# A Phase Ib randomised, controlled, single-blind study to assess the safety, immunogenicity of the Malaria Vaccine Candidate R21 with Matrix-M1 adjuvant in West African adult volunteers.

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| Author(s): | **CNRFP:** Alfred B. Tiono, Issa N. Ouédraogo, Sodiomon B. Sirima<br>**UOXF:** Egeruan Babatunde Imoukhuede, Adrian VS Hill |

## MODIFICATION HISTORY

**List of Versions**

| Version | Date | Author (s) |
|---|---|---|
| Final v2.0 | 11 June 2015 | UOXF: Egeruan Babatunde Imoukhuede, Adrian VS Hill<br>CNRFP: Alfred B. Tiono, Issa N. Ouédraogo, Sodiomon B. Sirima |
| Final v2.1 | 14 Oct 2015 | UOXF: Egeruan Babatunde Imoukhuede, Adrian VS Hill<br>CNRFP: Alfred B. Tiono, Issa N. Ouédraogo, Sodiomon B. Sirima |
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**PROTOCOL SIGNATURE SHEET**

**Confidentiality Statement**

This document contains confidential information that must not be disclosed to anyone other than the Sponsor, the Investigator Team, members of the Independent Ethics Committee and the Burkina regulatory authority. This information cannot be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Professor Adrian Hill.

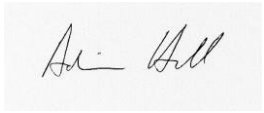
**Statement of Compliance**

The trial will be conducted in compliance with the protocol, International Conference on Harmonisation Good Clinical Practice Guideline E6 (R1) (ICH-GCP) and the applicable regulatory requirements.

**Signatures**

"I have read this protocol and agree to abide by all provisions set forth therein. I agree to comply with the principles of the Declaration of Helsinki and the International Conference on Harmonisation Tripartite Guideline on Good Clinical Practice."

Principal Investigator: _____ Date: 14 Oct 2015

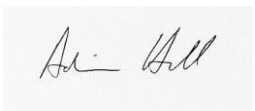


UOXF Chief Investigator: __ _____ Date: 14 Oct 2015

**Conflict of Interest**

"According to the Declaration of Helsinki, 2008, I have read this protocol, and declare no/the following (delete as appropriate) conflict of interest"

Principal Investigator: _____ Date: 14 Oct 2015



UOXF Chief Investigator: _ _____ Date: 14 Oct 2015

**Details of conflict of interest (if any)**

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## KEY ROLES AND GENERAL INFORMATION

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|---|---|
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## LIST OF ABBREVIATIONS

| | |
|---|---|
| **AdCh63** | Chimpanzee Adenovirus 63 |
| **AE** | Adverse event |
| **ALT** | Alanine aminotransferase |
| **AS01** | Adjuvant Systems 01 |
| **BCG** | Bacille Calmette-Guerin |
| **CCVTM** | Clinical Centre for Vaccinology and Tropical Medicine |
| **CBF** | Clinical Biomanufacturing Facility |
| **ChAd63** | Chimpanzee Adenovirus 63 |
| **CMI** | Cell-mediated immunity |
| **CRF** | Case report form |
| **CSP** | Circumsporozoite Protein |
| **CTL** | Cytotoxic T lymphocytes |
| **DSMB** | Data Safety and Monitoring Board |
| **EC** | Ethics Committee |
| **EDCTP** | European and Developing Countries Clinical Trials Partnership |
| **ELISA** | Enzyme-linked immunosorbant assay |
| **ELISPOT** | Enzyme-linked immunospot |
| **FBC** | Full blood count |
| **FP9** | Fowlpox 9 |
| **GCP** | Good Clinical Practice |
| **GMP** | Good Manufacturing Practice |
| **HBsAg** | Hepatitis B surface Antigen |
| **Hib** | Haemophilus Influenzae type b |
| **IB** | Investigator's Brochure |
| **ICS** | Intracellular Cytokine Staining |
| **IDT** | Impfstoffwerk Dessau-Tornau GmbH |
| **IEC** | Independent Ethics Committee |
| **IFN-γ** | Gamma interferon |
| **IMP** | Investigational Medicinal Product |
| **IRB** | Independent Review Board |
| **HBV** | Hepatitis B virus |
| **HIV** | Human Immunodeficiency Virus |
| **HLA** | Human Leukocyte Antigen |
| **LFT** | Liver Function Test |
| **LSM** | Local Safety Monitor |
| **ME-TRAP** | Multiple epitope string with thrombospondin-related adhesion protein |
| **MHRA** | Medicines and Healthcare products Regulatory Agency |
| **MVA** | Modified vaccinia Virus Ankara |
| **MVVC** | Malaria Vectored Vaccines Consortium |
| **NHS** | National Health Service |
| **OXTREC** | Oxford Tropical Research Ethics Committee |
| **PBMC** | Peripheral blood mononuclear cells |
| **PCR** | Polymerase Chain Reaction |
| **pfu** | Plaque forming units |
| **PI** | Principal Investigator |
| **R21** | Recombinant HBsAg protein particle expressing CSP |
| **SAE** | Serious adverse event |
| **SC** | Subcutaneous |
| **SOP** | Standard Operating Procedures |
| **SUSAR** | Suspected unexpected serious adverse reaction |
| **vp** | Virus particles |

 

## 1. VAC060 STUDY SYNOPSIS

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| **Trial Title** | A Phase Ib randomised, controlled, single-blind study to assess the safety and immunogenicity of the Malaria Vaccine Candidate R21 with Matrix-M1 adjuvant in West African adult volunteers. |
| **Trial Identifier** | VAC060 |
| **Clinical phase** | Ib |
| **Active ingredients of vaccines/products** | R21: Recombinant HBsAg protein particle expressing the central repeat and the C-terminus of the circumsporozoite protein (CSP)<br>Matrix-M1: A saponin adjuvant |
| **Finished products** | R21/ Matrix-M1 |
| **Dose(s)** | R21: 10µg and 50µg<br>Matrix-M1: 50µg |
| **Route(s)** | R21/ Matrix-M1 i.m. to deltoid muscle |
| **Principal Investigator**<br>**Trial Centre** | Dr Alfred B. Tiono<br>Centre National de Recherche et Formation sur le Paludisme (CNRFP) Unité de Recherche Clinique, Banfora, Burkina Faso. |
| **Planned Trial Period** | Q3 2015 – Q2 2016 |
| **Study Duration** | Approximately 9 months |
| **Participant duration** | Approximately 6 months |
| **Primary Objective** | To assess the safety and reactogenicity of three (3) doses of 10 & 50 µg of the malaria vaccine candidate R21 adjuvanted with Matrix-M1, given intramuscularly at 0, 1, 2 months schedule in healthy West African adult volunteers living in a malaria-endemic area. |
| **Secondary Objective** | To assess the immunogenicity of three (3) doses of 10 & 50 µg of the malaria vaccine candidate R21 adjuvanted with Matrix-M1, given intramuscularly at 0, 1, 2 months schedule in healthy West African adult volunteers living in a malaria-endemic area. |
| **Population** | Healthy Burkinabe adults aged 18 – 45 years |
| **Planned Sample size** | A total of 24 volunteers will be enrolled into the groups outlined below: |

| Day | Group 1 (n=8) | Group 2 (n=8) | Group 3 (n = 8) |
|---|---|---|---|
| **0** | 10µg R21/ Matrix-M1 | 50µg R21/ Matrix-M1 | saline |
| **28** | 10µg R21/ Matrix-M1 | 50µg R21/ Matrix-M1 | saline |
| **56** | 10µg R21/ Matrix-M1 | 50µg R21/ Matrix-M1 | saline |

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| **Vaccination Schedule** | **Group 1**: Volunteers in group 1 will receive 10µg of R21/ Matrix-M1 at Day 0, 28 and 56 to the deltoid muscle alternately. The first 3 volunteers will be vaccinated in a staggered fashion.<br>**Group 2**: Volunteers in group 2 will receive 50µg of R21/ Matrix-M1 at Day 0, 28 and 56 to the deltoid muscle alternately. The first 3 volunteers will be vaccinated in a staggered fashion.<br><br>All vaccine administrations will be by the i.m. route |
| **Follow-up duration** | All volunteers will be followed up to Day 140 post-first vaccination |
| **Blood Sampling** | Screening, Days 0, 7, 28, 35, 56, 63, 84, 140 |
| **Evaluation Criteria for Safety** | Local and systemic solicited and unsolicited adverse events |
| **Evaluation Criteria for Immunogenicity** | Measures of immunogenicity of R21/ Matrix-M1<br>• Antibodies to CSP and HbSAg by ELISA<br>• Ex vivo gamma-interferon T cell ELISPOT assays (Day 0 and 84 on frozen cells)<br>• ICS and flow cytometry (Day 0 and 84 on stimulated frozen whole blood) |

 

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| | Exploratory immunology, including RNA analysis and DNA analysis to include parasite and human genetic analysis. |
| **Study design** | Randomised, controlled, single-blind clinical trial design |
| **Statistical Analysis** | Observational and Descriptive |

## 2. BACKGROUND INFORMATION

With the estimated 219 million cases of malaria worldwide in 2010 coupled with approximately 660,000 deaths occurring in predominantly children under the age of five years[1] in Africa (where 90% of deaths are recorded), malaria is still the preeminent tropical infectious disease globally, with a devastating effect on human health and society. The enormous economic and social consequences of malaria have been well documented[2]. Malaria is still a potentially fatal hazard for travellers visiting malaria-endemic regions. The development of an effective vaccine against malaria is of high priority in the context of coordinated efforts to reduce the burden of malaria and is considered necessary for the global eradication of malaria[3].

The Roll Back Malaria (RBM) Partnership (www.rollbackmalaria.org) launched in 1998 by the World Health Organization (WHO) has as its major goal to support the development of a vaccine against malaria as a key future strategy for reducing mortality from malaria. The essence of this strategy is highlighted by the limitations of other measures aimed at reducing the burden of malaria include the development of resistance of Anopheles mosquitoes to certain insecticides; the development of resistance of malaria parasites to chemotherapeutic agents[4]; the absence of a gametocidal drug suitable for mass administration[5], and the risk of re-importation of malaria into geographic regions despite environmental elimination measures.

### 2.1. Lifecycle of the malaria parasite

The malaria lifecycle is complex with stages in both human and mosquito hosts (Figure 1). The bite of infected female Anopheles mosquitoes transmits malaria sporozoites to the human host where they travel via the bloodstream to the liver and invade hepatocytes. Here, during the liver stage, they mature into merozoites for 6 to 7 days. Malaria parasites are not detectable in the blood stream during the liver stage. The hepatocytes then rupture, releasing a large number of merozoites into the bloodstream signalling the onset of the blood stage.

Merozoites invade erythrocytes where they multiply and after 2 days cause the erythrocyte to rupture, releasing progeny merozoites that in turn invade new erythrocytes. A small percentage of merozoites differentiate into gametocytes, which when ingested by a mosquito, unite with another gametocyte to create a zygote. The zygote matures and releases sporozoites which migrate to the mosquito's salivary glands and are injected into the human when the mosquito feeds. Patency refers to the ability to detect parasites on examination of the peripheral blood during the blood stage.

