PAL_Cambodia

An open-label individually randomised controlled trial to assess the efficacy of artemether-lumefantrine prophylaxis for malaria among forest goers in Cambodia Short title: Study to assess efficacy of artemether-lumefantrine prophylaxis against forest malaria in Cambodia

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ACRONYM: PAL-Cambodia

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Investigator Agreement and Conflict of Interest

"I have read this protocol and:

- agree to abide by all provisions set forth therein.
- agree to comply with the principles of the International Conference on Harmonisation Tripartite Guideline on Good Clinical Practice.
- and declare no conflict of interest, according to the current version of the Declaration of Helsinki"

Prof. Richard J. Maude

Principal Investigator Principal Investigator's Signature Date :

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1. LIST OF ABBREVIATIONS

ACT	Artemisinin-based combination therapy
AE	Adverse event
A/L	Artemether-lumefantrine
AQ	Amodiaquine
CNM	National Center for Parasitology, Entomology and Malaria Control
CRF	Case record form
CTSG	Clinical Trials Support Group (MORU)
DHA	Dihydroartemisinin
DNA	Deoxyribonucleic Acid
EDC	Electronic data capture
EDTA	Ethylene-diamine-tetra-acetic acid
G6PD	Glucose-6-phosphate dehydrogenase
GCP	Good Clinical Practice
GPS	Global Positioning System
Hb	Haemoglobin
Hct	Haematocrit
IRS	Indoor residual spraying
LLIN	Long-lasting insecticide treated bednets
MDR1	Multi-Drug Resistance Gene 1
MQ	Mefloquine
MORU	Mahidol-Oxford Research Unit
NMCP	National Malaria Control Programme
PA	Pyronaridine-artesunate
PAL	Prophylaxis with artemether-lumefantrine study
PCR	Polymerase Chain Reaction
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event
SNP	Single-nucleotide polymorphism
SOP	Standard Operating Procedure
WHO	World Health Organisation
WWARN	Worldwide Antimalarial Resistance Network

2. SYNOPSIS

Study Title	An open-label individually randomised controlled trial to assess the efficacy of artemether-lumefantrine prophylaxis for malaria among forest goers in Cambodia
ACRONYM	PAL-Cambodia
Trial Design	An open-label randomised trial comparing the ACT artemether-lumefantrine (Coartem) with a multivitamin preparation, evaluating efficacy in preventing malaria among forest goers
Trial Participants	People planning to travel the forest within the next 72 hours in areas at high risk for malaria
Sample size	4400 participant episodes, with half allocated to each study arm
Inclusion Criteria	• Male or female, aged between 16 and 65 years • Planning to travel to the forest within the next 72 hours and stay overnight • Written informed consent • Willingness and ability of the participants to comply with the study protocol for the duration of the study
Exclusion Criteria	• For females: known pregnancy or breast feeding • Participants who have received artemisinin or a derivative or an artemisinin-containing combination therapy (ACT) within the previous 7 days • History of allergy or known contraindication to artemisinins, lumefantrine or multivitamins • Documented or claimed history of cardiac conduction problems. • Severe vomiting or diarrhoea • Signs/symptoms of clinical malaria (febrile or history of fever in the previous 24hours) confirmed by RDT
Planned Trial Period	12 months (September 2019 – July 2020) enrolment
Primary Objective	To compare the efficacy of the ACT artemether-lumefantrine versus a multivitamin preparation as defined by the 28-day PCR parasite positivity rate and incidence of confirmed clinical malaria of any species.
Secondary Objectives	1. To compare the efficacy of the ACT artemether-lumefantrine versus a multivitamin preparation as defined by the 28-day, 56-day and 84-day PCR parasite positivity rate and incidence of confirmed clinical malaria for each species. 2. To quantify the impact of the ACT artemether-lumefantrine as prophylaxis for forest goers on overall malaria transmission using mathematical modelling.

