Cover Page

Official Study Title: Phase 1 Clinical Trial with Controlled Human Malaria Infection (CHMI) for Safety, Protective Efficacy and Immunogenicity of Plasmodium falciparum Malaria Protein 013 (FMP013) Administered Intramuscularly with ALFQ in Healthy Malaria-Naïve Adults

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DEPARTMENT OF THE ARMY
WALTER REED ARMY INSTITUTE OF RESEARCH
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Walter Reed Army Institute of Research
Consent for Research Participation Part B: Controls

Title: Phase 1 Clinical Trial with Controlled Human Malaria Infection (CHMI) for Safety, Protective Efficacy and Immunogenicity of Plasmodium falciparum Malaria Protein 013 (FMP013) Administered Intramuscularly with ALFQ in Healthy Malaria-Naïve Adults

Sponsor: Office of the Surgeon General (OTSG), Department of the Army

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IND Number: 18762

You are being asked to take part in a research study. This study is supported by the United States Department of Defense. The box below tells you important things you should think about before deciding to join the study. We will provide more detailed information below the box. Please ask questions about any of the information before you decide whether to participate. You may also wish to talk to others (for example, your family, friends, or your doctor) about this study, before agreeing to join.

Please contact one of the below if you have any questions concerning the study or if you have any other questions or concerns.

Paul M. Robben, MD, PhD, LTC, US Army **(301) 651-0351**

WRAIR Clinical Trials Center * **(301) 319-9660**

*Open 6:00AM-2:30PM Monday-Friday

Key Information for You to Consider
• **Voluntary Consent**. You are being asked to volunteer for a research study. It is up to you whether you choose to participate or not. There are no penalties and you will not lose anything if you decide not to join or if after you join, you decide to quit. However, if you decide to leave the study after you have been challenged with malaria, you will be asked to complete follow-up visits, diagnostic tests for malaria, treatment, and safety blood work to ensure your safety. • **Purpose**. We are doing this research to investigate a new malaria vaccine candidate. This is a first-in-human research study to examine the safety of this vaccine. Up to 46 individuals will participate in this trial. **Duration.** Your part of the study will last up to 16 weeks (approximately 4 months), including today's screening visit. • **Procedures and Activities.** During this study we will ask you to undergo exposure to malaria infection through mosquito bites, and then be followed for approximately 1 month, during which time **YOU ARE EXPECTED TO BECOME INFECTED WITH MALARIA**. During most of this period you will have daily blood draws and visits with medical providers to monitor your safety and look for evidence of infection. If and when you are diagnosed with malaria you will be given effective treatment to cure it. • **Risks.** Most studies have some possible harms that could happen to you if you join. In this study, we expect that **YOU WILL BECOME INFECTED WITH MALARIA**, but you will monitored, and given effective treatment to cure your infection once it occurs. Symptoms of malaria may include fever, headache, joint aches, tiredness, body aches, shaking chills, nausea, diarrhea, low back pain, and sometimes stomach tenderness. Other risks are described elsewhere in this document. • **Benefits**. There is no direct benefit to you for participating in this study. There may be a general health benefit from getting examined by a doctor and having blood tests done for your general health. Others may benefit in the future from the information that will be learned from the study, as it may help in the development of a successful vaccine to reduce significant morbidity and mortality caused by malaria. • **Alternatives.** Participation is voluntary and the only alternative is to not participate.

Why are we doing this research?

Malaria is caused by *Plasmodium* parasites that are transmitted from human to human by the bite of an infected *Anopheles* mosquito. The parasites first infect cells in the liver and then they move into the blood stream, resulting in high fevers, shaking chills, flu-like symptoms and anemia. There are multiple medications approved to treat malaria but these medications are costly, have side effects, and are not readily available worldwide. Also, some strains of malaria parasites are becoming resistant to the drugs currently used to prevent and treat this infection. The most vulnerable population to malaria infection consists of people with little or no immunity against the disease such as young children, pregnant women, and travelers. A vaccine to prevent the infections would be helpful to people living or working in places where these parasites are found. This includes US military personnel deploying to areas in Africa, Southeast Asia, Central and South America, where the malaria parasites are often located. The ideal malaria vaccine would stop the parasites from infecting the liver thereby preventing infection.

Currently, there is no vaccine approved by the United States Food and Drug Administration (FDA) to protect against malaria. However, scientists at WRAIR and throughout the world are working to develop new drugs and vaccines to combat this infection. The experimental vaccine used in this study is a vaccine designed to stop malaria before it infects the liver. It is for this purpose that we are conducting the trial described in this document. This study is looking at the FMP013+ALFQ vaccine, which has not been studied in humans before. This means that FMP013+ALFQ vaccine is considered experimental for prevention of malaria.

The main purpose of this study is to determine if this new vaccine is safe and tolerable.

It is important to note that this study will be the first time the vaccine will be used in humans. The vaccine is made from a malaria protein mixed with an immune adjuvant. The vaccine CANNOT give anyone malaria infection. The adjuvant is included to help boost immune responses to the malaria protein. The adjuvant is called ALFQ. The malaria protein is called FMP013, and is based on a protein that is found on the surface of the malaria parasite, called the circumsporozoite protein or CSP. This protein was designed in the lab to “look” like the natural malaria protein and prompts your body to make antibodies to the malaria parasite. Not all of the side effects of this vaccine are known. In order to test whether the vaccine can protect against malaria infection, we need non-vaccinated volunteers to compare with vaccinated volunteers.

The only way to prove new drugs and vaccines will protect humans against malaria is to give them to human subjects and then expose those subjects to malaria to see if they are protected. This exposure can be accomplished by sending the subjects to countries and environments where malaria is present (i.e., Africa, Asia, South America, etc.), or by purposefully exposing them to malaria in a controlled environment.