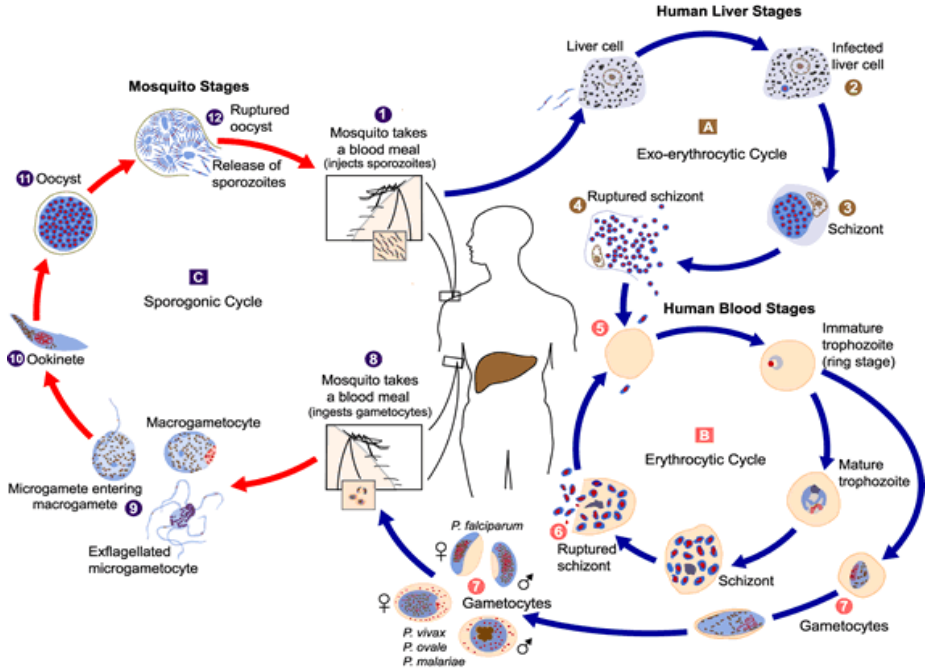



**Figure 1** *Lifecycle of Malaria*

## 2.2. Progress towards a malaria vaccine

The most advanced candidate malaria vaccine, RTS,S, targets antibodies against the circumsporozoite protein (CS), which is expressed by the sporozoite at the pre-erythrocytic stage. RTS,S formulated with the $AS01_E$ adjuvant has now shown partial efficacy in Phase II[6,7] and in analyses of a large Phase III trial[8]. The co-primary end point of the trial has recently been published[6, 7]. Vaccine efficacy (VE) against clinical malaria after 12 months of follow-up post dose 3 in the first 6000 children enrolled in the 5 to 17 month group was 55.8% (97.5% CI: 50.6, 60.4; p<0.001) and against severe malaria 47.3% (95% CI: 22.4, 64.2; p<0.001). In the younger age category, VE against clinical malaria after 12 months of follow-up post dose 3 was 31.3% (p<0.0001) and VE against severe malaria was 36.6% (p=0.02).

The only other vaccination approach that has demonstrated partial efficacy in humans involves using heterologous vectored vaccines in prime-boost sequence to induce a T cell response against the pre-erythrocytic antigen, TRAP[9, 10, 11]. T cell responses provide protection against malaria in animal models[12], in the field[13-15], following irradiated sporozoite inoculation[16-18] and following vaccination. Immunisation of mice with irradiated sporozoites of murine *Plasmodium* provides protection against later challenge with murine malaria sporozoites[12]. This protective immunity can be transferred to non-immune mice by transferring the CD8+ T lymphocyte clones specific to pre-erythrocytic malaria surface antigens, the circumsporozoite protein (CS), or thrombospondin related adhesion protein (TRAP) that were induced by irradiated sporozoites[16,17]. In the heterologous prime-boost strategy, two different vectored vaccines, both containing ME-TRAP, are given in sequence. This achieves an expansion of T cells reactive to TRAP, and to the ChAd63 vector. Heterologous prime-boost vaccination with DNA containing ME-TRAP (DNA ME-TRAP) followed by recombinant MVA containing ME-TRAP (MVA ME-TRAP) led to significant reductions of an estimated 80% in parasite burden in the liver on human challenge with malaria infection[19-21]. In one study[21], one of eight vaccinees was sterilely protected and in another[19], there was a significant delay in the time to patency. Several clinical trials using this heterologous prime-boost approach and several vectors (FP9, ChAd63) have been consistently carried out in Oxford. Vaccination with FP9 ME-TRAP followed by MVA ME-TRAP led to an estimated 90% reduction in parasite burden in the liver, with two of sixteen vaccinees protected against malaria challenge[20, 22]. Following these promising findings, studies were undertaken in adults and then children in The Gambia and Kilifi[23-25]. Immunogenicity was lower than expected[25], and efficacy was not seen in a study of 400 children in Kilifi district[26]. From these studies it has emerged that T cell responses are a correlate of protection induced by these vaccination strategies, as measured by delay in time to patency or reduction in parasite burden in the liver on malaria challenge.[20,27] Further development of T cell inducing vaccination in Oxford examining more immunogenic vectors in order to attain greater efficacy has led to preclinical and phase I and II clinical development of malaria vaccination strategies using adenoviral and MVA vectors in heterologous prime-boost vaccination strategies with TRAP inserts. These clinical trials in UK and Africa have shown that these vaccines have been safe, tolerable and have induced adequate immune responses[28, 29] that have been shown to be protective[9]. An efficacy clinical trial in 700 children aged 5-17 months old is on-going in Burkina Faso and results are expected at the end of Q3 2015.

The potential to combine these two vaccine approaches is evident. The rest of this section provides background on the vaccination approach relevant to this protocol. Section 3 highlights and summarises the clinical trials relevant to this protocol.

## 2.3. PRE-ERYTHROCYTIC STAGE OF INFECTION AS A VACCINE TARGET

The pre-erythrocytic stage of *P. falciparum* infection presents an attractive target for an efficacious human vaccine, as sufficient reduction in the number of viable merozoites reaching the blood from the liver will prevent parasitisation of red blood cells and initiation of the blood stage of infection. Anti-CS antibodies can target sporozoites, facilitating destruction of sporozoites prior to hepatocyte invasion. As sporozoites travel from the skin to liver within minutes, it may be difficult for a vaccine to achieve complete protection against *P. falciparum* based solely on antibodies to sporozoites. The liver stage of infection provides a longer window of opportunity for cell mediated immunity to recognize and destroy infected hepatocytes. Research suggests that, in isolation the RTS,S vaccine targeting the pre-erythrocytic stage antigen, CS, and vaccines targeting ME-TRAP do not delay the initial emergence of parasites in to the blood, nor the rate of parasite multiplication in the blood, but rather reduce the size of this initial inoculum[20]. A delay to patent blood stage infection in persons receiving these vaccines reflects a reduced liver-to-blood inoculum. The efficacy of these pre-erythrocytic vaccine strategies can be assessed experimentally by subjecting volunteers to inoculation with *P. falciparum* sporozoites by the bite of infected mosquitoes. Complete protection against blood-stage infection, or a delay in the time to patent blood stage infection in vaccinees compared to controls, are interpreted to understand vaccine-induced protection.

### 2.3.1. R21 vaccine development

RTS,S/AS01 vaccine, induces very strong antibody responses to the conserved central repeat of CSP, of the order of 100 - 600 micrograms per ml, very weak mainly IL-2 containing CD4+ T cells and no CD8+ T cells to CSP.[7] The most reproducible correlate of protection in clinical studies is with antibody levels[7,8]. We propose here to test clinically a biosimilar of the RTS,S vaccine called R21 adjuvanted with Matrix M-1. As a biosimilar of the RTS,S vaccine, the R21 particle contains no sequences that are not present in RTS,S, which has been safely used in thousands of individuals. It is a hybrid protein of the majority of the CS protein of *P. falciparum* fused to the hepatitis B surface antigen (Figure 2). It spontaneously forms a particle just like RTS,S. However, we anticipate that R21 may be a more immunogenic particle than RTS,S in humans (although this has yet to be tested) for two reasons. It induces predominantly malaria rather than hepatitis antibodies in pre-clinical studies probably because it has a higher proportion of malaria to hepatitis antigen in its composition than RTS,S. This is made possible by expressing R21 in the better expressing yeast *Pichia pastoris*, rather than in *Saccharomyces cerevisiae*. Secondly, in pre-clinical studies R21 has been found to be exceptionally immunogenic for induction of anti-NANP antibodies, likely the key protective immune mechanism of RTS,S, yielding titres of a mean of 800,000 ELISA units after two immunisations which exceeds historical immunogenicity data obtained with the RTS,S vaccine of 150,000 ELISA units, at the UOXF laboratory. (K Collins and A Hill, unpublished data).

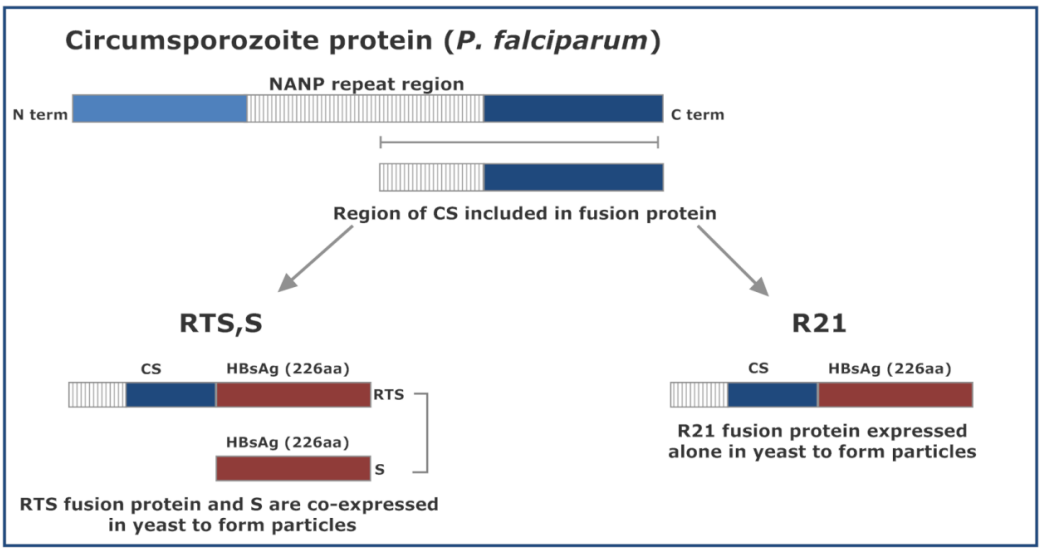



**Figure 2**: *Schematic diagram showing RTS,S and R21 fusion proteins*

### 2.3.2. Pre-clinical studies of R21

**Immunogenicity**: Initial pre-clinical assessment of immunogenicity was undertaken in BALB/c mice that were immunised intramuscularly with 0.5mg of R21 alone or in combination with an adjuvant (Alhydrogel, Abisco). Immune responses including antibody levels to the central NANP repeat region and antigen–specific T cell responses were measured three weeks after a 3-dose immunisation schedule (Figure 3). R21 + Abisco-100, a potent saponin-based adjuvant used in animal studies resulted in the greatest humoral immune response at each time point in the vaccination schedule.

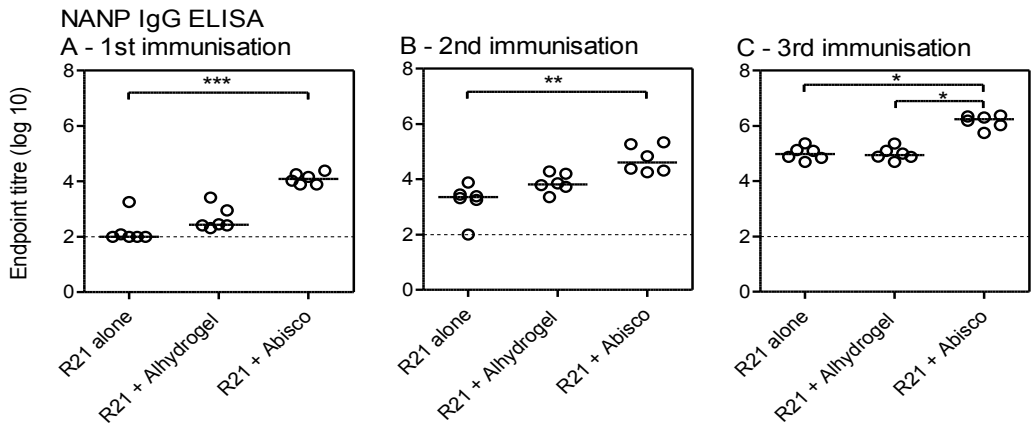



**Figure 3***: Pre-clinical assessment of immunogenicity with 0.5mg of R21 alone or in combination with an adjuvant (Alhydrogel, Abisco).*

The responses in all groups were boosted by a third immunisation and R21 + Abisco-100 induced the highest titres of NANP specific IgG and the response for this group was significantly higher than both the R21 + Alhydrogel and R21 alone groups after the final immunisation (Figure 3.1).