	3. To assess the impact of artemether-lumefantrine prophylaxis on the spread of genetic markers of artemisinin (such as *Kelch13* mutations) and partner drug resistance. 4. To obtain data on the place of residence, work, recent travel history and risk behaviours of forest goers in order to improve the understanding of high risk groups, locations of malaria transmission and possible routes spread of malaria and artemisinin resistance. 5. To explore the duration, location and purpose of individual forest visits. 6. To obtain detailed data and GPS mapping on a subset of participants and their peers relating to the behaviours and risk factors associated with malaria infection in order to improve understanding of local malaria transmission among forest goers. 7. To determine the prevalence of asymptomatic Plasmodium infections in high risk populations at varying seasonal time points. 8. To determine the prevalence of other infectious diseases that affect the study population.
Primary endpoints	1. 28-day PCR Plasmodium positivity rate of any species 2. Proportion of participants with confirmed clinical malaria of any species reported between day 0 and day 28
Secondary endpoints	1. 28-day, 56-day and 84-day PCR Plasmodium positivity rate for each species 2. Proportion of participants with confirmed malaria reported between day 0 and day 28 for each species 3. Description of epidemiological situation of malaria in the study areas from passive surveillance data. 4. Prevalence of *Kelch13* mutations and other genetic markers of antimalarial drug resistance of known functional significance. 5. Incidence of adverse events and serious adverse events by study arms during the course of prophylaxis. 6. Data on the place of residence, work, recent travel history and mobile phone use. 7. Detailed data and GPS mapping on a subset of participants and their peers relating to the behaviours and risk factors associated with malaria infection. 8. Overall prevalence of Plasmodium at baseline, stratified by season and risk factors. 9. 0, 28, 56 and 84-day capillary blood levels of lumefantrine. 10. Prevalence of serological diagnostic markers of other infectious diseases.
Drugs (See Appendix 2 for dosing regimens)	Artemether-lumefantrine for 3 days followed by 2 doses weekly. VERSUS Multivitamin 3 days followed by 2 doses weekly.

3. BACKGROUND AND RATIONALE

In the Greater Mekong Subregion (GMS) adults are at highest risk for malaria. The most relevant disease vectors bite during daytime and outdoors which makes forest work a high-risk activity for malaria. The absence of effective vector control strategies and limited periods of exposure during forest visits suggest that chemoprophylaxis could be an appropriate strategy to protect forest workers against malaria.

3.1 Background

In the Greater Mekong Subregion (GMS) a large proportion of malaria transmission occurs in forested areas, which serve as perpetual sources of transmission [1-5]. Studies have demonstrated increased risk of malaria among forest goers, particularly in men of working age [6, 7] although these have largely been restricted to small geographical areas. Protecting forest goers from Plasmodium infections would not only benefit them directly but also people residing around their home. Malaria elimination efforts which do not consider the reinfection risk from forest workers are unlikely to succeed. However, preventing infections in forest workers is a major challenge. The biting rhythm and resting behaviour of *Anopheles dirus* reduces the impact of the two most commonly employed control measures, long-lasting insecticide treated bednets (LLIN) and indoor residual spraying (IRS). Several studies have also demonstrated poor use of personal protection measures against malaria transmission [8-10]. Two factors that increase malaria risk among forest workers are the basic character of overnight forest accommodation [9] and exposure to the Anopheles vectors (e.g. *An. dirus*), which tend to bite outdoors in daytime. LLIN have a high protective efficacy against nocturnal, indoor malaria transmission [11] but are less protective against daytime, outdoor-biting vectors like An. dirus. The improvised housing of forest workers is frequently poorly suited to hanging bed nets.[12] Imaginative interventions such as supplying forest workers with insecticide treated hammocks do not address the biting rhythm and resting behaviour of the vectors and have a disappointing uptake in field studies.[10, 12] In the absence of simple, effective, and affordable vector control interventions, providing forest goers with effective antimalarial prophylaxis seems a promising alternative approach to protect them against malaria.[13]

We propose to evaluate the feasibility and protective efficacy of antimalarial prophylaxis during forest work. It has been demonstrated in sub-Saharan Africa that chemoprophylaxis (SMC) of children, the highest risk group for malaria in tropical Africa, can reduce malaria cases by 75%, is cost effective and safe and can be given by community health workers [14, 15]. We propose to provide chemoprophylaxis to forest workers, the population group with the highest malaria risk in the GMS. In the proposed study we compare chemoprophylaxis with an antimalarial drug, artemether-lumefantrine (AL). A recent mass drug administration in Cambodia demonstrated that DHA/piperaquine remains effective to clear low-density, subclinical *P. falciparum* infections, but there are increasing treatment failures of clinical malaria cases [16] and markers of resistance to piperaquine in Cambodia are increasing. Although artesunate-pyronaridine has recently been introduced for treatment in parts of Cambodia, there are unresolved concerns about potential liver toxicity[17]. Evidence to date suggests that efficacy of artemether-lumefantrine remains high in Cambodia and is very well tolerated with an excellent toxicity profile and is thus the preferred potential option for prophylaxis by the National Malaria Control Programme. However, it must be taken with fat to maximize absorption. Previously it has been difficult or impossible to detect very low-density Plasmodium infections. The availability of more sensitive PCR methods allows us to detect Plasmodium infections with much lower densities [18, 19]. By use of PCR, we will be able to detect a difference in the prevalence of low density, subclinical *P. falciparum* infections between the two study arms in a relatively small sample of study participants.

