possible risks of the vaccines before you join the study.

The most common side effects seen with R78C plus RH5.1 with Matrix-M are described below.

We expect that most symptoms will be mild. However, some may be moderate or severe. Symptoms should last no more than a few days. You would be able to take medications such as paracetamol for relief of pain and fever. You may have any of the following:

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

There is a chance you could have a side effect that is different or more severe than those described.

Severe Reactions

With any vaccination there is low risk of serious reactions. These may be related to the immune system or the nervous system.

Severe allergic reactions to vaccines (anaphylaxis) are very rare. But these can be fatal if not immediately treated. Therefore, we will have doctors or nurses qualified in the management of anaphylaxis at each vaccination. Appropriate equipment and medication will also be present.

Reactions in the nervous system are also extremely rare. However, vaccines can cause an illness called Guillain-Barré syndrome. This is an illness in which people can develop severe weakness. It may be fatal. However, these reactions have not previously been seen with the type of vaccine used in this study.

If you have unexpected symptoms or become in any way concerned you should contact one of the study doctors. Study doctors are available 24 hours a day. We will give you emergency contact details when you attend the vaccination visit.

Blood Transfusion Reaction

The malaria challenge involves receiving a very small number of malaria-infected red blood cells. If blood is given from one person to another there is a risk of an allergic reaction. The donor of the blood we will be using is blood group O negative. This means the donor's blood can be given to people with any blood group. However, although extremely unlikely, we will monitor you closely for any signs of an allergic reaction. This is why we ask you to stay in the clinic for 1 hour after you have received the malaria

challenge.

There is a very small risk that, even if you don't develop a transfusion reaction, you may still silently develop antibodies to other surface proteins on the red blood cells in the malaria challenge inoculum. Over 400 people in 30 studies have received a malaria challenge from the same falciparum malaria donation that we are using in this study. There have been only 2 individual instances of red cell antibodies developing which may have been due to the challenge inoculum. In both cases, the antibodies were not felt to pose any ongoing risk to the participants, and they disappeared after retesting.

The risk for development of red cell antibodies in this study is therefore considered extremely low. However, we need to make you aware it because, if you were to develop one or more so-called "allo-antibodies", it may affect the type of blood transfusion you can safely be given in the future. We will therefore test for the development of these antibodies in your blood after the malaria challenge. If these were to be detected they would be identified and discussed with a group of independent experts. This may result in advice that any blood transfusion you need in the future may need to be restricted to a unit of blood that doesn't contain any proteins that the alloantibody may otherwise target. This would be clearly communicated to you and (with permission) to your GP.

Transmission of Blood-borne Infection

The blood transfused in this study has a smaller risk of carrying any blood borne infections than normal blood transfusions. There are 3 reasons for this.

1. The person who donated the malaria-infected blood was screened for a wide range of blood borne diseases. This was done both before and after the blood was collected. The blood was then kept frozen for over a year while the donor was observed and retested for any sign of infection. During this time the donor remained healthy. Repeat screenings did not show any infections that may have not been detected by initial tests. This took place over 20 years ago. The donor has remained healthy since.
2. The volume of blood injected for this study (0.1mL) is thousands of times smaller than the volume in a transfused unit of blood (~400mL).
3. The blood cells have been washed and the white blood cells removed. Both processes lower the risk of infection due to transfusion.

The donor was known to have had two types of viral infections called 'CMV' and 'EBV' (also known as 'glandular fever') in the past. This means there is a possibility of transmitting these infections from the donor to someone receiving the transfused blood. This can happen because these viruses remain within white blood cells after the initial infection. This risk is extremely small; however, as the white blood cells have been removed from the blood. The blood has also been tested to look for the viruses. These tests were negative.

Malaria Infection

If untreated, the malaria infection that we give you could result in death.

Worldwide over 2600 people have been infected with malaria on purpose in malaria challenges. All have made a complete recovery with no long-term problems reported. In Oxford, nearly 600 people have been infected with malaria. The risks of taking part in this study are low, as long as you return for all follow-up visits.

The early symptoms of malaria include a flu-like illness, fever, chills, headache, muscle aches, diarrhoea

and vomiting. In previous studies most participants did have some of these symptoms. If you have any severe symptoms or are concerned about your symptoms then **you should let one of the study doctors know immediately.** Study doctors can be contacted 24 hours a day. About 1 in 5 people temporarily develop severe symptoms. These are symptoms that prevent daily activities. It is possible that you might need to take one or two days off work. We will prescribe paracetamol and anti-sickness medication. You can take these as needed. You should not take more than the dose we recommend (see below). If you take any additional over-the-counter medication, you should first discuss this with the study doctors. Symptoms can start or carry on after treatment has started. They usually last no more than 1 to 3 days.