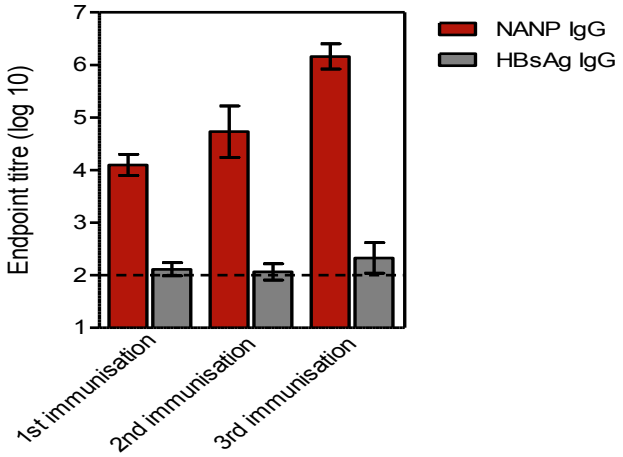



**Figure 3.1**: *Relative proportions of IgG to NANP and HBsAg after immunisation with R21 + Abisco-100 in BALB/c mice.*

CS-specific IFN-γ producing T cells measured after the third immunisation were only detected at a significant level in mice immunised with R21 + Abisco-100 (Figure 3.2). R21 alone was ineffective at inducing CS-specific T cell responses on its own. Further comparison to other adjuvants including a squalene-based oil-in-water emulsion (Addavax) and a polyionic carbomer (Carbopol) showed that Abisco-100 was the ideal adjuvant to induce high levels of humoral and cell-mediated immunity.

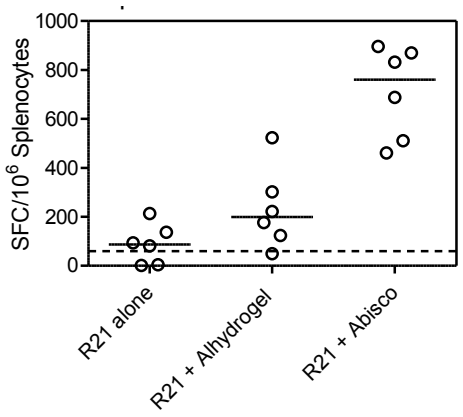
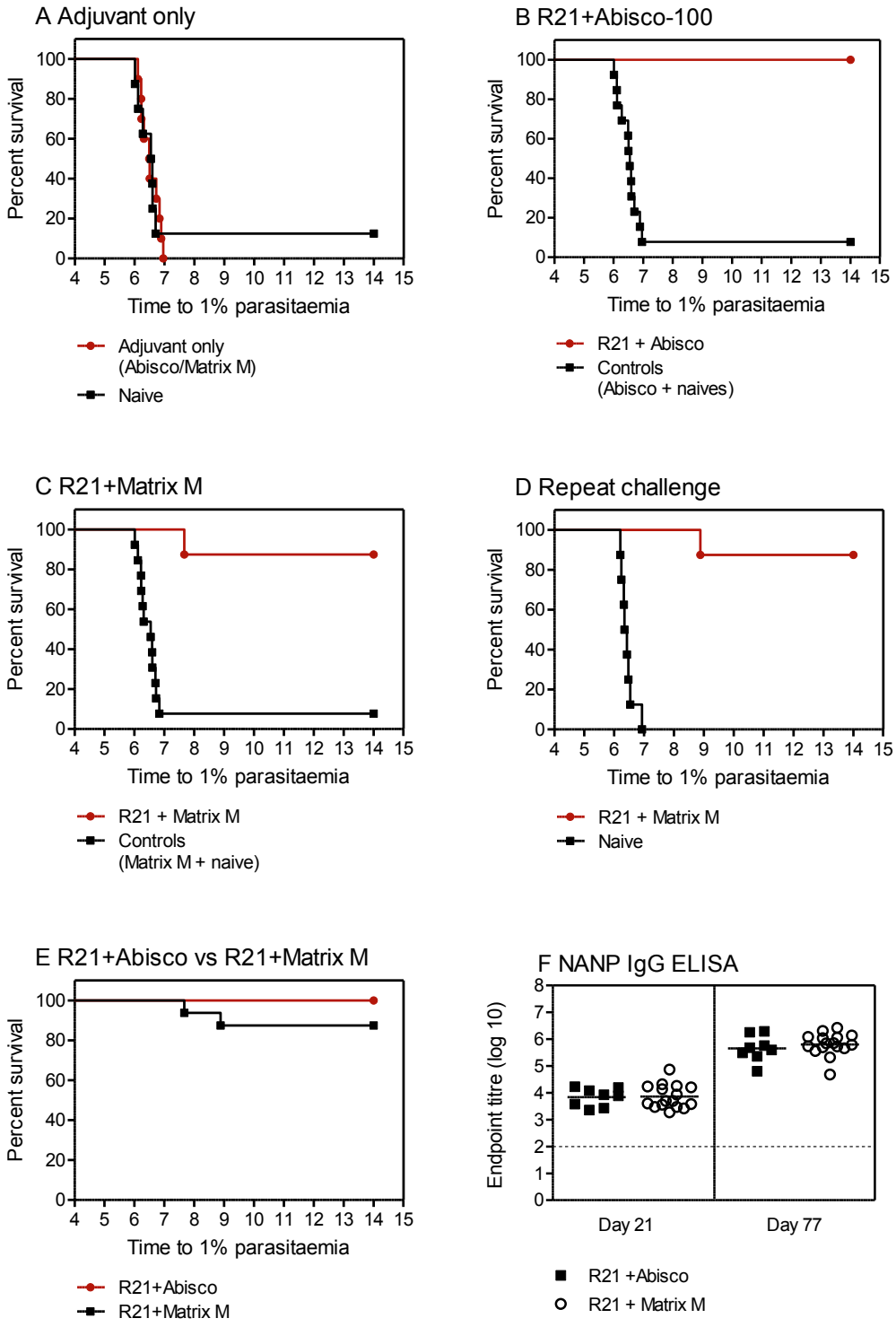



**Figure 3.2**: *CS-specific IFN-γ producing T cells measured after the third immunisation*

**Efficacy:** Sporozoite challenge (1000 sporozoites per mouse injected intravenously) using transgenic *P. berghei* parasite were performed in BALB/c mice (Figure 3.3). R21 + adjuvant were given twice, eight weeks apart and mice were challenged three weeks after the second dose. Thin blood films looking for parasitaemia were performed daily from day 5 post-challenge. Sterile protection was defined as remaining slide negative at day 14 and significant delay in development of 1% parasitaemia compared to non-immunised control mice was regarded as partial efficacy.
R21 + Abisco-100 steriley protected 100% of the challenged mice (p=< 0.0001) and R21 + Matrix M steriley protected 87.5% (p=0.0002) and this was confirmed in a second independent challenge. (p = < 0.0001). There was no significant difference between the two adjuvants.

**Figure 3.3 (A-F):** *Protective efficacy elicited by saponin based ISCOM adjuvants with R21 in a transgenic sporozoite model.*
*BALB/c mice were immunised i.m. with 0.5µg R21 + adjuvant (Abisco-100 or Matrix M), twice eight weeks apart (n=8/group). Mice were challenged three weeks after the final vaccination by i.v. injection of 1000 sporozoites (P. berghei transgenic for P. falciparum CSP) along with eight naïve mice. Two groups of adjuvant control mice (n=5/group) were also challenged three weeks after receiving two shots of adjuvant (Abisco-100 or Matrix M) i.m., eight weeks apart. Blood stage parasitemia was monitored from day 5 after challenge by thin-film blood smear, and time to 1% parasitemia was calculated using linear regression. The results are presented in the Kaplan-Meier survival graphs and survival curves were compared by Log-rank (Mantel-Cox) Test.* ***(A)*** *Adjuvant control = no significant difference,* ***(B)*** *R21 + Abisco-100 p<0.0001,* ***(C)*** *R21 + Matrix M p=0.0002,* ***(D)*** *R21 + Matrix M repeat p=<0.0001,* ***(E)*** *R21 + Abisco vs R21 + Matrix M = no significant difference. Blood was taken three weeks after each vaccination (Day 21 and Day 77) for immunology and NANP specific IgG was assayed by ELISA* ***(F)****, group mean responses shown and dotted line indicates the limit of detection.*




The durability of efficacy was assessed by undertaking sporozoite challenge in mice seven and fourteen weeks after immunisation. Efficacy was maintained very well at seven weeks post immunisation with 75% of mice sterilely protected (6/8) and this was not significantly different when compared to efficacy at three weeks post immunisation (p=0.4468, by Log-rank (Mantel-Cox) Test). At 14 weeks post immunisation however, sterile efficacy was reduced to 50% (2/4) and this was 37% lower than the efficacy at three weeks. This was not significantly lower due to the small number in the group (p=0.0636), had there been eight mice in the group 50% sterile efficacy would have been significantly lower than 87.5%. Sterile efficacy 14 weeks after immunisation is 37% lower than efficacy three weeks after immunisation. This reduction in protective efficacy can however be boosted to 100% if mice are challenged once (three weeks post immunisation) within the 14 weeks. Therefore efficacy after vaccination and one sporozoite infection is very durable and 100% sterile efficacy is maintained for at least 14 weeks.

Manufacture of the clinical grade R21 particle was performed at the University of Oxford CBF (www.cbf.ox.ac.uk), with financial support from the UK Medical Research Council (MRC) and the EC FP7 programme. A Phase 1 CT is due to commence at CCVTM, University of Oxford in Q3 2015.

### 2.3.3. Matrix-M1 adjuvant

Matrix M™ is a saponin-based product produced using the matrix adjuvant technology patented by Isconova (now owned by Novovax). Matrix-M1 is a novel adjuvant designed to stimulate both humoral and cellular immune responses to vaccines. Matrix-M1 is formed from selected purified saponin fractions formulated separately into different Matrix particles, Matrix A and Matrix C. Matrix-M1 is constituted from a mixture of Matrix A and Matrix C in a ratio of 85:15.

Matrix M™ has previously been used to adjuvant an intranasal DNA vaccine, leading to improvements in local antibody responses, and increased expression of Th1 and Th2 cytokines. Matrix M™ significantly enhanced antibody responses to a commercial trivalent seasonal influenza vaccine. Mixed with a virosomal H9N2 avian influenza vaccine, Matrix-M1 induced enhanced antigen-specific humoral and CD8+ T cell response. Matrix M™ administered with an intramuscular H5N1 virosomal influenza vaccine induced a strong immediate and long-term humoral and cellular immune response and showed a dose-sparing potential.