3.2 Study Rationale

Chemoprophylaxis of forest workers could protect this high-risk group and could reduce or even interrupt transmission in villages. The highly encouraging results of seasonal malaria chemoprophylaxis (SMC) in selected regions of sub-Saharan Africa provide hope that targeting another high-risk group, forest workers, could reduce malaria transmission in Cambodia and the wider GMS. In sub-Saharan Africa, children remain the main risk group for Plasmodium infections. In SE Asia the main risk group are adults working and sleeping outdoors hence we propose to provide chemoprophylaxis for these adults. A major challenge for this strategy is the choice of an

appropriate chemoprophylactic regimen in the GMS. The chemoprophylactic regimen of choice in Africa is sulfadoxine/pyrimethamine (S/P) plus amodiaquine despite high level resistance against the S/P component of the regimen. Similarly, we propose the use of AL, a drug whose efficacy remains high in the GMS, unlike, for example DHA/piperaquine [20]. The proposed study will help to assess the efficacy and feasibility of prophylaxis to prevent malaria in forest workers, help to identify the optimal regimen, and predict its efficacy in reducing overall transmission. The proposed study is a critical step for future use of chemoprophylaxis to protect forest workers in the GMS against malaria.

3.3 Proposed activities

Artemether-lumefantrine prophylaxis trial

The study of AL versus a multivitamin will be a two-arm randomised open label comparative study. Laboratory assessments of malaria infection at baseline and day 28 post forest will be performed blind to treatment allocation and incidence of clinical cases during follow-up will be recorded.

Activities/outcomes

The main activity proposed is an *in vivo* clinical assessment of prophylaxis to prevent malaria in 4400 participant episodes in 50 villages in Stung Treng and Pursat Provinces, Cambodia. The subjects will be randomized in a one-to-one ratio between the ACT AL and a multivitamin preparation with no antimalarial activity.

The study sites have been chosen based on current information on incidence of malaria, known predominance of malaria among forest goers, presence of an established clinical research programme and feasibility to perform the proposed research activities.

Efficacy of AL ACT will be assessed through follow up visits 28 days (+/-7 days) after returning from the forest upon completing each course of prophylaxis when temperature, symptom questionnaires, brief physical examinations, and malaria parasite PCR, and, in selected individuals, parasite genetics will be performed. Episodes of confirmed clinical malaria among study participants at any time point between enrolment and follow-up will also be recorded.

All the organisations in this collaboration will work closely with local counterparts including the National Malaria Control Programmes (NMCPs), non-governmental and other relevant organisations. Training is an integral part of this collaborative working relationship, and the building of local research capacity is an essential component of all research plans.

All research-related activities, from study design, planning, implementation through to analysis and writing of reports will be performed jointly with local counterparts. Both on-the-job training and formal training will be provided when needed, in particular for Good Clinical Practice (GCP) skills.

The close interaction between WHO and its regional offices will ensure that new knowledge is disseminated efficiently and effectively throughout the region.

4. OBJECTIVES

4.1. Primary Objective

To compare the efficacy of the ACT artemether-lumefantrine versus a multivitamin preparation as defined by the 28-day PCR parasite positivity rate and incidence of confirmed clinical malaria of any species.

4.2. Secondary Objectives

1. To compare the efficacy of the ACT artemether-lumefantrine versus a multivitamin preparation as defined by the 28-day, 56-day and 84-day PCR parasite positivity rate and incidence of confirmed clinical malaria for each species.