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

Abnormal blood tests are common after malaria infection. These may include low numbers of white cells and platelets. No bleeding or clotting problems have ever been reported after a malaria challenge. Abnormal liver tests are also common. These have only ever caused symptoms in one participant who had stomach pain and vomiting. These abnormal results have all got better on their own after a few weeks. We will monitor your blood tests in order to detect whether any of these abnormalities develop.

To minimise the chance of abnormal results:

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

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

Over the past 20 years, there have been five serious health problems that occurred unexpectedly in participants in malaria challenge studies in the Netherlands.

- There was one case of a possible heart attack. This occurred 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. These occurred between 2007 and 2014.
- There was one case of chest pain in 2020. This was 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 they received, the malaria infection, malaria treatment or some other cause.

These challenges in the Netherlands all used a strain of malaria called NF54. As a result, the team in the Netherlands has stopped using NF54. In Oxford we use a different strain called 3D7. There have never been any heart problems reported in challenges using the 3D7 strain of malaria.

Still, we will exclude people at high risk of heart disease from this study. These individuals will be identified by medical history and family history. We will also check cholesterol levels and perform an ECG.

In 2010, in a malaria challenge study in Oxford, a participant failed to attend for a study visit after being infected with malaria. In order to ensure the participant's safety, the police were immediately informed. They began a nationwide search for the individual that involved the national media. The participant was found 17 days following challenge when he had mild malaria symptoms. He received treatment for malaria and made a full recovery. The reason for the participant's disappearance was unrelated to the study. **It is important that you understand that if you fail to attend a clinic appointment after challenge, but before you have completed a full course of anti-malaria medication, the police may be notified. Your name may be released to the national media in order to find you. This would be necessary to ensure your personal safety and wellbeing.**

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

Treatment of Malaria

The drug you will be treated with is called Malarone. It is an approved medication in the UK for the type of malaria you will be infected with.

A **Malarone** dose is 4 tablets. This needs to be taken once a day for 3 days. We will observe you taking 2 out of 3 doses during your clinic visits. Malarone is generally well tolerated. It may, however, cause some side effects. These include headache, diarrhoea, nausea, vomiting, stomach pain, dizziness, rash, fever, low mood, reduced appetite, cough or sleep disturbance.

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

If for any reason you cannot take Malarone there are other anti-malaria medications that can be used. If the study doctor thinks this is the case, they will discuss with you another medication (Riamet). They can give you an information sheet about this medication.

Treatment of Symptoms Associated with Challenge

If there are no reasons that you cannot take them, you will be given medications to help with symptoms of malaria. These are licensed, commonly used, medications. You can ask to see the information sheets about these medications prior to taking part in the study. As with all medications, antimalarial medications 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.

Cyclizine: This can be taken to help reduce nausea and vomiting. Cyclizine is generally well tolerated. However, side effects include skin rashes or itching, drowsiness, headache, dry mouth, nose or throat, or blurred vision. Others are awareness of a fast and/or irregular heartbeat, difficulty urinating, constipation, anxiety, or difficulty sleeping. Drowsiness may affect your performance of skilled tasks such as driving. Participants may be given an alternative anti-sickness medication if they are unable to take cyclizine.

Paracetamol: This can be taken to reduce fever and pain. Paracetamol is generally well tolerated. However, you should not take more than 3 grams (6 tablets) of paracetamol per day. This is to minimise the chance of developing abnormal liver blood results. Malaria can sometimes inflame your liver leading to abnormal

blood tests, and too much paracetamol can theoretically make this worse. However, any liver inflammation, if it was to occur, is only temporary and will resolve.

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

What are the possible benefits of taking part?

This study will not benefit you. The information from the trial might help to make a new malaria vaccine for those who live in areas with malaria. There are other malaria vaccines in various stages of development.

PART 4: OTHER INFORMATION ABOUT THE STUDY

What if new information becomes available?

Sometimes during the course of a research project, new information becomes available. If this happens, we will tell you about it. We will discuss whether you want to or should stay in the study. If you decide to stay in the study, you will be asked to sign an updated consent form. On receiving new information, we may judge it to be in your best interests to withdraw you from the study. Your taking part 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?

You are free to withdraw from the study at any time. You do not have to give a reason. This will not result in any penalty, or loss of benefits to which you are otherwise entitled. Your data and blood samples will continue to be used unless you state otherwise. You may ask for your blood samples and research data to be destroyed at any time during or after the study. However, once the study data is fully anonymised it will not be possible to withdraw this.