ChAd63/Matrix-M1 and MVA ME-TRAP/Matrix-M1 adjuvanted mixed vaccine combinations have been shown to be safe and immunogenic in the VAC048 clinical trial currently on-going in Oxford, UK. Adverse events such as pain and swelling related to inflammation at the site of vaccination were observed. Systemic symptoms were also observed but these were generally flu-like symptoms. Adverse events were generally mild and resolved completely within 24-48hrs. To date, no significant safety concerns relating to the administration of the mixture of ChAd63/Matrix M-1 and MVA ME-TRAP/Matrix M-1 vaccine have emerged from clinical or preclinical studies.

In this protocol, we plan to conduct a phase I / IIb randomised, controlled, single-blind study to assess the safety, immunogenicity of the malaria vaccine candidate R21 with Matrix-M1 as adjuvant, in Burkinabe adult volunteers aged 18-45 years.

## 3. RATIONALE

In summary, the vaccination regime described here targets the pre-erythrocytic stage of the malaria parasite life cycle and induce specific immune responses through distinct mechanisms. The RTS,S/AS01$_B$ vaccination regime has demonstrated pre-erythrocytic stage immunity that has translated into sterile efficacy against experimental human *P. falciparum* infection. R21 is a bio similar of the RTS,S vaccine. A Phase 1/IIa clinical trial of the R21/ Matrix-M1 vaccination regime is scheduled to start in Q3 2015 at CCVTM, University of Oxford and it is expected that this trial will produce equally good results as obtained with the RTS,S/AS01$_B$ vaccination regime. This will be the first time this vaccine will be administered to humans. Interim results of this clinical trial will be available in late Q4 2015.

Here we propose to evaluate, for the first time in an African population, the R21/ Matrix-M1 vaccination regime in a phase 1b safety and immunogenicity evaluation clinical trial in West African adults living in Burkina Faso.

## 4. OBJECTIVES

### 4.1. Primary Objective

To assess the safety and reactogenicity of three (3) doses of 10 & 50 µg of the malaria vaccine candidate R21 adjuvanted with Matrix-M1, given intramuscularly at 0, 1, 2 months schedule in healthy West African adult volunteers living in a malaria-endemic area.

### 4.2. Secondary Objective

To assess the immunogenicity of three (3) doses of 10 & 50 µg of the malaria vaccine candidate R21 adjuvanted with Matrix-M1, given intramuscularly at 0, 1, 2 months schedule in healthy West African adult volunteers living in a malaria-endemic area.

# 5. DESCRIPTION AND JUSTIFICATION OF STUDY DESIGN

## 5.1. Overview

A randomised, controlled, single-blind clinical trial is proposed to evaluate the safety and immunogenicity of the malaria vaccine candidate regime of three (3) doses of R21/ Matrix-M1 compared with placebo, in healthy West African adult volunteers living in a malaria-endemic area.

## 5.2. Vaccines

**R21**: Recombinant HBsAg protein particle expressing the central repeat and the C-terminus of the circumsporozoite protein (CSP).
**Matrix-M1**: A saponin adjuvant. It will be administered with the R21 vaccine.

## 5.3. Evaluation Criteria

### *5.3.1. Safety endpoints*

Local and systemic solicited and unsolicited adverse events, considered possibly, probably, or definitely related to vaccination, occurring for 28 days after each vaccination. Solicited adverse events will be measured up to 7 days after each vaccination. Unsolicited adverse events will be measured up to 28 days after each vaccination.
Solicited local (injection site) adverse events to be observed and recorded include pain/limitation of limb movement, swelling and redness/discoloration. Solicited systemic adverse events include fever, chills, headache, malaise, joint pains, myalgia, fatigue and nausea.

SAEs occurring from first vaccination until the end of the study will be recorded

### *5.3.2. Immunogenicity endpoints*

Measures of immunogenicity of R21/ Matrix-M1 will include:

- Antibodies to CSP and HbSAg by ELISA
- Ex vivo gamma-interferon T cell ELISPOT assays (Day 0 and 70 on frozen cells)
- ICS and flow cytometry (Day 0 and 70 on stimulated frozen whole blood)
- Exploratory immunology, including RNA analysis and DNA analysis to include parasite and human genetic analysis.

## 5.4. Study site

The study will take place at the Banfora clinical trial site, which is located about 400 km from Ouagadougou, the capital city of Burkina Faso. The Unite de Recherche Clinique de Banfora (URC-B) research unit is situated within the complex of the Regional hospital. The trial participants will be drawn from Banfora Health demographic system that covers a total population of 30,000 inhabitants. From recent surveys, the bed net coverage was 80%. There is no implementation of Indoor Residual Spray (IRS) or Intermittent Preventive Treatment (IPT) in infants or children in the area. Malaria transmission is perennial with peaks during the high transmission season (June to November). The main malaria vectors are *Anopheles gambiae* and *Anopheles funestus*. The cumulative annual entomological rate varies from 55 to 400 infective bites/person/year (Moussa G et al, unpublished). *P. falciparum* is the main parasite present in more than 90% of infections. The incidence rate of uncomplicated malaria (fever and parasitaemia 5000/µL or more) in less than five years is 1.18 episodes/child-year at risk and around 60% of the total annual number of malaria episodes occurs during the high malaria transmission season[41] (). The asymptomatic carriage of *P. falciparum* is very common. In 2010, during the high transmission period, the prevalence was 46.6%, 72.5% and 38.5% in 0-4 years, 5-14 year and 15-24 years respectively. During the low transmission season, the prevalence in the same age range was 27.2%, 60.4% and 25.5% respectively. (Tiono et al, unpublished). Overall to date there is no evidence of the decline in malaria incidence in Burkina similar to what has been recently reported from other parts of sub-Saharan Africa. The annual malaria death toll is reaching 15,000 people and across the country's hospitals, malaria is reportedly responsible for 30.7% of all hospitalization with a mortality rate of 23%.

## 5.5. Study groups

A total of 24 volunteers in 3 equal groups as outlined below:

| Day 0 | Group 1 (n=8) | Group 2 (n=8) | Group 3 (n=8) |
|---|---|---|---|
| **0** | 10µg R21/ Matrix-M1 | 50µg R21/ Matrix-M1 | saline |
| **28** | 10µg R21/ Matrix-M1 | 50µg R21/ Matrix-M1 | saline |
| **56** | 10µg R21/ Matrix-M1 | 50µg R21/ Matrix-M1 | saline |

### 5.6. Vaccination Schedule

The vaccination groups are outlined below:

**Group 1**: Volunteers in group 1 will receive 10µg of R21/ Matrix-M1 at Day 0, 28 and 56 to the deltoid muscle alternately. The first 3 volunteers will be vaccinated in a staggered fashion.

**Group 2**: Volunteers in group 2 will receive 50µg of R21/ Matrix-M1 at Day 0, 28 and 56 to the deltoid muscle alternately. The first 3 volunteers will be vaccinated in a staggered fashion.

All vaccine administrations will be by the i.m. route.

*Before vaccinations commence in this clinical trial, a DSMB review of the interim safety report for the low and high dose of R21 given to volunteers in the Phase I CT in Oxford will be assessed.* A DSMB review of the interim safety report after vaccination of the first 3 volunteers in Group 1 will be required before vaccinations commence in Group 2.

The control group will undergo similar tests to the vaccinated groups including ELISA, ex-vivo and cultured ELISPOT and ICS

## 5.7. Follow-up of volunteers

### 5.7.1. Safety follow-up

All volunteers will be followed up to Day 140 post-first vaccination for adverse events following vaccination. SAE's will be collected throughout the duration of the study for each volunteer.

Study clinicians and field workers (supervised by medical officers) will assess and record local adverse events post vaccination including pain, swelling and limited arm movement. In addition, systemic Adverse Events (AE's) including fever, chills, headache, malaise joint pains, myalgia, fatigue and nausea will be recorded. Each side effect will be classified as absent, mild, moderate or severe. Information on AE's will also be collected at each clinic visit by the study clinician. Each volunteer will be seen at home by field workers on Days 1-6 following each vaccination. Day 7 will be a clinic visit. The study clinicians will review reports from home visits conducted by field workers, and arrange to see the volunteers in person when required. The volunteers will be asked to present themselves to the study clinic should they develop any illnesses during follow up. Any emerging safety data that is considered cause for concern by the DSMB will be relayed to the participants during the study visits.

## 5.8. Sample size justification

This is an observational and descriptive safety study, where volunteers 8 volunteers each will be vaccinated with either 10µg of R21/ Matrix-M1 or 50µg of R21/ Matrix-M1 at Day 0, 28 and 56. A further 8 volunteers will receive normal saline (placebo) as control group. The sample size for this clinical trial balances the need to avoid exposing a large group to an unknown risk with the need for data from an adequate sample. This sample size should allow determination of the magnitude of the outcome measures, especially of severe and serious adverse events, rather than aiming to obtain statistical significance for differences between groups.

Specific immunogenicity to CSP and HbSAg will be assessed by a variety of immunological assays. The key immunogenicity assessment in this trial is whether administration of 3 doses of either 10µg of R21/ Matrix-M1 or 50µg of R21/ Matrix-M1 induces adequate vaccine immunogenicity at the peak of the response, in comparison to a placebo.

## 5.9. Potential risks for volunteers

The risks of study participation are those relating to vaccination and blood sampling. Volunteers will receive three vaccinations with a 3-dose regimen or a placebo four weeks apart. Vaccinations are expected to be generally well tolerated. Local reactions are expected at the injection site such as pain, swelling or erythema, and less commonly there may be minor fever or malaise as a systemic reaction. These reactions should generally be mild and resolve completely after two (2) days.

### 5.9.1. Phlebotomy

The maximum volume of blood drawn over the study period approximately 190 mls should not compromise these otherwise healthy volunteers. There may be minor bruising, local tenderness or pre-syncopal symptoms associated with venepuncture, which will not be documented as AEs if they occur.

### 5.9.2. Safety and tolerability of R21/Matrix- M1 vaccination

The most frequent adverse reactions observed in previous clinical trials using the RTS,S antigen and $AS01_B$ adjuvant system include pain, swelling, erythema, and tenderness at the site of injection, and systemic symptoms such as low-grade fever and short-term flu-like symptoms: fatigue, myalgia, headache, malaise. It is expected that R21 antigen (a biosimilar of RTS,S) with Matrix-M1 as adjuvant will produce similar or better AE profile.

As with any vaccine, unexpected serious adverse events, including severe allergic reactions to the vaccine components may occur. Some individuals vaccinated with adjuvant components identical to those that will be used in this study have reported autoimmune diseases (AID). A causal association between the adjuvant components and occurrence of autoimmune diseases has however not been established, as these can occur in people who get other vaccines, or no vaccines at all. A meta-analysis of a GSK adjuvanted vaccine showed no increased risk of AID associated to the adjuvant.[35]

## 5.10. Potential benefits for volunteers

Participants will not directly benefit from participating in this clinical trial except for adequate information on their health status and free medical care for the volunteers during the course of the clinical trial.

In terms of protection against malaria, a biosimilar of R21 (RTS,S adjuvanted in $AS01_B$) is the leading malaria vaccine candidate and has shown consistent partial efficacy in field clinical trials in Africa. We expect similar or better results with the R21/Matrix M-1 vaccine regime. However, because malaria mainly affects young children, the benefits of participating in this study may be considered as being altruistic in nature as they would potentially benefit the wider society at large, if the vaccine is eventually proved to be safe and efficacious. Volunteers will be advised that participating in the study does not reduce the need for continuing to use known preventive measures against malaria.

# 6. Inclusion and Exclusion Criteria

The inclusion criteria will be used at screening to identify volunteers eligible for the study, and will be checked prior to vaccination to confirm ongoing eligibility. Eligible volunteers will fulfil all of the inclusion criteria and none of the exclusion criteria. We will continue to recruit and screen volunteers until at least 24 eligible volunteers have been identified, preferably until 24 eligible volunteers have been identified. If volunteers withdraw consent prior to receiving their first vaccination, we will replace the volunteer or screen and recruit in order to replace the number withdrawing consent.