2. To quantify the impact of the ACT artemether-lumefantrine as prophylaxis for forest goers on overall malaria transmission using mathematical modelling.
3. To assess the impact of artemether-lumefantrine prophylaxis on the spread of genetic markers of artemisinin (such as *Kelch13* mutations) and partner drug resistance.
4. To obtain data on the place of residence, work, recent travel history and risk behaviours of forest goers in order to improve the understanding of high risk groups, locations of malaria transmission and possible routes spread of malaria and artemisinin resistance.
5. To explore the duration, location and purpose of individual forest visits.
6. To obtain detailed data and GPS mapping on a subset of participants and their peers relating to the behaviours and risk factors associated with malaria infection in order to improve understanding of local malaria transmission among forest goers.
7. To determine the prevalence of asymptomatic Plasmodium infections in high risk populations at varying seasonal time points.
8. To determine the prevalence of other infectious diseases that affect the study population

5. TRIAL DESIGN

5.1 Study sites

The study will take place at up to 50 villages in selected malaria endemic districts in Stung Treng and Pursat Provinces, Cambodia. As the malaria situation in these areas is dynamic, the villages will be identified prior to the start of the trial from analysis of up to date malaria incidence from passive surveillance collected by the Cambodia National Center for Parasitology Entomology and Malaria Control. If there are found to be insufficient villages with malaria cases in Stung Treng Province at the time of trial commencement, we will include additional sites in Pursat Province. MORU has existing study sites and teams in both provinces which will support the running of this trial. The rationale for choosing these areas include high forest cover and ongoing malaria transmission among forest goers.

5.2 Summary of trial design

An open-label randomised trial among forest goers comparing the ACT AL with a multivitamin with no antimalarial activity to evaluate the efficacy of prophylaxis, and to better understand high risk groups and locations of malaria transmission.

5.3 Study duration

The recruitment phase of the study is expected to last 12 months following the intended start of recruitment in September 2019. Training and community sensitization will precede study execution for 3 months. Data management and analysis, sample analysis (PCR, parasite genetics), mathematical modelling and report writing are expected to take about 5 months. Therefore, the total time to complete the study will be about 20 months.

5.4 Primary and secondary endpoints

5.4.1. Co-primary Endpoints

1. 28-day PCR positivity rate of Plasmodium infections of any species.
2. Proportion of participants with confirmed clinical malaria of any species reported between day 0 and day 28

5.4.2. Secondary Endpoints

1. 28-day, 56-day and 84-day PCR Plasmodium positivity rate for each Plasmodium species

2. Proportion of participants with confirmed malaria reported between day 0 and day 28 for each species

3. Description of epidemiological situation of malaria in the study areas from passive surveillance data.

4. Prevalence of *Kelch13* mutations and other genetic markers of antimalarial drug resistance of known functional significance.

5. Incidence of adverse events and serious adverse events by study arms during the course of prophylaxis.

6. Data on the place of residence, work, recent travel history and mobile phone use.

7. Detailed data and GPS mapping on a subset of participants and their peers relating to the behaviours and risk factors associated with malaria infection.

8. Overall prevalence of Plasmodium at baseline, stratified by season and risk factors.

9. Day 0, 28, 56 and 84 capillary blood levels of lumefantrine.

10. Prevalence of serological diagnostic markers of other infectious diseases.

5.5 Trial Participants

5.5.1 Overall Description of Trial Participants

Male and non-pregnant female participants aged between 16 years and 65 years planning to visit the forest within 72 hours are the target study population. All study participants must meet the applicable inclusion and exclusion criteria.

5.5.2 Inclusion criteria

- Male or female, adults aged between 16 and 65 years.
- Planning to travel to the forest within the next 72 hours and stay overnight.
- Written informed consent.
- Willingness and ability of the participants to comply with the study protocol for the duration of the study.

5.5.3 Exclusion criteria

- For females: known pregnancy or breast feeding
- Participants who have received artemisinin or a derivative or an artemisinin-containing combination therapy (ACT) within the previous 7 days.
- History of allergy or known contraindication to artemisinins, lumefantrine or multivitamins
- Documented or claimed history of cardiac conduction problems
- Severe vomiting or diarrhoea
- Signs/symptoms of clinical malaria (febrile or history of fever in the previous 24 hours) confirmed by RDT.

6. PROCEDURES

Study procedures will be performed according to the schedule of assessments (Appendix 1). This will require that participants are followed up every 28 days for up to 3 periods upon completion of a course of prophylaxis.