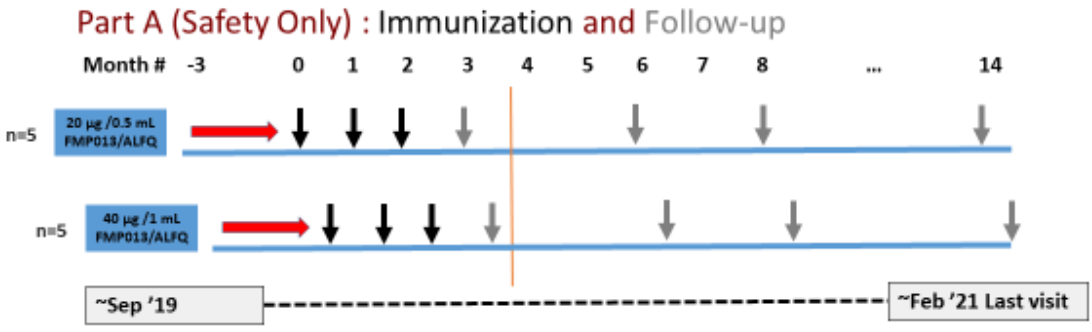
It is this second method we are using for evaluation in this trial. For over 30 years, researchers from the Department of Defense and other organizations worldwide have utilized controlled exposure to malaria, known as “malaria challenge” or “controlled human malaria infection (CHMI)” to safely evaluate how well new drugs and vaccines work in preventing malaria. This kind of malaria challenge has been safely and

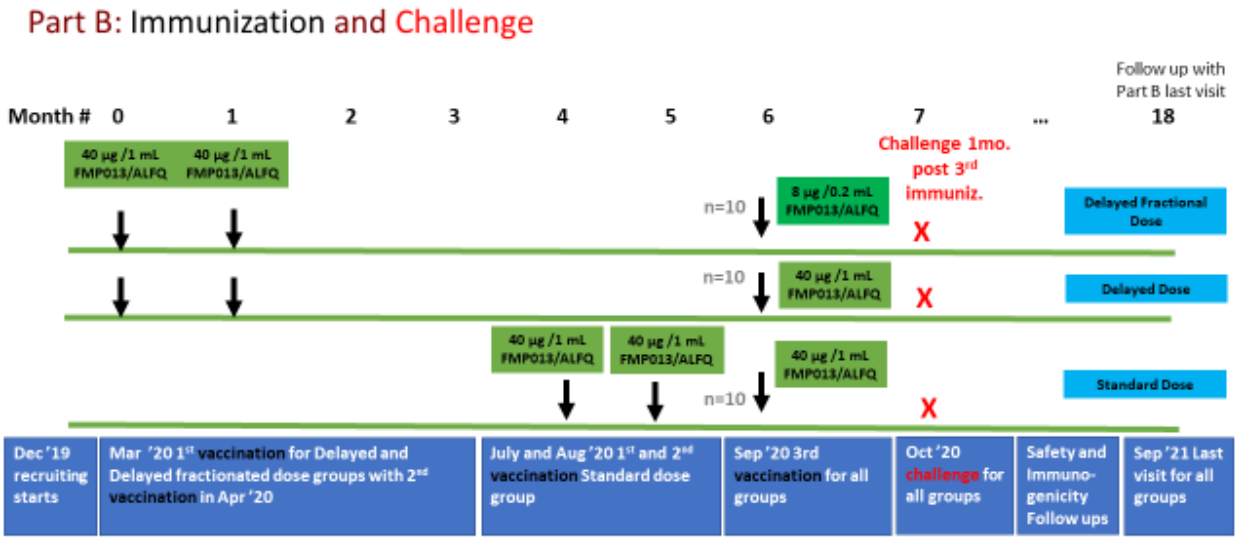
successfully accomplished at WRAIR for multiple clinical trials studying malaria vaccines, including one called the RTS,S vaccine. In the RTS,S vaccine trials, volunteers received three immunizations and then were challenged with malaria to see if they were protected against infection. RTS,S uses similar ingredients as our vaccine, but we are testing if we can get better protection from malaria with our design. In a typical CHMI, subjects are exposed to a known type of malaria parasite through the bites of a small number of infected mosquitoes, and then are followed for approximately 1 month to see if they develop symptoms or other signs of malaria infection. Subjects who are diagnosed with malaria during this time are treated. Those who do not develop malaria during this period are considered to have been protected from infection by whatever drug or vaccine was being tested.

This is a first-in-human research study to examine the safety of this vaccine. In order to do this we need non-vaccinated volunteers to compare with vaccinated volunteers. In this case we are able to observe any side effects due to immunization and to make sure the malaria infection is working as expected in non-immunized patients. It is for this purpose that we are recruiting malaria control volunteers for this trial. You will be enrolled as a malaria control volunteer.

There will be 46 people taking part in the overall study at WRAIR, over a period of approximately 2 years. Figures below provide an overview of our entire study design. Part A of the study is designed to give the vaccine (for two different groups of volunteers, at either low or high doses) and monitor the safety of the vaccine in the volunteer receiving the vaccination. The goal of Part A is to observe any side effects that may result from the low dose first, and then the higher dose after the low dose is tested. For Part B of the study, we will vaccinate with different doses and at different time-points and challenge with malaria to test if the vaccine is protective against infection.

Figure 1: Study Design Overview





How long will I be in this research study?

If you complete the study, you will be in the study up to approximately 16 weeks (or about 4 months including screening period). A study schedule will be provided along with this form. It lists the study activities and gives the approximate length of time for each study visit.

Where will this study take place?

The screening visit(s) and malaria challenge will take place at the Walter Reed Army Institute of Research (WRAIR) in Silver Spring, Maryland.

What will happen if I decide to be in this research study?

If you agree to be in this research, you will be expected to complete a number of visits and procedures, beginning with today's screening visit. A basic outline of these activities is as follows:

Screening Visit (up to 3 months before the malaria challenge day)

- There will be two screening visits. Your first visit, you can do today if you consent and if you meet all study requirements described below. If you agree to be in this study, you will be asked to sign this consent form and an HIV test consent form. You must take a short quiz, to test your understanding of the study, and score at least 80%, or get 8 out of 10 answers correct. If you do not score 80% on your first try, we will review the study information with you, and you will be able to take the quiz again. If you get less than 80% the second try, you will not be able to be in the study.
- You will be asked questions to determine if you are eligible to participate in this study. You will not be able to take part in this study if you have a medical

condition that could get worse if you get the vaccine or if you are exposed to malaria. You also will not be able to be in the study if you are not able to understand the study as explained to you and give proper consent.