Even if you decide to stop participating, you must finish the malaria medication to ensure your health.
Your compensation would be paid as a proportion of the total compensation according to the length of your participation.

What if there is a problem?

If you are harmed as a result of taking part in this study, the study doctor can advise you of further action. If necessary, they will refer you to a doctor within the NHS for treatment. The University of Oxford, as Sponsor, has insurance in place in the unlikely event you suffer any harm as a direct result of your taking part in this trial.

The Investigators recognise the important contribution that participants make to medical research. They make every effort to ensure your safety and well-being. In the event of harm, the University will cooperate with any claim. However, you may wish to seek independent legal advice to ensure that you are properly represented in pursuing any complaint.

Complaints procedure

If you wish to complain about the way in which you have been approached or treated during this study, you should contact your local trial 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 head 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 trial volunteer.

Will my taking part in this study be kept confidential?

All information that is collected about you during the study will be coded with a study number and kept confidential. Personal details will be stored securely and separately from the research data. Responsible members of the University, independent monitors 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 being done to applicable regulations.

Any information about you that leaves the clinic will have your name and address removed so that you cannot be identified. Your information is stored electronically on a secure server. 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 need to sign a form to say that you agree for us to contact your GP (see above). This is to tell them that you are interested in taking part in the study. Your GP may be asked to share information about your medical history. They may be asked to give access to any other medical records as needed, including electronic medical records. Information from records maintained by NHS England or the NHS Central Register may be used to provide information about your health status or to contact you for safety reasons. The researchers will not enrol you in the trial if your GP has concerns about your eligibility or safety. We will write to your GP to let them know if you are enrolled in the study. We will also write to let them know if you completed the study, so they can update your medical records.

Prevention of 'Over Volunteering'

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

What will happen to any research samples I give?

Clinical safety blood samples are sent to Oxford University Hospitals NHS laboratories and follow local sample labelling requirements (which may include personal identifiers such as name, date of birth, NHS number, and/or hospital number). As part of processing the clinical safety blood samples, the laboratories may be required to add the results to your medical records. Samples (blood samples and/or cells and fluid from fine needle aspirate samples) sent to research laboratories for processing will not have personal identifiers (they will be identified by study number and participant number only). Some cells from your blood and/or fine needle aspirate (if applicable) may be used to produce specific antibodies ('monoclonal antibodies'). These could be used for commercial activity in the future. Other tests on blood and/or cells and fluid from fine needle aspirate (if applicable) to look at the response of your body to the study vaccine will be done with collaborating laboratories in the UK and in other countries.

After the study, your leftover blood samples and/or fine needle aspirate samples (if applicable) will be stored indefinitely at the University of Oxford. These samples will be coded with a study number. Your personal details will also securely and separately from the research data and samples until the samples have been used or destroyed. This is in order to comply with the Human Tissue Act. The blood samples and/or fine needle aspirate samples (if applicable) may be used for further related research. You will agree to this when you sign the consent form. This research may include testing of the human body's immune response, vaccine research and/or your safety. This research also may include the transfer of

samples to other countries or use for commercial gain. Any such future research will have an appropriate ethical review. You may ask that remaining blood samples and/or fine needle aspirate samples (if applicable) be destroyed at any time by informing the study team. Urine samples will be destroyed immediately after testing.

Will any genetic tests be done?

Yes. Some blood and/or fine needle aspirate samples (if applicable) will be used to look at the pattern of your genes that can affect the immune system. This is called "gene expression" analysis. We will not examine your entire genetic code, only parts of it related to how your body fights infections. As these tests are not done to look at your health we would not give you these test results.

What will happen to my data?

Data protection regulations require that we state the legal basis for processing information about you. In the case of research, this is 'a task in the public interest'. The University of Oxford is the sponsor for this study. It is the data controller and is responsible for looking after your information and using it properly. We will be using information from you and your GP records in order to undertake this study and will use the minimum personally-identifiable information possible. We will store any research documents with personal information, such as consent forms, securely at the University of Oxford for at least 5 years after the end of the BIO-005 study, as part of the research record. 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. 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. Your bank details will be stored for 7 years in accordance with University of Oxford financial policy. We will keep any other identifiable information about you for at least 5 years after the study has finished. For vaccines that may be licensed, secure storage of research data may be required for at least 15 years after the end of the study. This is subject to changes in clinical trials regulations.