6.1. Informed Consent

Prior to the start of enrollment we will conduct community mobilisation and sensitisation activities in each village community where the trial will recruit participants. During the trial, the participant (or witness if illiterate) must personally sign and date the latest approved version of the informed consent form before any study specific procedures are performed. Written and verbal versions of the participant information and informed consent in the local language will be presented to the participants detailing no less than: the exact nature of the study; the implications and constraints of the protocol; the known side effects and any risks involved in taking part. It will be clearly stated that participation is voluntary and that the participant is free to withdraw from the study at any time for any reason without prejudice to future care, and with no obligation to give the reason for withdrawal.

The participant will be allowed as much time as possible to consider the information and take the opportunity to question the Investigator, or other independent parties to decide whether they will (or allow his/her charge to) participate in the study. Written informed consent will then be obtained by means of participant dated signature or thumb print (if unable to write) and dated signature of the person who presented and obtained the informed consent.

A copy of the signed informed consent document(s) will be given to the participants.

Children aged 16 - <18 years will be required to sign the latest approved version of the written informed assent form in addition to their parent or guardian signing a consent form.

6.2. Screening, Eligibility and Baseline Assessments

Participants who present at the participating sites will be screened to assess eligibility. Full consent will be obtained before any enrolment procedures are conducted. It will be made clear from the outset that refusal to participate will not jeopardise subsequent antimalarial treatment (if applicable). A screening log will be kept.

6.2.1. Demographics and Medical History

Basic demographic and epidemiological data (e.g. sex, age, weight, address, bed net use, malaria risk factors, travel history, prior malaria episodes, prior treatment and previous participation in this or previous studies), and a full medical history will be recorded by the study staff.

6.2.2. Physical Examination and Vital Signs

Brief physical examination and vital sign will be conducted by a qualified study team member. Weight and temperature. A symptom questionnaire will be performed.

6.2.3. Drug history

All prescribed or over-the-counter and traditional antimalarial medications used within the last 7 days will be recorded. Any drug allergies will be recorded.

6.2.4. Clinical malaria

Participants who are screened and are found to be febrile or have a current history of fever will not be enrolled (as per exclusion criteria) but will be tested for malaria and, if positive, given antimalarial treatment by the village malaria worker or local clinic. All this will be done in accordance with the current national malaria treatment guidelines in Cambodia. Individuals treated for malaria in this way will not be enrolled in the study as per the exclusion criteria.

6.3. Randomisation and blinding

Participants who fulfil all the inclusion criteria and have none of the exclusion criteria will be randomised 1:1 to one of the two treatment arms according to a randomisation schedule. Randomisation will be in blocks of size that will be determined by the trial statistician and the block

size will not be revealed to the investigating team. Allocation will be done by drawing the next sequential numbered opaque envelope (or other equally reliable randomisation administration procedure), which contains the study number and treatment allocation.

The participants will be assigned a study arm through a computer-generated randomisation schedule. Individual, sealed and sequentially numbered envelopes will be provided for each trial site with one envelope per participant, indicating the treatment allocation.

This is an open-label study so the blinding of investigators and participants is not applicable. However, the randomisation procedure allows for adequate drug allocation concealment before envelopes are opened. All laboratory investigations will be performed without knowledge of the treatment allocation.

6.4. Blood sampling on study enrolment

On study enrolment, immediately before drug administration, blood will be collected for the following:

- Parasite PCR (Up to 1 ml).
- Dried blood spot for capillary blood level of lumefantrine (200 µl)
- Storage for later identification of other causes of fever (2ml).

6.5. Study drug administration

Overview PAL drug regimens	
ACT arm	Multivitamin arm
Artemether -lumefantrine x 3 days followed by 1 day per week	Multivitamin x 3 days followed by 1 day per week

Participants will be treated with weight-based doses according to the schedule in Appendix 2.

The study drugs will be administered by trained study staff.

If the participant vomits within half an hour after intake of the antimalarial drugs, the dose will be repeated. If vomiting occurs between half and one hour, half of the dose will be repeated. If vomiting occurs more than one hour after drug administration, no repeat dosing will be done. Repeat doses will be recorded on the CRF. If vomiting within 1 hour occurs more than one time, no repeat dosing is allowed. The participant will then be treated at the discretion of the investigator.