- You will be able to speak with a study physician who will get your medical history, review medications, perform a physical examination, and answer any of your questions.
- You will have your height and weight recorded as well as your vital signs (blood pressure, temperature, and heart rate).
- You will give blood samples for laboratory tests. We will collect blood by placing a small needle in a vein in your arm. The blood tests will include complete blood count (CBC), liver and kidney function tests, glucose (a type of sugar in your blood), and tests for HIV, hepatitis B and hepatitis C.
- An electrocardiogram or ECG (tracing of the electrical action in your heart) will be performed. This is a simple, painless test in which leads are attached to your chest, arms and legs. It shows us the “electrical activity” of the heart, and can reveal warning signs for heart disease.
- Will assess you for cardiac risk factors using a medical survey.
- If you are a female of childbearing potential, a urine pregnancy test will be performed.
- Your second screening visit will taking your medical history since last visit including medications taken, a review of eligibility criteria along with a blood draw for additional lab work.

These tests are done to ensure you are in good health and able to safely participate in this study. The results will be discussed with you. Upon request we will give you the results of our medical history, physical exam, and lab tests so that you can give them to your regular doctor. Blood is drawn for lab tests throughout the study to monitor your health and safety. It is possible that the physician may order additional lab testing either for safety or to clarify your clinical condition. These lab tests would be discussed with you throughout the process.

If any of your test results are abnormal, you will be informed about the test result and instructed to see your primary care provider. If you are female and your pregnancy test is positive, you will not be able to be in the study. At your request, we will provide you a copy of your laboratory test results. State regulations require that if any of your tests show that you have HIV, hepatitis B, or hepatitis C infection, we must report the information to the Maryland Department of Health. If you are a military service member, this information will also be reported to the military preventive medicine service.

If you meet all study requirements and wish to continue in the study, you will then be assigned to the control group.

Malaria Challenge

The malaria challenge will take place at the Walter Reed Army Institute of Research Insectary, which is located in building 503 Robert Grant Avenue, Silver Spring, MD.

The malaria challenge will use mosquitoes that are raised in a laboratory. The infection caused by the malaria parasite used in the malaria challenge can be cured with medication.

During the malaria challenge, you will be asked to do the following:

- You must provide the names and phone numbers of at least 2 emergency contacts to the study staff, and agree that they can be contacted before the challenge.
- You will be asked to NOT use any cologne, perfume, after-shave lotion, deodorant soap or body creams/lotions on any part of your body because they may stop the mosquitoes from biting.
- We will review your medical history since your last visit, undergo a short physical exam, review medications, record vital signs and collect approximately 4 tablespoons (approximately 59 mL) of your blood for safety laboratory tests and a baseline test to show you did not have malaria before you were challenged. We will review eligibility and elimination criteria.
- If you are a female, you will have a urine pregnancy test. If your pregnancy test is positive, we will not allow you to be bitten by infected mosquitoes.
- Five mosquitoes will be placed in the container and allowed to bite you through mesh for 5 minutes. If fewer than 5 malaria-infected mosquitoes bite you, more will be added to the container and allowed to bite you for another 5 minutes. We will do this until a total of 5 malaria-infected mosquitoes have bitten you.
- You will be asked to stay for at least 30 minutes after the challenge so we can monitor you for any reactions.
- You will be given a card that shows that you have been bitten by mosquitoes carrying malaria parasites. The card will have the contact information of the study principal investigator. You will be asked to carry this card with you at all times until the end of the study.
- In the days after the challenge, you will be checked for signs and symptoms of malaria infection. The expectation is that **YOU WILL GET MALARIA FROM THE MOSQUITO BITES.**
- You will be instructed to contact the study personnel immediately should you develop any signs and/or symptoms that may be consistent with malaria.

Post-Malaria Challenge: (Day 5 to morning of Day 20 after the malaria challenge)

From Day 5 to Day 20 after challenge, you will be required to come to the clinic once a day for brief visits to review your medical history, undergo a short physical exam, review

medications, record vital signs and have a small amount of blood drawn (less than1 teaspoon, approximately 4 mL each time) to check for the presence of malaria in your blood. You will also be seen in the clinic on the morning of Day 16 after challenge for the same purpose. Though, the blood draw on this visit will be larger (approximately 2 teaspoons, approximately 11 mL), as the study will be taking blood both to check for the presence of malaria and for safety labs. While it is unlikely you will develop malaria this early, if a diagnosis is made, you will be treated.

- You must check in with study staff at WRAIR each morning. Each morning you will be seen by a study doctor, and your blood will be drawn and tested for malaria parasites (less than 1 teaspoon, approximately 4 mL each time).
- Malaria symptoms may develop either before or after the parasites are detected in your blood.
- Symptoms of malaria may include fever, headache, joint aches, tiredness, body aches, shaking chills, nausea, diarrhea, low back pain, and sometimes stomach tenderness
- If you are diagnosed with malaria, an extra blood sample will be taken for safety labs to assess your wellbeing (approximately 2 teaspoons, approximately 11 mL).
- If you are diagnosed with malaria, you will be treated with an FDA-approved drug for malaria. You will be seen by the clinical study team every day until you complete the treatment course.
- If you are diagnosed with malaria, blood samples will continue to be collected once a day (less than 1 teaspoon, approximately 4 mL each time) to make sure that malaria parasites are no longer in your blood. This is the best way for the study team to determine if the malaria treatment is working. These blood collections will end after you have no evidence of malaria parasites for 2-3 days.
- If you get malaria, finish the treatment, and the parasites can no longer be found in your blood, the study doctor may release you from daily visits.