## 6.1. Inclusion Criteria

The volunteer must satisfy all the following criteria to be eligible for the study:

- Healthy adults aged 18 to 45 years.
- Willingness to remain in study area for the period of the study.
- Able and willing (in the Investigator's opinion) to comply with all study requirements.
- Women only: Must practice and show documented evidence of continuous effective contraception (e.g depo-progesterone) or must be willing to take contraceptive measures not to become pregnant for the duration of the study. Willing to have pregnancy tests at screening and vaccination time points.
- Agreement to refrain from blood donation during the course of the study
- Written informed consent to participate in the trial.

### 6.2. Exclusion Criteria

The volunteer may not enter the study if any of the following apply:

- Hb less than 10.0g/dl
- Receipt of an investigational product in the 30 days preceding enrolment, or planned receipt during the study period.
- Prior receipt of an investigational malaria vaccine or any other investigational vaccine likely to impact on interpretation of the trial data.
- Any confirmed or suspected immunosuppressive or immunodeficient state, including HIV infection; asplenia; recurrent severe infections and chronic (more than 14 days) immunosuppressant or other immune-modifying drugs medication (for corticosteroids, this will mean prednisone, or equivalent, ≥ 0.5 mg/kg/day) within the past 6 months (inhaled and topical steroids are allowed).
- Use of immunoglobulins or blood products within 3 months prior to enrolment.
- History of allergic disease or hypersensitivity reactions likely to be exacerbated by any component of the study vaccines.
- Any history of anaphylaxis post-vaccination.
- History of clinically significant contact dermatitis.
- Pregnancy, lactation or intention to become pregnant during the study.
- Disturbances of electrolyte balance, e.g., hypokalaemia or hypomagnesaemia
- History of cancer (except basal cell carcinoma of the skin and cervical carcinoma in situ).
- History of serious psychiatric condition that may affect participation in the study.
- History of splenectomy
- Any other serious chronic illness requiring hospital specialist supervision.
- HIV or Hepatitis B surface antigen seropositivity
- Volunteers unable to be closely followed for social, geographic or psychological reasons.
- Any clinically significant abnormal finding on biochemistry or haematology blood tests, urinalysis or clinical examination. In the event of abnormal test results, confirmatory repeat tests will be requested.
- Any other significant disease, disorder, or finding which may significantly increase the risk to the volunteer because of participation in the study, affect the ability of the volunteer to participate in the study or impair interpretation of the study data.

### 6.3. Withdrawal criteria

Participants may be withdrawn from the study:

- By withdrawing consent
- On the decision of the investigator
- On the advice of the Data Safety Monitoring Board (DSMB)

The investigator may withdraw the subject for the following reasons:

- Any adverse event which results in the inability to comply with study procedures or affect the participant safety.
- Ineligibility either arising during the study or retrospectively (having been overlooked during screening)
- Significant protocol deviation.

## 7. INVESTIGATIONAL MEDICINAL PRODUCTS

R21 adjuvanted with Matrix-M1 is the only study vaccine for this clinical trial.

### 7.1. Manufacturing and presentation of vaccines

#### 7.1.1. R21 vaccine

R21 vaccine is manufactured under Good Manufacturing Practice (GMP) conditions by the Clinical Biomanufacturing Facility (CBF), University of Oxford. Final QP certification and associated labelling will take place at the CBF, University of Oxford. R21 will be supplied in a sterile pharmaceutically suitable container with appropriate closure. The product will be stored frozen (-80°C)

### Supply of R21

R21 will be supplied to the clinical sites by the CBF, University of Oxford, where the vaccines were manufactured, vialed and labelled for trial VAC060.

### Supply of Matrix-M1

Matrix-M1 was manufactured in compliance with cGMP by Apoteket Produktion & Laboratorier AB (APL) Formvägen 5B, SE-903 03 Umeå, Sweden. Matrix- M1 is supplied as a sterile 1mg/ml solution in 2ml glass vials.

## 7.2. Storage, dispensing and handling of Investigational Medicinal Products

All study vaccines to be administered to the volunteers must be stored in a safe and locked place with no access by unauthorised personnel. Vaccine accountability, storage, shipment and handling will be in accordance with local SOPs.

### 7.2.1. Storage of R21/Matrix M-1

The R21 vaccine must be stored at the defined temperature of (-80°C). The storage conditions will be under the responsibility of the sponsor and then the clinical site after shipment has occurred. Any temperature deviation outside the defined range must be reported to the sponsor as soon as detected. Matrix–M1 will be stored between + 2 and +8 °C.

## 7.3. Vaccination of volunteers

Each volunteer will be monitored for one hour (or longer if necessary) after each vaccination. Resuscitation (including intubation) equipment and medication will be available in the clinic site and a clinician trained in resuscitation will be present at all times during this vaccination time period. Advanced Life Support drugs and resuscitation equipment will be immediately available for the management of anaphylaxis.

All vaccinations will be by the intramuscular route. The study vaccines should under no circumstances be administered intravascularly or intradermally. For all intramuscular injections, the needle should be long enough to reach the muscle mass and prevent the vaccine from seeping into subcutaneous tissue, but not so long as to involve underlying nerves, blood vessels or bone. Vaccinators should be familiar with the anatomy of the area into which they are injecting vaccine. Firm pressure should be applied to the injection site (without rubbing) for at least two minutes.

### 7.3.1. R21/Matrix-M1 vaccinations

The R21/Matrix-M1 vaccine mixture containing either 10µg or 50µg of R21 with 50µg Matrix-M1 will be administered intramuscularly into the deltoid muscle starting with the left arm then alternately for the remaining two doses. Matrix-M1 and R21 will be mixed at the bedside immediately prior to administration according to the specific mixing SOP.

All vaccines will be kept at room temperature between removal from the refrigerator or freezer and administration. If for any unforeseen reason the preferred administration site could not be used at the time of the vaccination, an alternative administration site will be used. The alternative site will be documented in vaccine administration records as well as the reasons why alternative site was used.

## 7.4. Concomitant medication/vaccination

At each study visit, the investigator should question the enrolled volunteer about any medication(s) taken.
All antipyretic, analgesic and antibiotic drugs, administered at any time during the period starting with administration of each dose and ending 28 days after each dose of vaccine are to be recorded with generic name of the medication (trade names are allowed for combination drugs), medical indication, total daily dose, route of administration, start and end dates of treatment.

Any immunoglobulin, blood products and any immune modifying drugs administered at any time during the study period are to be recorded with generic name of the medication (trade names are allowed for combination drugs only), medical indication, total daily dose, and route of administration, start and end dates of treatment.

Any vaccine not foreseen in the study protocol administered during the volunteer participation in the trial is to be recorded with the trade name, route of administration and date(s) of administration.

Any concomitant medication administered as prophylaxis in anticipation of reaction to the vaccination must be recorded in the CRF with generic name of the medication (trade names are allowed for combination drugs only), total daily dose, route of administration, start and end dates of treatment and coded as 'Prophylactic'

### 7.5. Indications for deferral of vaccine administration

The following constitute conditions for deferring administration of vaccines at vaccination time points. If any one of these occurs at the time scheduled for vaccination, the volunteer may be vaccinated at a later date or withdrawn, at the discretion of the Principal Investigator. Medical care including inpatient care if necessary will be offered.

- Acute disease at the time of vaccination. Acute disease is defined as the presence of a moderate or severe illness with or without fever. All vaccines can be administered to persons with a minor illness at the discretion of the investigators. Details of any minor illness will be recorded in the CRF.
- Axillary temperature of ≥37.5°C (99.5°F) at the time of vaccination.
- Receipt of any other vaccinations within one week of study vaccine

### 7.6. Absolute contraindications to further vaccination

The following AEs constitute absolute contraindications to further administration of any vaccine used in the study. If any of these AEs occur during the study, the subject must not receive additional doses of vaccine, but may continue other study procedures at the discretion of the investigator. The AE should be followed-up as per protocol requirement.

- Acute allergic reaction (significant IgE-mediated events) or anaphylaxis following the administration of the investigational product.
- Any confirmed or suspected immunosuppressive or immunodeficient condition, including human immunodeficiency virus (HIV) infection.

## 8. STUDY SCHEDULE AND PROCEDURES

Prior to the commencement of community sensitisation, the CNRFP study team will be trained on the procedures for community sensitisation, with the clinical trial protocol, volunteer information sheets and consent forms as training guides.

### *8.1.* Identification of Study Participants

Community sensitisation will be undertaken to engage the community with the study and recruit volunteers for participation in the study. Volunteers will be assessed at screening visits to determine if they are eligible to participate in the study.

#### 8.1.1. *Community sensitisation*

The CNRFP study team will hold local community meetings and explain the study to the potentially eligible adult volunteers. During these meetings the investigators will explain the following: the need for a vaccine; the current status of vaccine development (including the fact that this is likely to be a prolonged process); the study screening and informed consent procedure; risks of vaccination and the unproven benefits of vaccination. It will be stressed that these are experimental vaccine regimens and cannot be guaranteed to provide protection, and that it will therefore still be necessary to seek treatment for possible malaria even after vaccination and they should continue to use other protective measures such as bed nets. It will be explained that to aid identification, a photograph of the volunteer will be taken if they are eligible to be enrolled in the trial.

After this meeting based on the list of adults of suitable age for participation in the trial drawn from the DSS database, volunteers will be asked to participate in a public lottery that is made to randomly select participants who will be invited for a screening visit.

A set of sealed envelopes containing "YES" or "NO" will be prepared. When the proposed volunteer's name is called by the investigator, the volunteer will come and randomly pick one envelope. If the envelope containing a "YES" is picked, the proposed volunteer's name will be entered into the screening log sheet. If it is "NO", the proposed volunteer will not be invited for screening. This method has been used in previous trials and is accepted by the communities as a fair way of giving the chance to each eligible volunteer at the meeting who meets the age criteria, to

be invited for the screening visit. All proposed volunteers thus selected will be invited to the Banfora clinical trials centre for the screening visit.

### *8.1.2. Screening Visit*

The Volunteer Information Sheet (VIS) will contain detailed information about the study and will be distributed to the proposed volunteers. The investigators will endeavour to ensure that all volunteers fully understand the risks. Any volunteer who appears to have less than complete understanding will be considered unable to give consent. Volunteers must also understand the very small chance of anaphylactic reactions and thereby the importance of complying with the one-hour (1hr) observation period after each vaccination. The information sheet covers these points in detail, and each volunteer will have the contents of the sheet explained in individual meetings. If it is determined by the investigator conducting the screening visit that free and informed consent is given by the volunteer to participate in the trial, the volunteer will be asked to complete the consent form.

If unable to sign, the volunteer will be asked to thumbprint the consent form in the presence of an impartial witness who will be present during the screening procedures and will countersign the consent form.

Fully consented volunteers will undergo the full screening procedures. This consists of medical history, physical examination, and blood sampling for screening tests as detailed below (Laboratory Evaluations). In summary, each consented volunteer will be screened for clinically significant acute or chronic disease, using both general physical examination and screening laboratory tests (full blood count (FBC), Hepatitis B, alanine transaminase (ALT) and creatinine. Likelihood of migration will be an important factor for non- enrolment. All volunteers will be informed of results of laboratory tests and referral to an appropriate health facility done where necessary. Volunteers will be informed of the need to conduct anonymous HIV testing. All volunteers will receive pre-test counselling from a trained counsellor who will also do post-test counselling after giving the results. HIV positivity will be an exclusion criterion. In order to maintain the confidentiality of those volunteers infected with HIV, we will make it clear that during screening one can be excluded due to a range of diseases (not just HIV) as well as abnormal laboratory results. Enrolment will be done within 14 days of screening.