The prophylaxis will start with a 3-day course of twice daily AL. This will be followed by 2 doses 8 hours apart on one day per week during the time that the person is travelling in the forest and for 4 weeks after leaving the forest.

6.6. Follow-up

Participants will be asked to return for a follow-up assessment any time from 28 to 35 days after commencing prophylaxis. This will be regardless of the duration of their visit to the forest or the number of times they visited it in that period. At this assessment, they will be interviewed about how long they spent in the forest, where they went, why, who they travelled with and about risk factors for infection. Brief physical examinations, vital sign and symptom questionnaire will be performed. They will also be asked to report any diagnostic tests and/or treatment for malaria during the preceding 28-35 days.

Blood sampling at follow-up

At each follow-up visit, the following blood will taken:

<u>All individuals</u>:

- Parasite PCR (Up to 1 ml).

- Dried blood spot for lumefantrine level (0.2 ml)

In those with confirmed clinical malaria at any time point between enrolment and follow-up:

- Dry blood blots (0.4 ml, 3 spots) collected on filter papers for:
  - Parasite DNA genotyping for genetic markers of antimalarial resistance.
  - Parasite whole genome sequencing and barcoding to identify geographical origin of parasites and compare genotypes to identify persistent infections.

In individuals who are planning to return again to the forest within the following 28 days after the follow up visit, they will be asked to continue their weekly prophylaxis according to the original treatment allocation on enrolment. They will then be asked to return for a second follow-up visit a further 28 to 35 days later when the above procedure will be repeated. This will be repeated one more time. If the person cannot be followed up within the scheduled period, e.g. because they do not return from the forest in time, then they will be followed up at the first opportunity and this will be recorded in the CRF.

Thus individuals may take prophylaxis continuously for a maximum of 3 periods of 28-35 days in the forest plus 4 weeks after returning totaling 112 days. The choice of study medication for each individual will follow the initial assignment on enrolment throughout the follow-up period.

In those who do not declare an intention to return to the forest within 28 days at any follow-up visit, no further follow-up visits will be offered at that time but they will be asked to complete 4 weeks of prophylaxis following their last day in the forest as post-exposure prophylaxis.

Individuals who have been enrolled in the study may be enrolled into the study up to two more times during the 12 months study period only if a minimum period of 28 days (4 weeks) has elapsed following their last dose of prophylaxis. Thus they can be enrolled in the study a maximum of three times. If an individual is enrolled again in this way, they will be re-randomised following the same procedure as enrolment.

6.6.1 Time windows

The time-window for the follow-up visits is 28-35 days. If a participant does not attend, the study team will try to locate the participant and bring them to the village.

6.6.2 Additional visits

Participants presenting to the village malaria worker, mobile malaria worker or clinic with a fever or other symptoms at any time after enrolment that is not a scheduled study follow-up visit will be assessed and treated by the healthcare workers in the local healthcare system as per routine clinical practice in Cambodia.

On enrolment, participants will be encouraged to attend a village malaria worker or government clinic for the assessment of fever or other symptoms and to report this to the study team as soon as possible after the symptoms occur. Information on these healthcare encounters including malaria test result and treatment will be recorded in the study CRF.

6.6.3 Clinical Malaria during Follow-up

Participants who have an episode of confirmed clinical malaria at any time after enrolment up to the last follow-up visit and for one month afterwards will have blood taken for parasite genetic analysis.

6.7. Blood volumes

The blood volumes for the protocol mandated tests are as follows:

1. PCR: 1ml
2. Dried blood spots for lumefantrine level: 0.2ml
3. Dried blood spots for genetics: 0.4ml
4. Storage for serology at baseline 2ml

Maximum blood volumes are presented below for adults for the maximum of three periods (84 days) of follow up. The maximum blood volume is the total amount taken if the participants returns

for follow-up on 3 consecutive occasions and had all blood samples taken. The maximum blood volume will be approximately 10.4 ml (less than 10% of total blood volume taken over 8 weeks as recommended by WHO- *Bulletin of the World Health Organization 2011:89:46-53)*.

Allowing for the possibility that we may need to repeat blood tests, we may add 10.4 ml to these estimated maximum blood volumes.

Blood samples collected from this study will be stored no longer than 10 years using codes assigned by the study team or their designee(s). Access to research samples will be limited using either a locked room or a locked freezer.