Other Post-Challenge Follow-Up Visits:

You will be asked to return to the WRAIR Clinical Trials Center (CTC) for several follow-up visits.

- If you do not develop malaria during days 5 through 20 post-challenge, we will continue to follow you every other day (Days 22, 24, 26, 28) except weekends and holidays at the CTC to make sure you do not develop malaria and require treatment. On these days you will be required to return to the WRAIR CTC for follow up to review your medical history, undergo a short physical exam, review current medications, record vital signs and do blood tests. On days 22, 24 and 26 we will collect less than 1 teaspoon, (approximately 4 mL each time).

- If you have no evidence of malaria by the morning of Day 28, you will be empirically (that is, without a diagnosis) treated for malaria.
- If you have been diagnosed but not completed your treatment for malaria by the morning of Day 28, you will be required to return to WRAIR CTC for necessary daily visits until you have completed the necessary treatment and parasite clearance blood tests (less than 1 teaspoon, approximately 4 mL each time).
- Unless you are still undergoing treatment, your last visit will take place at the WRAIR CTC on Day 28. A final evaluation will be performed by a study physician, and blood collected for safety labs and future malaria research (approximately 4 tablespoons, approximately 61 mL).

What requirements do I have to meet in order to participate in this study?

You may be allowed to participate in the study if you meet the following requirements:

- You are between the ages of 18 and 55 years old.
- You have a valid state or government-issued photo ID (e.g. driver's license, military ID, or U.S. passport) & be able to pass a background check in order to gain access to the base & participate in a study with us.
- You are willing and able to participate in all planned study visits for the duration of the study.
- You must provide two emergency contacts who will be made aware of your participation in this trial and the vital importance of being reached during the challenge phase of the study. Both contacts must be verified by phone prior to your enrollment. Verification will be defined as either speaking to your emergency contacts over the phone, hearing their name included in the voicemail response, or confirming the emergency contact uses the number if someone else answers the phone.
- You are in good general health based on your medical history, physical examination, ECG, and screening laboratories.
- You are able to understand and sign this informed consent.
- You pass the written test called the 'Assessment of Understanding' with a score of at least 80% (8 out of 10 questions correct) in one out of two attempts.
- You agree not to donate blood during the study and for 3 years after the malaria challenge.
- You agree not to travel to place(s) where there is malaria from the beginning of the study until the end of the post-malaria challenge phases. Travel to these places during the study period may exclude you from the study depending on circumstances at the discretion of study physician.

- If you are a female, you must agree to consistently use effective birth control (e.g., oral or implanted contraceptives, intrauterine device (IUD), diaphragm with spermicide, abstinence, cervical cap) at least 30 days before enrollment (the day of malaria challenge) and through 3 months after the malaria challenge.
- If you are male, you are encouraged but not required to use highly effective birth control measures to avoid pregnancy in your partner. This is due to the potential impact of malaria and antimalarial medications on your sperm.
- You must be willing to take anti-malarial treatment after CHMI.
- You must agree to visit WRAIR during the designated post-CHMI follow-up period from approximately 5 days after malaria challenge until 20 days after challenge or until antimalarial treatment is completed, whichever comes first.
- If you are a military employee, you must have approval from your supervisory chain to participate. The appropriate approval form will be provided to you.
- You are reachable (24/7) by mobile phone or other method of communication (email, landline, etc.) during the period between CHMI and 28 days post-CHMI, per volunteer report.
- You must not have a fever in order to participate in the malaria challenge.

You are not allowed to participate in this study if any of the following criteria apply to you:

- Any history of malaria infection or having been given a malaria vaccine.
- Any history of travel to a country with malaria in the past 6 months, or planned travel to such an area during the course of the study.
- Any history of having lived in an area with malaria for more than 5 years.
- Any use of medications that prevent or treat malaria during the 1 month prior to challenge or planned use during the study (outside of the drugs provided by the study team).
- Any serious medical illness or condition involving the heart, liver, lungs, or kidneys.
- Any significant risk for developing heart disease in the next 5 years. The risk for developing heart disease in the next 5 years will be determined by a combination of the following factors: high blood pressure, smoking, weight, family history of heart disease and the presence of diabetes.
- Any medical illness or condition involving your blood or immune system (to include sickle cell trait or thalassemia trait).

- Any abnormal (as determined by a physician) screening laboratory test results.
- Any history of neurologic disease (including migraines or seizures).
- Any history of psoriasis (itchy skin rash) or porphyria (rare disturbance of metabolism), since these conditions could get worse after treatment with chloroquine (a medication for treating malaria).
- You have had your spleen removed.
- Any past or current infection with HIV, Hepatitis C, or Hepatitis B.
- Any use of investigational drugs or vaccines within 30 days before starting the study
- Any allergy to or inability to take the anti-malaria medications used in this study.
- Any history of allergic reaction to mosquito bites that required hospitalization.
- You must not be pregnant or nursing, or have any plans to become pregnant or breastfeed during the period from now through 3 months after malaria challenge.
- Any chronic use of steroids or other medications that affect the immune system in the 6 months before malaria challenge. Inhaled and topical (used on the skin) steroids are allowed.
- You plan to have surgery between enrollment and 3 months after malaria challenge.
- Any active alcohol or drug abuse.
- History of active/recent cancer still within treatment or active surveillance follow-up (except basal cell carcinoma of the skin and cervical carcinoma in situ). Treated/resolved cancers with no likelihood of recurrence may be deemed acceptable at Principal investigator discretion.
- Concurrent participation in another clinical research study.
- Receipt of antibodies or blood products within three (3) months before enrollment.
- Current anti-tuberculosis preventative medication or treatment.
- History of Diabetes mellitus (type I or II), with the exception of gestational diabetes.
- History of Thyroid disease (except for well controlled hypothyroidism).
- History of chronic hives within the past year.