The investigator will determine whether the volunteer is eligible to participate in the study, using the findings at screening, including the results of the screening blood tests. Volunteers to participate in the study will fulfil all of the inclusion criteria, and meet none of the exclusion criteria. Volunteers enrolled will be given photo identity (ID) cards for ease of identification and also to serve as a reminder of the appointment dates. These will be destroyed at the end of the study. The village of residence of the participant will be documented, along with the GPS coordinates of the homestead.

### *8.1.3. HIV Testing*

Volunteers will have access to a trained counsellor who will do pre and post-test counselling. HIV status will be established using the standard rapid diagnostic kits and testing algorithm used by the Burkina Faso Ministry of Health. Those diagnosed positive will be referred to an appropriate health centre or District Hospital HIV clinic (Comprehensive Care and Research Centre) for further counselling and treatment.

## *8.2.* Allocation of participants to Study Groups

Volunteers will be randomised to receive either three (3) doses of R21/ Matrix-M1 or placebo (normal saline) as control. Simple randomisation into the study groups will be done by an independent statistician based at the UOXF. A randomisation code list will be generated by the independent statistician and its use guided by a clear Standard of Operating Procedure (SOP). Allocation concealment will be employed by use of opaque sealed envelopes. As this is a single-blind clinical trial design, the laboratory scientists will be blinded to vaccine allocation until the end of the study.

## 8.3. Enrolment

**8.4. PARTICIPANTS ARE CONSIDERED ENROLLED INTO THE STUDY WHEN THEY HAVE RECEIVED THE FIRST STUDY VACCINATION. THIS SHOULD OCCUR ≤ 14 DAYS AFTER THE SCREENING VISIT. THEY WILL REMAIN IN THE VACCINATING HEALTH FACILITY FOR 1 HOUR MINUTES POST-VACCINATION IN ORDER TO ENABLE MONITORING BY THE STUDY CLINICIANS. THE STUDY CLINICIANS WILL**

**ASSESS AND RECORD LOCAL AS WELL AS SYSTEMIC ADVERSE EVENTS AFTER 1 HOUR HAS ELAPSED.STUDY VISITS AND PROCEDURES**

**Table 2** shows the window periods for the visits and outlines the study procedures at each visit for all study Groups.

## Screening: (Clinic Visit)

Ongoing eligibility for participation will be confirmed according to the inclusion and exclusion criteria, prior to blood sampling.

Medical history and physical examination will be performed at screening to exclude any significant medical conditions.

The following lab tests will be done: FBC, ALT, urinalysis, Creatinine, rapid Hepatitis B surface antigen test, Serum β-HCG pregnancy test (where applicable), and HIV testing

## Day 0 (Vaccination with R21/Matrix-M1 vaccine or placebo)

Ongoing eligibility for participation will be confirmed according to the inclusion and exclusion criteria, prior to blood sampling and vaccination.

Medical history, temperature monitoring, physical examination will be performed.

Venepuncture for exploratory immunology (for all volunteers) and safety assessment for all participants will also be done prior to vaccination. Analysis of blood samples will be performed as detailed below (Laboratory Evaluations).

Volunteers are considered enrolled into the study when they receive the first study vaccination. The vaccine will be administered as detailed in Section 7 and according to local SOPs. The volunteer will be monitored for one hour (or longer if necessary) after vaccination.

The CRF will be updated.

## Days 1-6 Field worker home visits)

Each volunteer will be visited at home daily for 6 days post-vaccination by a field worker for assessment and recording of any solicited and unsolicited AEs in diary cards. If necessary the volunteer will continue to be seen regularly until any observed AEs have resolved or stabilised.

## Day 7 ±2 (Clinic visit)

Medical history, temperature monitoring, physical examination will be performed and recorded. Analysis of blood samples will be performed as detailed below (Laboratory Evaluations). Any solicited/ unsolicited AEs will be reviewed and recorded.

The CRF will be updated including the records of AEs, concomitant vaccination and concomitant medications.

## Day 28 ±2 (Vaccination with R21/Matrix M-1 vaccine or placebo)

Medical history, temperature monitoring, physical examination will be performed and recorded. Any solicited/ unsolicited AEs will be reviewed and recorded.

Venepuncture for exploratory immunology and safety assessment for all participants will be done prior to vaccination. Analysis of blood samples will be performed as detailed below (Laboratory Evaluations).

Vaccines will be administered as detailed in Section 6 and according to local SOPs. The volunteer will be monitored for one hour (or longer if necessary) after vaccination.

The CRF will be updated including the records of AEs, concomitant vaccination and concomitant medications.

## Days 29-34 (Field worker home visits)

Each volunteer will be visited at home daily for 6 days post-vaccination by a field worker for assessment and recording of any solicited and unsolicited AEs in diary cards. If necessary the volunteer will continue to be seen regularly until any observed AEs have resolved or stabilised.

**Day 35 ±2 (Clinic visit)**

Medical history, temperature monitoring, physical examination will be performed and recorded. Analysis of blood samples will be performed as detailed below (Laboratory Evaluations). Any solicited/ unsolicited AEs will be reviewed and recorded.

The CRF will be updated including the records of AEs, concomitant vaccination and concomitant medications.

**Days 56 ±2 (Vaccination with R21/Matrix M-1 vaccine or placebo)**

Medical history, temperature monitoring, physical examination will be performed and recorded. Any solicited/ unsolicited AEs will be reviewed and recorded.

Venepuncture for safety assessment for all participants and exploratory immunology (for all volunteers) will be done prior to vaccination. Analysis of blood samples will be performed as detailed below (Laboratory Evaluations).

Vaccines will be administered as detailed in Section 6 and according to local SOPs. The volunteer will be monitored for one hour (or longer if necessary) after vaccination.

The CRF will be updated including the records of AEs, concomitant vaccination and concomitant medications.

**Day 57-62 (Field worker home visits)**

Each volunteer will be visited at home daily for 14 days post-vaccination by a field worker for assessment and recording of any solicited and unsolicited AEs in diary cards. If necessary the volunteer will continue to be seen regularly until any observed AEs have resolved or stabilised.

**Day 63 ±2 (Clinic visit)**

Medical history, temperature monitoring, physical examination will be performed and recorded. Analysis of blood samples will be performed as detailed below (Laboratory Evaluations). Any solicited/ unsolicited AEs will be reviewed and recorded.

The CRF will be updated including the records of AEs, concomitant vaccination and concomitant medications.

**Day 84 ±2 (Clinic visit)**

Medical history, temperature monitoring, physical examination will be performed and recorded. All AE's/SAE's will be reviewed.

Venepuncture for safety assessment for all participants and exploratory immunology (for all volunteers) will be done prior to vaccination. Analysis of blood samples will be performed as detailed below (Laboratory Evaluations).

The CRF will be updated including the records of AEs, concomitant vaccination and concomitant medications.

**Day 140 ±7 (Clinic visit)**

Medical history, temperature monitoring, physical examination will be performed and recorded. All AE's/SAE's will be reviewed.

Venepuncture for safety assessment for all participants and exploratory immunology (for all volunteers) will be done prior to vaccination. Analysis of blood samples will be performed as detailed below (Laboratory Evaluations).

The CRF will be updated including the records of AEs, concomitant vaccination.

## 8.5. Laboratory Evaluations

### Descriptions of Blood sampling and Laboratory Evaluations

5 mls of blood will be collected at screening (similar for all sampling groups) to test eligibility. 5 mls of blood will also be collected on days 0, 7, 28, 35, 56, 63, 84, and 140 for the evaluation of safety. The following tests will be performed;

- Full blood count

- Serum ALT and creatinine
- HIV antibody testing (pre-vaccination only)

25 mls of blood will be collected on days 0, 28, 56, 84 and 140. The following tests will be performed at these time points;

- Antibodies to CSP and HbsAg by ELISA
- Cellular immunology studies, including *ex vivo* IFNg ELISPOT and stimulation of whole blood for flow cytometry with intracellular cytokine staining.
- Lymphocytes remaining after the primary immunological readout assay (IFNg ELISPOT) will be stored for later immunological studies. This will allow further characterisation antigen-specific T cells.
- Plasma for antibody studies of immunity to malaria antigens.
    - Stimulated PBMCs from the ELISPOT plate will be retained and preserved for transcriptomics analysis
    - An aliquot of whole blood will be preserved for transcriptomics analysis

## 8.6. Provision of care to the study participants

Study contact personnel will be available 24 hours a day at the trial site clinic and at the different health facilities of the study population catchment areas, seven days a week, to attend to volunteers who report ill. Volunteers requiring in-patient care will be admitted to the hospital where study personnel will be posted. Laboratory and radiological investigation will be carried out when appropriate. If necessary, volunteers requiring more specialised care (treatment or diagnostic procedures) will be transported to a referral hospital. Treatment for medical conditions will be given according to the standard treatment regimens locally. Any expenses including transport costs incurred by the volunteers for clinical care related to acute conditions will be borne by the trial according to the appropriate local arrangements. Long-term care for chronic conditions unrelated to study procedures will be delivered following local guidelines with no financial support from the trial.

**Table 2: VAC060 Schedule of study visits and procedures for participants**

| | S | R21/ Matrix-M1 or Normal Saline | | | R21/ Matrix-M1 or Normal Saline | | | R21/ Matrix-M1 or Normal Saline | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Attendance number** | **1** | **2** | | **3** | **4** | | **5** | **6** | | **7** | **8** | **9** |
| **Timeline (days)** | | 0 | 1-6 | 7 | 28 | 29-34 | 35 | 56 | 57-62 | 63 | 84 | 140 |
| **Window (days)** | -14 | - | | ±2 | ±2 | | ±2 | ±2 | | ±2 | ±2 | ±7 |
| **Inclusion / Exclusion criteria** | X | X | | | X | | | X | | | | |
| **Informed consent** | X | X | | | | | | | | | | |
| **Medical History** | X | X | | X | X | | X | X | | X | X | X |
| **Physical Examination** | X | X | | X | X | | X | X | | X | X | X |
| **Urinalysis** | X | | | | | | | | | | | |
| **Serum Pregnancy Test (women only)** | X | X | | | X | | | X | | | | |
| **Review contraindications** | X | X | | | X | | | X | | | | |
| **Vaccination** | | **X** | | | **X** | | | **X** | | | | |
| **Field Worker Home Visit/Diary Cards** | | | X | | | X | | | X | | | |
| **Concomitant Vaccination** | | X | | X | X | | X | X | | X | X | X |
| **Concomitant medication** | | X | | X | X | | X | X | | X | X | |
| **AEs reviewed** | | X | | X | X | | X | X | | X | X | X |
| **Diary card reviewed** | | | X | | | X | | | X | | | |
| **Blood smear, Blood spot** | X | | | | | | | | | | | |
| **HLA typing (mL)** | X | | | | | | | | | | | |
| **HBV, HIV (mL)** | X | | | | | | | | | | | |
| **Haematology (mL)** | X | X | | X | X | | X | X | | X | X | X |
| **Biochemistry (mL)** | X | X | | X | X | | X | X | | X | X | X |
| **Immunology** | | X | | | X | | | X | | X | X | X |
| **Blood volume per visit (mL)** | 5 | 30 (25+5) | | 5 | 30 (25+5) | | | 30 (25+5) | | 30 (25+5) | 30 (25+5) | 30 (25+5) |

**Schedule of Visits**: S = Screening; Window *(days) refers to time since last visit*

## 8.7. Safety follow-up

Trained field workers under the supervision of the investigators will visit each enrolled volunteer for 6 consecutive days post-vaccination (Table 2). If necessary the volunteers will continue to be seen by the field worker on subsequent days for follow-up of adverse events. In the event that the field worker finds any Grade 3 solicited general or unsolicited symptoms, the volunteer will be brought to the vaccination centre for examination by a study clinician. During the field worker visits, volunteers will be asked retrospectively if any medical event that might be a SAE occurred since the last visit and this information will be recorded. Unreported SAEs detected in this way will be investigated and reported by the PI or delegate on the corresponding SAE.