6.8. Analysis of blood samples

6.8.1 Parasite PCR

This is required for the primary study objective. Blood samples will be analysed in the Molecular Tropical Medicine Laboratory, Bangkok, Thailand using PCR to identify which individuals have malaria parasites of any species. It is anticipated that results will be available around 3 to 6 months after collecting each sample, thus they will not be used to guide antimalarial treatment at the time of testing. The study teams will be informed which samples were positive for malaria and they will follow-up positive participants to conduct a brief clinical assessment. Any individuals who are symptomatic will be referred to the village malaria worker or clinic for testing and treatment.

6.8.2 Parasite genetic analysis

Blood samples (dried blood spots) for parasite genetic analysis will be obtained and stored from all subjects recruited with subject's consent. In individuals in whom parasites are found by PCR, samples will be processed for parasite genetic analysis. Genetic samples (in the form of dried blood spots or extracted DNA) will be stored (for a maximum of 10 years) at the Molecular Tropical Medicine Laboratory, Bangkok, Thailand. In those with confirmed clinical malaria, parasite genotyping will be performed at the Wellcome Trust Sanger Institute in Hinxton, UK or other suitable laboratory using a set of informative single nucleotide polymorphisms selected from whole genome sequencing. The subject will be asked for consent for this transfer during the initial informed consent process. A material transfer agreement will be in place if required before any samples are shipped. The results of the parasite genotyping will not be reported back to the subjects. This analysis will only be done for those with confirmed clinical malaria as it is anticipated that there will be insufficient genetic material in samples taken from those with asymptomatic infection due to the low parasite burden in these individuals.

6.8.3 Lumefantrine level

Blood samples (dried blood spots) for lumefantrine level will be taken at each follow-up visit. These will be analysed in the Pharmacology Laboratory at MORU in Bangkok, Thailand.

6.8.4 Serology

Among those who specify by written consent, the serology samples will be analysed for diagnostic markers of other infectious diseases.

6.9 Study drug

6.9.1 Artemether-lumefantrine

Currently available as standard tablets containing 20 mg artemether and 120 mg of lumefantrine, in a fixed-dose combination formulation. It is included in this formulation on the WHO Model List of Essential Medicines [21].

Target dose/range:
The dose of artemether-lumefantrine is administered as a twice daily dose for 3 days for a total of 6 doses (an initial dose, second dose after 8 hours and then twice daily – morning and evening – for the following two days) followed by twice daily once a week according to the treatment schedule in Appendix 2.

6.9.2 Multivitamin

The multivitamin will be multivitamin (HEXA CMP, Chemephand Medical Co., Ltd.) or suitable equivalent alternative administered as a once daily dose using the treatment schedule in Appendix 2. This multivitamin does not contain any compound with antimalarial activity. Its components are: Vitamin-A: 5000 USP units, Vitamin D: 400 USP Units, Ascorbic acid: 75 mg, Thiamine Mononitrate: 2 mg, Riboflavin: 3 mg and Niacin amide: 20 mg.

6.10 Epidemiological data on place of residence, work, travel history and malaria risk

In order to have a greater understanding of the possible sites of malaria transmission, and to relate genetic diversity to geographical location, participants will be asked a short set of questions on their place of residence, place of work and their history of travel plus possible risk factors for malaria. This is to obtain a detailed understanding of the behaviours and risk factors for malaria infection. We will collect GPS coordinates of the places of residence of all participants. In a subset of participants, GPS coordinates will be collected for their travel patterns during follow-up including place of work, forests, forest camps, farms or plantations to identify places where their infection may have occurred. The size of this subset will be determined by the availability of GPS devices with the number being limited to 50 participants at any one time. The GPS devices will be offered to unselected trial participants whenever they are available. We will collect all available local malaria treatment records to describe how the study population compares to the overall population who receive treatment for malaria and this will allow us to better understand local malaria epidemiology and transmission patterns. All personal information will be anonymised so that no individual can be identified from their treatment records, through interviews, or from mapping data.

6.11 Malaria incidence data

Passive surveillance data from all available sources for the study province collected by the Cambodia National Center for Parasitology Entomology and Malaria Control will be analysed to identify any changes in malaria incidence rate in study villages before, during and after the study where PA prophylaxis was administered compared to non-study villages.

Enrolled participants who experience an episode of confirmed clinical malaria during follow-up will be linked back to their individual case records to quantify the incidence of clinical malaria in each study arm.