- History of bleeding disorder diagnosed by a doctor (e.g., factor deficiency, coagulopathy, or platelet disorder requiring special precautions) or significant bruising or bleeding difficulties with IM injections or blood draws.
- History of arthritis diagnosis other than general 'wear and tear' arthritis (osteoarthritis).
- History of other diagnosed rheumatoid disorders.
- You have any other physical or psychologic condition or laboratory abnormality that the study doctor thinks may increase your risk of having side effects or compromise the results of the study.

What are my responsibilities as a participant in this research study?

If you agree to participate in this study, you will be expected to keep all of your study visit appointments. If you cannot make your scheduled appointment, call the WRAIR CTC at 301-319-9660 during operating hours (Monday to Friday 06:00AM to 2:30PM).

What happens to the information and specimens collected for this research?

Information and data collected from you for this research will be used to help us determine whether a new malaria vaccine is safe and protects against infection.

The blood samples you provide during the study will be used for laboratory tests to assess your safety, to help us diagnose you with malaria and/or confirm your successful treatment, and to compare with vaccinated volunteers. Some of your blood samples without any personally identifiable information may be sent to specialty labs in the United States and Europe to better understand how the body's immune system responds to malaria vaccinations or make new medicines to fight malaria. In addition, one sample of blood will be taken and mixed with blood from other subjects to make what are known as positive control pools. A positive control pool is an anonymous blood collection known to be infected with malaria that is used to make sure malaria laboratory tests are working properly. Any blood left over after pool creation will be stored for up to 20 years, with your permission, for future use in malaria research.

Any information discovered from your data or samples during this trial that may negatively impact your health (for example, if we discover you have high blood pressure or hepatitis) will be shared with you, and if appropriate you will be counselled by a study investigator and referred to a health care provider for further evaluation and care.

After the study is complete, you may request to find out the overall study results from the study investigators.

Your data and samples will not have your name or other identifying information about you. Your data and samples will be labeled by a code (such as a number) and may be sent to investigators at WRAIR or other research scientists throughout the country who work with us, without asking for your permission.

No whole genome sequencing will be conducted on your samples in this study. Whole genome sequencing involves the analysis and description of your entire genetic code, or DNA. Whole genome microarrays of transcriptional profiling may be conducted on your samples. This testing measures how much the genes in your body are being used at the different times the samples are collected (before vaccination or after the different vaccinations). Comparisons of these results could help us find genes or groups of genes that are important in vaccine response. The test does not look at your genetic sequence directly or result in any identifiable information because gene expression varies by situation. If this testing were released with your personally identifiable information, it may pose a possible risk of discrimination or increased difficulty in obtaining certain types of insurance for you and your family members.

Your stored samples will be used for research only and will not be sold. Research using your blood samples may help develop new products in the future that have the potential for commercial profit**,** but you will not receive payment for such products.

It is your choice as to whether we can use your blood samples for future research. You can still participate in this study regardless of your decision related to blood samples to be used for future malaria research. Future research using the specimens collected from you might include work to develop and evaluate new products to prevent or treat malaria. However, any future use of your samples will not include whole genome sequencing but as clarified above, whole genome microarrays of transcriptional profiling may be conducted on your samples. You will not be informed if and when this future research occurs or what results come from it, but it is your choice as to whether we can use your blood samples for future research.

Once the study is complete, your records will be kept in secure storage at WRAIR for a period of at least 2 years. Records will be maintained until it has been deemed no longer necessary to retain them by the study Sponsor (US Army Surgeon General), and then destroyed as per applicable regulations. Any remaining blood specimens will be kept at WRAIR. Storage and destruction of these samples will be as per the applicable facility Standard Operating Procedures (SOPs). These samples, either individually, or in pool form, will be stored for a maximum of 20 years (counting from when the last subject performed the last study visit), unless regulations or guidelines arise in the interim which require different timeframes or different procedures.

Any future research using your data will require a research protocol and approval by an Institutional Review Board (IRB) (a committee responsible for protecting research participants) or other authorized official responsible for protecting human subjects in research studies. For instance, an IRB reviewed and approved this current study that you are taking part in. The data protections for privacy and confidentiality described in this document will apply to any future use of your stored data and samples.

What are the risks if I participate in this research?

If you decide to participate in this study, you should carefully consider the risks, which are described below. While participating in this study, you are not allowed to participate

in any other clinical trial. We will share information about new risks with you as the study continues.

Risks of Drawing Blood

Blood will be drawn from a vein in your arm using a needle. Blood drawing may cause pain and bruising at the site where the blood is drawn. There is also a small possibility that the area from where the blood is drawn may get infected. Redness and swelling around the site where blood is drawn may be a sign of infection. Sometimes people feel lightheaded or even faint when blood is being drawn. There is also a risk of getting anemia from the repeated blood draws.

We do the following to lower the risks:

- Blood is always collected using standard aseptic techniques to prevent infection.
- No more than 30 tablespoons (450 mL) of blood will be drawn during any 8-week period.

Risks of Getting Mosquito Bites (During Malaria Challenge):

You might develop redness, mild swelling, and itching on your arm where the mosquitoes bite you. We will have anti-itch cream available if you would like it. There have been very rare reports of severe allergic reactions after mosquito bites. This type of reaction occurs immediately after the bite and can be very serious. You will be observed in the Clinical Trials Center (CTC) for 30 minutes after you are bitten by mosquitoes. The staff of the CTC is trained to recognize allergic reactions and start treatment early. Equipment and medications to treat allergic reactions are available in the CTC and in the room where you will be bitten by mosquitoes. There have been **NO** reported human cases of HIV, Hepatitis B, or Hepatitis C being transmitted by mosquitoes; however, the blood used to infect the mosquitoes is provided by a blood donor. This blood will be tested for a large panel of blood-borne diseases, to include HIV, Hepatitis B, and Hepatitis C, syphilis, Human T-cell Lymphotropic Virus (HTLV)-1/2, West Nile Virus, and *Trypanosoma cruzi* (Chagas disease), and only be used if it is found to be negative for all of them. Additionally, there is also a very small risk that the mosquitoes that bite you could give you a disease other than malaria that we have no way of identifying ahead of time. We take several steps to reduce these theoretical risks:

- The mosquitoes used for challenge are hatched and raised in a controlled laboratory and do not feed on any other person before they bite you.
- Blood that is used to feed mosquitoes is obtained from healthy US volunteers with normal screening labs. As above, we test all blood that is used to feed mosquitoes to make sure that it is negative for Hepatitis B, Hepatitis C, HIV, syphilis, West Nile Virus, *Trypanosoma cruzi* (Chagas disease) and HTLV.