If a study volunteer is reported to be unwell at the time of a visit, the field worker will advise the volunteer to report to the trial site clinic or the nearest health facility where a study nurse will be posted and will notify this referral to the clinical team for follow up. In the event that the volunteer is seriously ill, the field worker will inform the PI or designate, and transport will be arranged, to the referral hospital (where a study physician is posted), if judged appropriate by the responsible clinician.

In case a study volunteer is unwell and referred to the trial site clinic or health facility, a duplicate blood film will be obtained should the volunteer present symptoms or signs compatible with malaria (axillary temperature ≥ 37.5°C, history of fever within the last 24 hours, loss of appetite, malaise, joint pains)

A study clinician will review the volunteer for safety and reactogenicity assessment at the Clinic Visits, on Days 0, 7, 28, 35, 56, 63, 84, and 140.

## 8.8. Immunogenicity measurements

These will mainly consist of measurements of humoral immunity using ELISA and cellular responses using *ex vivo* IFNg ELISPOT. In addition, flow cytometry on whole blood, and gene expression profiling will be performed.

The interferon-gamma (IFNγ) enzyme-linked immunospot assay (ELISPOT) can be performed in two ways; the *ex vivo* assay that enumerates effector memory T cells and which has correlated directly with protection in two mouse models of malaria[36]; and the cultured ELISPOT that measures central memory T cell responses and correlates with protection in the field trial of RTS,S/AS02 in the Gambia[37] and in sporozoite challenge studies of viral vector vaccinations in Oxford[27]. IFNγ secreted by T cells after interaction with infected liver cells has been shown to induce death of liver-stage parasites[38]. The *ex-vivo* assay will be used as the primary readout for vaccine immunogenicity in this study. PBMC will be stimulated with pools of 20mer peptides spanning the length of the ME-TRAP insert and overlapping by 10 amino acids. Additional information on T cell responses will be obtained by intracellular cytokine staining and flow cytometry to determine whether responding T cells are CD4+ or CD8+ and assess production of other cytokines such as IL-2 and TNFα .

RNA analysis may also be used to examine the profile of gene expression following vaccination and during exposure as there is mounting evidence that gene expression profiles can predict characteristics of the immune response to vaccination and may possibly be used to prospectively determine vaccine efficacy[39].

Immune responses to vaccination may be affected by genetic factors; therefore we will assess sequence variation in DNA from vaccinees by sequencing or other genotyping methods.

## 8.9. Data collection

Adverse events will be documented in individual case report forms (CRFs) for each volunteer. They will be recorded under two headings; local and systemic. There will be documentation of concomitant medication, concomitant vaccination, non-serious adverse event documentation, serious adverse event documentation and study conclusion. Case report forms will be kept securely.

The following data will be collected for concomitant medications: medication name (generic name), dose, frequency and route; start and stop dates; and indication.
Concomitant medication will be recorded according to the time period below:

- Antimalarial drugs, antibiotics with antimalarial activity, immune modifying drugs and blood transfusions will be captured for the duration of the trial.
- Antipyretics, analgesics, systemic antibiotics with unknown antimalarial activity will be collected from first vaccination until 1 month post-final vaccination.
- All vaccines administered, not specified in the study protocol, will be recorded for the duration of the trial.

### 8.10. Study termination

The study will be discontinued in the event of any of the following:

- New scientific information is published to indicate that volunteers in the study are being exposed to undue risks as a result of administration of the IMPs by any route of administration, or as a result of the follow-up schedule.
- Serious concerns about the safety of the IMPs arise as a result of one or more vaccine related SAE occurring in the subjects enrolled in this or any other ongoing study of the IMPs.
- For any other reason at the discretion of the Principal Investigator.

### 8.11. Definition of the Start and End of the Trial

The start of the trial is defined as the date of the first vaccination of the first volunteer. The end of the trial is the date of the last visit of the last volunteer.

## 9. ASSESSMENT OF SCIENTIFIC OBJECTIVES

### 9.1. Safety Evaluation

Evaluation criteria for safety will be local and systemic solicited and unsolicited adverse events.

Assessment of the safety and reactogenicity of three (3) doses of 10 & 50 µg R21/Matrix-M1 administered four (4) weeks apart will be undertaken by summary listing of all solicited and unsolicited local and systemic adverse events (including results of clinical laboratory investigations where deemed adverse events), considered possibly, probably, or definitely related to vaccination; and line listing of all SAEs.

Safety endpoints will be summarised for groups 1 and 2. The number and percentage of volunteers in each group who have any local reaction will be compared (using the chi-squared test, and by calculating confidence intervals on differences in percentages). Similarly, the numbers who have any systemic reaction or SAE will be compared between groups.

### 9.2. Immunogenicity evaluation

Evaluation criteria for immunogenicity will include measures of immunogenicity of R21/Matrix-M1

- Antibodies to CSP and HbSAg by ELISA
- Ex vivo gamma-interferon T cell ELISPOT assays (Day 0 and 84 on frozen cells)
- ICS and flow cytometry (Day 0 and 84 on stimulated frozen whole blood)
- Exploratory immunology, including RNA analysis and DNA analysis to include parasite and human genetic analysis.

Immunogenicity data will be analysed according to a detailed analytical plan.

## 10. SAFETY REPORTING

### 10.1. Definitions

Definitions for the terms adverse event (or experience), adverse reaction, and unexpected adverse reaction have previously been agreed to by consensus of the more than 30 Collaborating Centres of the WHO International Drug Monitoring Centre (Uppsala, Sweden). Although those definitions can pertain to situations involving clinical investigations, some minor modifications are necessary, especially to accommodate the pre-approval, development environment.

The following definitions, with input from the WHO Collaborative Centre, have been agreed:

#### *10.1.1. Adverse Event*

Any untoward medical occurrence in a clinical investigation subject occurring in any phase of the clinical study whether or not considered related to the vaccine. This includes an exacerbation of pre-existing conditions or events, intercurrent illnesses, or vaccine or drug interaction. Anticipated day-to-day fluctuations of pre-existing conditions that do not represent a clinically significant exacerbation will not be considered adverse events. Discrete episodes of chronic conditions occurring during a study period will be reported as adverse events in order to assess changes in

frequency or severity.

Adverse events will be documented in terms of a medical diagnosis (es). When this is not possible, the adverse event will be documented in terms of signs and symptoms observed by the investigator at each study visit.

Pre-existing conditions or signs and/or symptoms (including any which are not recognised at study entry but are recognised during the study period) present in a subject prior to the start of the study will be recorded on the Medical History form within the subject's CRF.

### *10.1.2. Adverse Drug Reaction (ADR)*

An ADR is any untoward or unintended response to a medicinal product. This means that a causal relationship between the study medication and an AE is at least a reasonable possibility, i.e., the relationship cannot be ruled out.

### *10.1.3. Serious Adverse Event (SAE)*

A serious adverse event (experience) or reaction is any untoward medical occurrence that at any dose:

- results in death,
- is life-threatening,
  **Note:** The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
- requires inpatient hospitalisation[‡] or prolongation of existing hospitalisation,
- results in persistent or significant disability/incapacity, or
- is a congenital anomaly/birth defect.

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious.

[‡]*Hospitalization: In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for treatment that would not have been appropriate in the physician's office or out-patient setting*
*Hospitalization for either elective surgery related to a pre-existing condition which did not increase in severity or frequency following initiation of the study or for routine clinical procedures¶ (including hospitalization for "social" reasons) that are not the result of an adverse event need not be considered as adverse events and are therefore not serious adverse events.*

In addition, important medical events that may jeopardise the patient or may require intervention to prevent one of the other outcomes listed above should be considered serious. (Examples of such treatments are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not results in hospitalisation; or development of drug dependency or drug abuse.)

### *10.1.4. Suspected Unexpected Serious Adverse Reactions (SUSARs)*

A SUSAR is a SAE that is unexpected and thought to be related to the investigational product. Administration of further vaccines within the trial will be suspended until a safety review is convened.

## 10.2. Collection of Adverse Events

At each post-vaccination visit all adverse events will be documented.

### *10.2.1. Local solicited Adverse Events*

The following solicited local reactions at the injection site will be documented:

- swelling,
- Redness/discoloration
- Pain/limitation of limb movement.

### *10.2.2. Solicited general AEs*

The solicited general AEs that will be documented include

- Fever (defined as axillary temperature ≥ 37.5°C)
- Chills
- Headache
- Malaise
- Joint pains
- Myagia
- Fatigue
- Nausea

The field workers will record these AEs during the home visits, according to the SOPs available at the study site.

### *10.2.3. Unsolicited adverse events*

Unsolicited adverse events will only be recorded in the CRF if they occurred up to 28 days post vaccination, unless they meet the criteria for serious adverse event as outlined above. Serious adverse events will be collected throughout the study period.

As a consistent method of soliciting adverse events, the participant will be asked a non-leading question such as: "Have you felt different in any way since receiving the vaccine or since the last visit?" The investigator will record only those adverse events having occurred within the time frames defined above.

Adverse events already documented in the CRF, i.e. at a previous assessment and designated as 'ongoing' will be reviewed at subsequent visits, as necessary. If these have resolved, the documentation in the CRF will be completed.

## 10.3. Follow-up of Adverse Events

All AEs will be followed until resolution, stabilization of the signs or symptoms or laboratory changes occur, or until a non-study related causality is assigned. Clinically significant laboratory abnormalities will be followed up until they have returned to normal, or a satisfactory explanation has been provided.

Volunteers who have moderate or severe on-going adverse events at the completion of the study will be advised to consult a physician if the event is not considered to be related to the study vaccine. A follow-up visit will be arranged to manage the problem and to determine the severity and duration of the event, if it is considered to be related to the study vaccine. If appropriate, specialist review will be arranged by CNRFP investigators.

Any serious adverse event possibly related to the vaccine and occurring after trial termination should be reported by the investigator according to the procedure described below.

## 10.4. Reporting of Adverse Events

Every SAE occurring throughout the trial must be reported by telephone, email or fax to the sponsor, LSM and DSMB by the investigator as soon as (s)he is alerted of it and within one working day, even if the investigator considers that the adverse event is not related to vaccination. The investigator will then complete a SAE report form as soon as possible and within five working days or seven calendar days. The contact details for reporting the SAE is sae@well.ox.ac.uk

Any relevant information concerning the adverse event that becomes available after the SAE report form has been sent (outcome, precise description of medical history, results of the investigation, copy of hospitalisation report, etc.) will be forwarded to the Sponsor in a timely manner. The anonymity of the subjects shall be respected when forwarding this information.

SAEs that are suspected to be related to the vaccine will be reported to the Ethics Committee within 15 calendar days of the site becoming aware of the event. If the event is fatal or life-threatening, the event will be reported within 7 calendar days.

Suspected unexpected serious adverse reactions (SUSARs) will be reported according to national regulatory guidelines. The sponsor pledges to inform the Authorities of any trial discontinuation and specify the reason for discontinuation.

Every effort should be made by the investigator to explain each adverse event and assess its causal relationship, if any to the administration of the investigational product. This interpretation will be based on the type of event, the relationship of the event to the time of vaccine administration (the event being temporally associated with vaccination or reproduced on re-vaccination), and the known biology of vaccine therapy (the event having often been reported in literature for similar types of vaccines).

All solicited local (injection site) reactions will be considered causally related to vaccination.