The study team at the Oxford Vaccine Centre will use your details (e.g. name, NHS number, home address, and contact details), to contact you about the research study, or to find out more about your medical history to assess eligibility, and to oversee the quality of the study. They will keep any other identifiable information about you from this study for at least 5 years after the study has finished. Data protection regulation provides you with control over your personal data and how it is used. When you agree to your information being used in research, however, some of those rights may be limited in order for the research to be reliable and accurate. Further information about your rights with respect to your personal data is available at https://compliance.web.ox.ac.uk/individual-rights. You can find out more about how we use your information by contacting our study team at info@ovg.ox.ac.uk.

Your information may also be shared with partners working with Oxford University. This information will be identified only by the unique trial number. You will not be directly identifiable. All data shared will be kept securely by these parties in line with all regulatory requirements. Any data that is shared with laboratories outside of the UK will be anonymised or shared only labelled with your trial (pseudonymised). If the study is paused due to safety concerns relating to the study vaccine, the local ethics committee and the manufacturers of the vaccine adjuvant will be informed. The data shared with these parties would also be anonymised or shared only labelled with your trial number (pseudonymised). These persons review records to be sure the research is done in a safe manner that protects you and others.

In all of the above cases, if personal data is shared with laboratories or parties outside of the UK and the European Union (EU), we will take extra precautions to protect your data in our Material Transfer Agreements (MTAs). However, you should be aware that such countries might not offer the same level of protection of privacy as that demanded by law in the UK and the EU.

Involvement of the OVG Quality Assurance Team (Independent Monitors)
The OVG Quality Assurance Team act as independent monitors on behalf of the sponsor. This is to ensure we are complying with the clinical trial regulations. They will conduct a site visit to prepare and set up the clinical trial prior to recruitment. They will also conduct monitoring visits to check the information being collected is accurate. 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 keep any data which could identify you personally. For remote monitoring to occur they may need secure online access to electronic documents - but they will not download or copy them. The OVG Quality Assurance Team will comply with the University's Information Security Policies, which are documented in the agreement with the University.

What happens when the research study stops?

If you have any queries or concerns once the study is over, please get in touch with us. When we know the results of the study, we will send participants a summary of findings.

The data from this study will be shared with the partners who are organising and funding this research work. 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 post-graduate degree, for example a MD or PhD.

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. A summary of the study will also be written for a non-scientific audience and published on the Draper Group website (https://draperlab.web.ox.ac.uk/). 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.

Taking part in future vaccine related research

With your consent, we would like to keep your contact details after your participation in this study is complete. This is so we can tell you of opportunities to take part in future vaccine related research. This is entirely optional. You can still take part in this study if you say "no".
Your details will be stored electronically on a secure server. Only authorised individuals at the CCVTM will have access to it. We will not, under any circumstances, share your contact details with any third-party institutions without your permission. Being contacted does not oblige you to agree to take part in future research. You can ask us to have your contact details removed from our database at any time.

Who is sponsoring, organising and funding the research?

The study is organised and funded by The Chancellor, Masters and Scholars of the University of Oxford. Neither your GP nor the researchers are paid for recruiting you into this study.

The Senior Laboratory Investigator, Professor Simon Draper, has an interest in patents relating to the RH5-based vaccines used in this study. He is also a founding shareholder in a company developing technology used in the R78C vaccine. The Chief Investigator, Professor Angela Minassian, has a family member who is an inventor on patents for RH5-based vaccines and who is a founding shareholder in a company developing technology used in the R78C vaccine. While both Prof Minassian and Prof Draper

therefore have a potential conflict of interest, the integrity of the trial is maintained by samples being analysed by independent researchers who cannot link the results to individuals. This ensures there is no bias, as does the monitoring of safety by an independent Data Safety Monitoring Committee.

Who has reviewed the study?

This study has been reviewed by the National Research Ethics Service Committee, South Central Oxford A . The study has been given a favourable ethical opinion. A Research Ethics Committee is an independent group of people who review research to protect participants' interests. Information regarding the study has also been reviewed and approved by the Medicines and Healthcare products Regulatory Agency (MHRA).

Thank you for reading this information sheet. If you are interested in taking part in the study, please visit our website or contact the study team to arrange a screening appointment. You can also contact us with any questions about what you have read.
Study website: https://www.ovg.ox.ac.uk/studies/bio005

Contact details for further information:
Participant Recruitment Co-ordinator
E-mail: info@ovg.ox.ac.uk
Tel: 01865 611400
CCVTM, Churchill Hospital, Old Road, Headington, Oxford, OX3 7LE