Risks of Getting Malaria

Infection with the type of malaria mentioned in this study is serious. If treatment is delayed, it may progress to multi-organ failure, seizures, and death. This is why it is so important that you come to each and every clinic visit after the challenge to be monitored and treated as soon as the malaria infection is found. The malaria challenge is considered safe because people are treated as soon as they are found to have a small amount of malaria. Over the past 30 years, both Army and Navy doctors have worked on studies where malaria-infected mosquitoes have bitten more than 1,500 volunteers. All volunteers have recovered from their malaria infections, no volunteers have ever been hospitalized for their infections, and none have ever died of malaria. You are not contagious to others after you develop malaria infection. When you become positive for malaria during this study and complete treatment; malaria symptoms should not recur. If you do not become infected with malaria during the study, it is very unlikely that you will become sick after that, however, you will still be treated empirically as a precaution. Please contact the CTC staff immediately or tell your personal doctor if you develop symptoms of malaria in the 6 months after the follow up visit. In the extremely unlikely event that malaria does recur we will make sure you receive appropriate evaluation and treatment. To reassure you, no one ever experimentally infected with this strain of malaria (NF54 clone 3D7) has ever had a recurrence of malaria after completing treatment.

Due to American Red Cross regulations, you will not be allowed to donate blood for 3 years after being exposed to malaria. **Infection with malaria does not protect you from getting malaria if you travel and are exposed to malaria again in the future.** If you travel to a country with malaria later, you still need to take all safety measures to prevent getting malaria such as taking anti-malarial medications.

You should be aware that the medications used to treat malaria in this study may uncommonly produce side effects in individuals taking them. These side effects are discussed further elsewhere in this document.

Risk of Loss of Confidentiality

If you participate in this study, there is a chance that limited information about you may be released to persons outside of this study, as explained in detail elsewhere in this document.

Risks during pregnancy

You should not get pregnant or breastfeed while taking part in this study.

Malaria infection during pregnancy is dangerous to both a pregnant woman and her fetus, and can be life-threatening to both. As such, pregnant women are not allowed to participate in this trial for safety reasons.

Malaria infection is not known to be transmitted to infants through breast feeding. However, some medications used to treat malaria can be transmitted to infants through breast milk, and potentially expose those infants to the side effects of those

medications. As such, breastfeeding women are not allowed to participate in this trial for safety reasons.

If you are a female who is able to become pregnant and you want to take part in this study, you must agree to consistently use highly effective birth control (e.g., oral or implanted contraceptives, intrauterine device (IUD), diaphragm with spermicide, abstinence, cervical cap) at least 30 days before enrollment and through 3 months after the malaria challenge. You will also have to take a urine pregnancy test today, and prior to being exposed to malaria. If either of these tests are positive, you will not be allowed to participate in this study.

If during this study you become pregnant or feel you might be pregnant, contact your personal physician and the principal investigator of this study listed in the Contact Information section at the end of this document. If you become pregnant during the study after being exposed to malaria, but before being diagnosed with malaria infection, you will be treated immediately as if you have malaria, with an appropriate drug from those described in the **Treatment of Malaria** section below. **You will not be challenged if you are determined to be pregnant prior to the challenge phase.**

Risks of Heart Disease

We do not believe the malaria challenge will cause heart disease; however, 3 individuals who took part in malaria challenges in Holland are known to have suffered from heart disease during these studies. None of those events was felt to be caused by the challenge. Instead, the heart disease was felt to be coincidental to the challenge in all 3 cases. The challenge was different than ours and the treatment medications used were not FDA-approved. This is why we need to ask you questions about your health before starting the study and check your heart rate and blood pressure at every visit. For your safety, if you are naturally prone to a moderate or higher risk of getting heart disease, you will not be allowed to participate in the study.

Unknown or Unanticipated Risks

There may be risks that are not known at this time or that have not been reported yet. If any new risk is reported, the study doctors will let you know as soon as possible.

Precautions for volunteers undergoing malaria challenge

Certain antibiotics (medicines that fight infection) can prevent or delay malaria parasites from growing. If your personal physician prescribes an antibiotic for you to be taken any time during the period from 4 weeks before the malaria challenge through the end of the study, you should tell a study physician, before you begin to take it if possible. For safety purposes and study integrity, if the study physician finds that this antibiotic might affect malaria parasites, you may not be allowed to participate in the malaria challenge, or if you are in the study, you may be withdrawn from it.

You should not travel outside the Baltimore/Washington DC area for 28 days after the malaria challenge. If you do have or make travel plans, please let the clinical team know about any travel plans you may have so we can coordinate your visits and give you safety advice. After you complete the study, if you travel to areas with malaria, you should take normal steps to prevent malaria as recommended by your doctors.

Treatment for Malaria

We will treat you with Malarone, which is FDA-approved for treating malaria. If you are allergic to Malarone, or a physician investigator feels that based on your medical history a different medication would be more appropriate, we will treat you with either chloroquine or Coartem, which are also FDA-approved malaria treatments.

The following side effects of Malarone are uncommon and occur in less than 5% of people who take this medication:

- Abdominal pain, nausea, vomiting
- Temporary elevation of liver function tests.
- Headache

If you receive chloroquine for treatment, you may have any of the following side effects:

- Abdominal cramps, loss of appetite, diarrhea, nausea, or vomiting,

- Headache, difficulty sleeping, dizziness, or blurred vision
- Itching
- Tinnitus (ringing in ears) or decreased ability to hear if you already have an existing hearing problem.
- When taken for a long period of time (greater than 1 month), chloroquine can cause permanent eye damage or deafness. Please note that your chloroquine treatment course will last for only 3 days, so it will be highly unlikely that you would develop eye damage or deafness from the medication.