The following are guidelines for assessing the causal relationship for the systemic adverse events:

No relationship:

No temporal relationship to study product; *and*

Alternate aetiology (clinical state, environmental or other interventions); *and*

Does not follow known pattern of response to study product

**Unlikely relationship**:

Unlikely temporal relationship to study product; *and*
Alternate aetiology likely (clinical state, environmental or other interventions); *and*
Does not follow known typical or plausible pattern of response to study product

Possible relationship:

Reasonable temporal relationship to study product; *or*
Event not readily produced by clinical state, environmental or other interventions; *or*
Similar pattern of response to that seen with other vaccines

Probable relationship:

Reasonable temporal relationship to study product; *and*
Event not readily produced by clinical state, environment, or other interventions *or*
Known pattern of response seen with other vaccines

**Definite relationship**:

Reasonable temporal relationship to study product; *and*
Event not readily produced by clinical state, environment, or other interventions; *and*
Known pattern of response seen with other vaccines

## 10.5. Grading the severity of adverse events

### *10.5.1. Local solicited AEs*

The largest diameter through the injection site of any local redness/discoloration will be recorded in millimeters. The largest diameter through the injection site of local swelling will be recorded in millimeters. Severity of these local findings will be graded using the scales below:

Grading for swelling

| Grade | **Diameter [mm]** |
|---|---|
| 0 | 0 |
| 1 | < 20 |
| 2 | 20 – 50 |
| 3 | > 50 |

Grading for redness/discoloration

| Grade | **Diameter [mm]** |
|---|---|
| 0 | 0 |
| 1 | < 50 |
| 2 | 50 – 100 |
| 3 | > 100 |

The presence and severity of local pain/limitation of limb movement at the site of vaccination will be determined using the following scale:

| **Grade** | **Description** |
|---|---|
| **0** | No pain at all |
| **1** | Painful on touch, no restriction in movement of limb |
| **2** | Painful when limb is moved |
| **3** | Unable to use limb due to pain |

### *10.5.2. Solicited general AEs*

| | | |
|---|---|---|
| Fever<br>Record axillary temperature | 0 | <37.5ºC |
| | 1 | 37.5 - ≤38.0ºC |
| | 2 | >38.0 - ≤39ºC |
| | 3 | >39ºC |
| Chills | 0 | None |
| | 1 | Chills that are easily tolerated |
| | 2 | Chills that interfere with daily activity |
| | 3 | Chills that prevent daily activity |
| Nausea | 0 | None |
| | 1 | Nausea that is easily tolerated |
| | 2 | Nausea that interferes with daily activity |
| | 3 | Nausea that prevents daily activity |
| Headache | 0 | None |
| | 1 | Headache that is easily tolerated |
| | 2 | Headache that interferes with daily activity |
| | 3 | Headache that prevents daily activity |
| Malaise | 0 | None |
| | 1 | Malaise that is easily tolerated |
| | 2 | Malaise that interferes with daily activity |
| | 3 | Malaise that prevents daily activity |
| Myalgia | 0 | None |
| | 1 | Myalgia that is easily tolerated |
| | 2 | Myalgia that interferes with daily activity |
| | 3 | Myalgia that prevents daily activity |
| Joint pain | 0 | None |
| | 1 | Joint pain that is easily tolerated |
| | 2 | Joint pain that interferes with daily activity |
| | 3 | Joint pain that prevents daily activity |
| Fatigue | 0 | None |
| | 1 | Fatigue that is easily tolerated |
| | 2 | Fatigue that interferes with daily activity |
| | 3 | Fatigue that prevents daily activity |

### *10.5.3. Non Solicited AEs*

For adverse events other than those for which the severity scales are detailed above, AEs will be graded according to the DAIDS AE grading table, published in 2004.[40] The DAIDS AE grading table classifies adverse events into one of four grades, ranging from mild to potentially life-threatening. The DAIDS AE grading table has indications for each of over sixty clinical parameters and forty laboratory parameters for grading adult and paediatric AEs. The table also includes general guidelines for estimating the grade of parameters not explicitly listed. Each grade is described broadly below:

- Grade 1 (mild): awareness of a symptom, but the symptom is easily tolerated and causes no or minimal interference with usual activity.
- Grade 2 (moderate): discomfort enough to cause greater than minimal interference with usual activity.
- Grade 3 (severe): incapacitating; symptoms causing inability to perform usual activities; requires absenteeism or bed rest.
- Grade 4 (potentially life-threatening): symptoms causing inability to perform basic self-care functions OR medical or operative intervention is indicated to prevent permanent impairment, persistent disability or death.

Laboratory tests will also be graded on the DAIDS AE grading table.

### *10.5.4. Pregnancy*

Participants who become pregnant during the study period must not receive additional doses of vaccine but may continue other study procedures to include blood draws for immunogenicity, safety and vaccine efficacy at the discretion of the principal investigator.

Participants should be instructed to notify the investigator if it is determined after completion of the study that they became pregnant either during the study or within 30 days of the study.

Although not considered an adverse event, pregnancy should be reported on the pregnancy report form and in the same way as a serious adverse event.
A pregnancy should be followed to term, any premature terminations reported, and the health status of the mother and child including date of delivery and the child's gender and weight should be reported to the sponsor.

# 11. DATA HANDLING AND RECORD KEEPING

## *11.1.* Data Management

Data management will be conducted at CNRFP and a copy of the anonymised database provided to the sponsor for archiving. The PI will be responsible for receiving, entering, cleaning, querying and storing all data that accrues from the study. Responsibility for this may be delegated to the data manager at CNRFP. The data will be entered into the volunteers CRFs. Data will be subsequently transferred to an electronic database for analysis.

If any changes to the protocol are necessary during the study a formal amendment will be presented to the sponsor prior to submission to the relevant ethical and regulatory agencies for approval unless to eliminate an immediate hazard(s) to study participant without prior ethics approval. Any unforeseen and unavoidable deviations from the protocol will be documented and filed in as a protocol deviation in the Trial Master File, with explanation.

### *11.1.1.* Data Capture Methods

Data capture will be on paper CRFs. The CRFs will be considered source documents as healthy volunteers may not have hospital case-notes.
Adverse events will be tabulated in an electronic database (OpenClinica®) for descriptive analysis.
Immunological data will be transferred to an electronic database for analysis without any volunteer identifier apart from the unique volunteer number.

### *11.1.2.* Types of Data

Data collected will include solicited and unsolicited adverse event data, concomitant medications, clinical laboratory and exploratory immunology data. Source documents will include laboratory results and the case record file containing the case report forms for each volunteer as the healthy volunteers participating in this study may not have medical notes.

## *11.2.* Timing/Reports

Annual Safety Report: Due on anniversary of Regulatory Approval – sent to Regulatory and Ethical Bodies
Annual Progress Report: Due on anniversary of Ethical Approval – sent to Ethics Committee

## *11.3.* Archiving

The investigator must keep all trial documents for at least 15 years after the completion or discontinuation of the trial.

## *11.4.* Protocol Deviations

Any unforeseen and unavoidable deviations from the protocol will be documented and filed in the study file with explanation.

# 12. DATA ACCESS AND QUALITY ASSURANCE

## *12.1.* Direct Access to Source Data/Documents

The PI will provide direct access to the source data documents to the Ethics Committee, to the regulatory agency, and to authorized representatives of the sponsor, permitting trial-related monitoring and audits.

## *12.2.* Quality Assurance

### 12.2.1. Modifications to the Protocol

Any amendments to the protocol that appear necessary during the course of the trial must be discussed by the investigator and sponsor concurrently unless to eliminate an immediate hazard(s) to study participants. If agreement is reached concerning the need for a substantial amendment, it will be produced in writing by the sponsor and/or the investigator and will be made a formal part of the protocol. Any substantial amendment requires Ethics Committee approval, but non-substantial amendments do not.

All substantial amendments must also be communicated to Regulatory Authorities, if appropriate.
An administrative or non-substantial change to the protocol is one that modifies administrative and logistical aspects of a protocol but does not affect the subjects' safety, the objectives of the trial and its progress. An administrative change does not require Ethics Committee approval. However, the Ethics committee must be notified whenever an administrative or non-substantial change is made.
The investigator is responsible for ensuring that substantial amendments to an approved trial, during the period for which Ethics Committee approval has already been given, are not initiated without Ethics Committee review and approval except to eliminate apparent immediate hazards to the subject.

### *12.2.2.* Monitoring

#### Initiation Visit

An initiation visit will be performed before the inclusion of the first volunteer into the study. The Monitor will verify and document that the material to be used during the trial has been received and that the investigational team has been properly informed about the trial and regulatory requirements.

#### Interim Monitoring Visits

The Monitor will carry out regular follow-up visits. The investigator commits to being available for these visits and to allow the monitoring staff direct access to volunteer medical files, if existing, and CRFs. The Monitor is committed to professional secrecy.
During the visits, the Monitor may:

- Carry out a quality control of clinical trial progress: in respect of protocol and operating guidelines, data collection, signature of consent forms, completion of documents, SAE, sample and product management, cold chain monitoring
- Inspect the CRFs, TMF and correspondent correction sheets

The Monitor will discuss any problem with the investigator and define with him the actions to be taken.

#### Close-out Visit

A close-out visit will be performed at the end of the trial. Its goals are to make sure that:

- The centre has all the documents necessary for archiving
- All unused material has been recovered
- All vaccines have been accounted for

## 13. ETHICAL CONSIDERATIONS

#### Ethical Review

Before the inclusion of the first participant in the study, the protocol must be approved by Ethical Review Committees in Burkina and Oxford (OXTREC).

#### Informed Consent

All volunteers are expected to sign an informed consent document before any study procedures begin.

The written information is provided in French only and the field workers will interpret the written information in a language the volunteers understand. The field workers involved in the informed consent discussion are trained on the study and the information sheet and consent form, and are trained to discuss the trial in the local languages the volunteers understand (Gouin, Karaboro, Dioula). The language of the consent process is documented on the consent form. If the volunteer is not able to read and write in French, an adult witness, impartial of the trial, will be present through the whole consent process and sign and date the consent form.

The volunteer should give written/thumb printed informed consent before included in the trial, after having been informed of the nature of the trial, the potential risks and their obligations. Informed consent forms will be provided in duplicate (original kept by the investigator, one copy kept by the volunteer).

#### Confidentiality

All data and information generated by the site as part of the study (other than a subject's medical records) will be kept confidential by the investigator and other site staff. This information and data will not be used by the investigator or other site personnel for any purpose other than conducting the study.

### Inducement

There may be a perception amongst volunteers of benefit from physical examination, laboratory screening in the current study, in addition to free health care provided during the study period for non-vaccine related medical problems. We will also offer compensation for transport expenses for all study subjects.

We do not feel these benefits are excessive, and believe it would be unreasonable to request the cooperation of a population in regular employment without offering compensation for time.

## 14. INDEMNITY/COMPENSATION/INSURANCE

### Indemnity

Compensation for any injury caused by taking part in this study will be in accordance with the guidelines of the Association of the British Pharmaceutical Industry (ABPI). Broadly speaking the ABPI guidelines recommend that 'the sponsor', without legal commitment, should compensate participants without them having to prove that the sponsor is at fault. This applies in cases where it is likely that such injury results from giving any new drug or any other procedure carried out in accordance with the CTP for the study. 'The sponsor' will not compensate participants where such injury results from any procedure carried out which is not in accordance with the CTP for the study. Participants' right at law to claim compensation for injury where negligence can be proven is not affected. In this instance the University of Oxford is the Research Sponsor Institution.

### Compensation

Participants enrolled in the study will be offered compensation for transport expenses.

### Insurance

Oxford University Investigators participating in this trial will receive insurance coverage from the University clinical trials insurance policy. The University has a specialist insurance policy in place: - Newline Underwriting Management Ltd, at Lloyd's of London – which would operate in the event of any participant suffering harm as a result of their involvement in the research.

## 15. REFERENCES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