If you receive Coartem for treatment, you may have the following side effects:

- Fever, chills, headache, dizziness, weakness, difficulty sleeping
- Loss of appetite, abdominal pain, nausea, vomiting
- Muscle aches, joint aches
- Cough

How will my privacy and data confidentiality be protected?

We will take measures to protect your privacy. Even with these measures, we can never fully guarantee your privacy will be protected. We will try our best to protect your privacy by doing the following:

- Your name and any identifiable information (for example, your address or social security number) will be removed from study files and your lab samples and be replaced with an identification code that consists of numbers and letters. Different codes may be used for you during the course of the study. Only the study investigators, study coordinators, research monitor and representatives from certain agencies (described below) will be allowed to know which codes belong to you, and to have access to your study information.
- Your study files will be kept in a safe, secure storage area at the WRAIR Clinical Trials Center for the duration of the study.

While we will do our best to protect your information there are some cases where we cannot guarantee complete confidentiality.

We may report medical information and lab results to authorities, to prevent serious harm of yourself or others.

- We are required to report information regarding certain infectious diseases (like HIV or AIDS and viral hepatitis) to the local health department. If your blood tests show that you have one of these infections, we will report this information to the health department, and they may need to interview you to get more information. This may cause you some distress, and could affect

your personal and professional relationships. We will provide trained counselling to discuss test results and refer you for further care as required.

- For volunteers who are in the military, information bearing on your health may be required to be reported to appropriate medical or command authorities. This may include information bearing on your safety, the safety of others, or your ability to perform your duties.
- Representatives from the following agencies may have access to review research records as part of their responsibility to protect humans in research and oversee the quality of the research efforts. As government agencies, they must also maintain confidentiality of your records within the limits of the law.
  - The Study Sponsor, US Army Surgeon General
  - The WRAIR Institutional Review Board (IRB)
  - The Naval Medical Research Center (NMRC) Office of Research Activities (ORA)
  - US Army Medical Research and Development Command (USAMRDC)
  - The US Food and Drug Administration

Please remember that even though we are doing our best to protect your information, we can never fully guarantee confidentiality of all study information.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

Will I be paid to take part in this research study?

You will receive compensation for your time and efforts.

- The compensation you will receive for your participation in this study is outlined in the 'Volunteer Schedule' found at the end of this document; it ranges from $50.00 at screening to $200.00 for the challenge day visit, Federal employees (both civilian and active duty) who are on-duty during study visits can only be compensated $50.00 per visit that includes blood draws (will not be compensated for visits that do have blood draws associated with them).

- The total amount of compensation will vary depending on if you are a federal employee presenting for visits while on-duty or if you are found to require extra visits for blood draws for any reason during the protocol.

- If you need to return to clinic for any additional unplanned visits the compensation will be $100.00 per visit.

- If you complete the study, the total compensation is a maximum of $3230.00 if you make all scheduled visits.

- For all volunteers receiving more than $600.00, an IRS form 1099 will be issued.

- Federal and military regulations place limits how much and for what federal civilian employees and active duty research volunteers may be compensated, if participating while on duty hours. Given the rigors of the malaria challenge, we require volunteers to participate during off-duty hours or when they are on leave. In this case, they can and will be paid the same as non-military or non-federal personnel. All scheduled blood draws are planned to occur during off duty hours.

In order to participate on- or off-duty, active duty military volunteers will require approval from their supervisor through branch director using the Statement of Supervisor's Approval, which will be provided to you.

- Other than medical care that may be provided and any other payment specifically stated in this informed consent, there is no other compensation available for your participation in this research study; however, you should also understand that this is not a waiver or release of your legal rights.

The maximum possible compensation for a volunteer who attends all study visits amounts to approximately $3230.00. The maximum possible compensation for an **on-duty** federal employee amounts to approximately $1000.00. Please note that we will not provide extra money to pay for costs you may have from being in this study, such as the cost of transportation to and from the study site or child care costs.

If you choose to leave or are removed from the study by the Principal Investigator prior to its completion, you will still be eligible for the compensation related to all study visits and procedures that you have successfully completed up until that point. If you do not complete all required study visits, you will not be eligible for the end of study bonus of $250.00.

Other than medical care that may be provided and any other payment specifically stated in this informed consent, there is no other compensation available for your participation in this research study; however, you should also understand that this is not a waiver or release of your legal rights.

Are there costs for participating in the research?

There is no cost to you to participate in the study. You will not have to pay for medical visits, physical examinations, blood tests, medical procedures, or hospitalizations that occur as a result of this study. However, **we will not pay for any transportation or childcare costs.**

Are there disclosures of financial interests or other personal arrangements from the research team?

The Principal Investigator and members of the research team have no financial interests or personal arrangements related to this trial to disclose at this time.

What happens if I am injured as a result of this research?

If you are injured because of your participation in this research and you are a Department of Defense (DoD) healthcare beneficiary (e.g. active duty in the military, military spouse or dependent, retiree), you are entitled to medical care for your injury within the DoD healthcare system, as long as you remain a DoD healthcare beneficiary. This care includes but is not limited to free medical care at DoD hospitals or clinics.

If you are injured because of your participation in this research and you are not a DoD healthcare beneficiary, you are entitled to medical care for your injury at an Army hospital or clinic; medical care charges for care at an Army hospital or clinic will be waived for your research-related injury. You are also entitled to care for your injury at other DoD (non-Army) hospitals, but such care for your injury at other DoD (non-Army) hospitals or clinics may be time-limited, and your insurance may be billed. It cannot be determined in advance which Army or DoD hospital or clinic will provide care. If you obtain care for research-related injuries outside of an Army or DoD hospital or clinic, you or your insurance will be responsible for medical expenses.

Transportation to and from hospitals or clinics will not be provided. No reimbursement is available if you incur medical expenses to treat research-related injuries. No compensation is available for research-related injuries. You are not waiving any legal rights.

If you believe that you have sustained a research-related injury, please contact the PI, Paul M. Robben, MD, PhD, or the WRAIR Clinical Trials Centers, whose contact information is given at the top of this document. In addition, an emergency contact card will be provided to you with numbers to contact at any time.

What happens if I withdraw from this research?

PARTICIPATION IN THIS STUDY IS VOLUNTARY. You may decide not to take part in this study. You can withdraw from (leave) this study at any time and for any reason without penalty or loss of benefits to which you are otherwise entitled. However, for your safety, we may need to continue to monitor or provide treatment to you. If you withdraw following the challenge you will be asked to complete follow-up visits, diagnostic tests for malaria, treatment, and safety blood work to ensure your safety.

If you decide to leave the study, we ask you to contact a study investigator or the CTC staff. The information you provided prior to withdrawal will be stored and treated in the same way as for other volunteers. Any data and specimens collected prior to your withdrawal will be used by the study in the same ways as for other volunteers. No more

payments will be made to you after the final blood work. The quality of the medical care you receive will not be affected by your decision to withdraw from the study.

The principal investigator, Paul Robben, MD, may decide not to allow you to continue participating in this study under the following conditions:

- If you develop a medical condition that would make it unsafe for you or others if you were to continue participating, or that would interfere with the study results.
- If other situations or conditions arise that would make participation harmful to your own health.
- If you fail to comply with the procedures as outlined in this form.
- If the study ends for any reason.
- If the investigator believes that it is in your best interest.

You should also know that the WRAIR Institutional Review Board (IRB), and the US Army Medical Research and Development Command (USAMRDC) can end this study at any time. If the study ends, or your participation ends, you may be asked to complete follow-up visits and/or medication for your safety.

We will tell you if we discover any significant or new information during the study that may affect your health and willingness to continue participation.

Who can I contact if I have questions about my rights as a research participant?

If you have questions about your rights as a research volunteer in this study, you may contact the Human Subjects Protection Branch, Walter Reed Army Institute of Research 503 Robert Grant Avenue, Silver Spring, MD 20910, phone number 301-319-9940 and email usarmy.detrick.medcom-wrair.mbx.hspb@mail.mil.

What is the volunteer registry?

It is the policy of the US Army Medical Research and Development Command (USAMRDC) that data sheets are to be completed on all volunteers participating in research for entry into this Command's Volunteer Registry Data Base. The information to be entered into this confidential data base includes your name, address, Social Security number, study name and dates. The intent of the data base is two-fold: first, to readily answer questions concerning an individual's participation in research sponsored by USAMRDC; and second, to ensure that the USAMRDC can exercise its obligation to ensure research volunteers are adequately warned (duty to warn) of risks and to provide new information as it becomes available. The information will be stored at USAMRDC for a minimum of 75 years. The Volunteer Registry Data Base is separate from and not linked to the treatment protocol database.

Consent for Future Research

Samples received for this project may also be subject to future testing. The results of these tests will not be made available to you. They will be used exclusively for research

purposes. The test results will not be linked to your name or other personally identifying information, but rather will be coded by the study number.

Future testing on your blood samples may include malaria related tests or tests to look at your immune system response to the vaccine and/or malaria infection.

Consent

If there is any portion of this document that you do not understand, ask the investigator before signing the form. Signing this form means that you consent to participate in this research, at this time.

A signed and dated copy of this document will be given to you.

Please initial the sentences that reflect your choices, and then sign below:

_____ *(initials)* I do not authorize the storage of my biological specimens for use in future malaria research studies.

_____ *(initials)* I authorize the storage of my biological specimens for use in future malaria research studies.

_____ *(initials)* I do not authorize the use of my individually identifiable data for future malaria research studies.

_____ *(initials)* I authorize the use of my individually identifiable data for future malaria research studies.

SIGNATURE OF PARTICIPANT

_____
Printed Name of Participant

_____ _____
Signature of Participant Date

_____
Permanent Address of Participant

SIGNATURE OF INDIVIDUAL ADMINISTERING CONSENT
(Can only be signed by an investigator or staff approved to administer consent)

_____
Printed Name of Administering Individual

_____ _____
Signature of Administering Individual Date

Purpose of the Visit	Study Day	Time Needed (Approximate)	Activity	Compensation [i)]
Screening visit 1	1 to 90 days before the Challenge	2 hours	Explanation about the study, informed consent, medical history, demographic information, physical exam including ECG, blood draw for lab work	$50
Screening visit 2	1 to 90 days before the 1st vaccination	1 hour	Medical history since last visit including medications taken, blood draw for lab work	$130
Challenge	Day 1	3 hours	Blood draw, medical history since last visit including medications taken, physical, urine pregnancy test for women, review elimination criteria and eligibility criteria,, Challenge (3rd floor of WRAIR), 30 minute evaluation, new emergency contact card issued	$200

Purpose of the Visit	**Study Day**	**Time Needed (Approximate)**	**Activity**	**Compensation** [i)]
Post-Challenge Follow-up	Post Day of Challenge 5-20	30 minutes	Medical history since last visit including medications taken, physical, blood draw	$130 each day (compensated for 16 days regardless of whether or not you get malaria)
Additional Visits Post-Challenge for those who did not develop malaria Days 5-20 PDOC	PDOC 22, 24, and 26	30 minute each	Every other day, if required: Medical history since last visit including medications taken, vital signs, physical, blood draw	$130 each day (compensated for 3 days regardless of whether or not you get malaria)
Final Visit	Day 28 Post Challenge	30 minutes	Medical history since last visit including medications taken, physical, blood draw	$130 + $250 more if all visits were completed

Note: If you are diagnosed with malaria and finish your treatment before the end of Post-challenge follow-up phase, you may still be compensated for 20 days of CTC visits, if you meet all of your required follow up visits and malaria treatment visits. If you do not complete all of your medical follow up visits, this benefit will not be available to you.

Note: Vitals will be taken at every study visit.