6.12 Analysis

6.12.1 PCR for parasites

PCR will be used to identify which individuals have parasites at enrolment (prior to taking the study medicine) and at each follow-up visit and is required for the primary study objective.

6.12.2 Parasite genetics

Parasite DNA will be used for genomic studies including but not limited to parasite species confirmation, microsatellite typing to identify parasite clones and single nucleotide polymorphisms (SNP) typing/whole genome sequencing to generate data for studies of the geographic origins of the parasites.

6.12.3 Lumefantrine levels

Lumefantrine levels will be used to confirm which patients had taken lumefantrine and to measure the amount present in the blood.

6.12.4 Serology

The serology sample will be used for anonymized investigation of the prevalence, incidence, association with fever, and risk factors for other common infectious diseases affecting the study population. Samples will be stored for later analysis.

6.13 Discontinuation/ Withdrawal of Participants from the Study

Each participant has the right to discontinue the study drug or the study at any time. Data accrued up until the time of discontinuation will be used in the analysis.

In general, the investigators will be required to make every effort to perform the study procedures until completion of follow-up (maximum 3 visits over 84 days), including in the following situations:

- Significant non-compliance with treatment regimen or study requirements
- An adverse event which requires discontinuation of the study medication or results in inability to continue to comply with study procedures
- Disease which requires discontinuation of the study medication or results in inability to continue to comply with study procedures
- Loss to follow up (every attempt should be made to re-contact the participant)

However, the investigator may discontinue participation in the study of a participant if he or she considers it necessary.

In addition, the participants always have the right to withdraw consent in writing or verbally.

The reason for withdrawal or discontinuation, if available, will be recorded in the CRF. If the study drug or participation in the study is discontinued due to an adverse event, the investigator will arrange for follow-up visits at least until the adverse event has resolved or stabilised.

If a participant does become pregnant during participation in the study, they will be withdrawn from the study immediately upon it being reported to the study team. Any pregnancy must be reported to the Principal Investigator within one working day of awareness. The PI must take all reasonable efforts to discover the outcome of the pregnancy and fill out the pregnancy form. If there is a congenital abnormality or a still born baby, this needs to be reported as a serious adverse event.

6.14 Source Data

Source documents are original documents, data, and records from which participants' CRF data are obtained. These include, but are not limited to, village malaria and clinic records (from which medical history and previous and concurrent medication may be summarised into the CRF), clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and CRFs.

CRF entries will be considered source data if the CRF is the site of the original recording (e.g., there is no other written or electronic record of data). In this study, the CRF will be used as the source document for most of the data points.

All documents will be stored safely in confidential conditions. On all study-specific documents, other than the signed consent form, the participant will be referred to by the participant number and initials, not by name.

7. STUDY DRUGS

7.1 Storage of Study Drugs

All efforts will be made to store the study drugs in accordance with the manufacturers' recommendations in a secure area. This may be difficult at some sites where air-conditioned storage rooms are not available. The ACT should be stored between 15°C to 30°C (59°F to 86°F).

Where this is not possible and monitored storage conditions do not meet the recommendations, the artemisinin-derivatives and partner drug content of batches of ACT will be retested at the end of the study.

7.2 Compliance with Study Drugs

Study drugs will be administered as Directly-Observed-Therapy (DOT) on the first day. Where possible, study drugs will also be administered as DOT on days 2 and 3. Where DOTs is not possible, the participant will be contacted by the study team by telephone or in person to ensure they take the second and third doses of medication and to ensure they follow the correct procedure in case of vomiting. If the participant vomits, and is re-dosed; this will be recorded in the CRF. If

vomiting within 1 hour occurs again after retreatment, no repeat dosing is allowed. All drug doses will be recorded in the CRF. To maximise adherence to the study medication, the study will be preceded by a period of community sensitisation and engagement including information sessions on the importance of taking all three doses of medication. The participants will be requested to take each dose with food to maximize absorption of the lumefantrine.

7.3 Accountability of the Study Treatment

All movements of study medication will be recorded. Both study medication of individual participant and overall drug accountability records will be kept up to date by the study staff.

7.4 Concomitant Medication

Throughout the study, investigators may prescribe concomitant medications or treatments deemed necessary (e.g. antipyretics or anti-emetics) to provide adequate supportive care except for antibiotics with antimalarial activity unless unavoidable (e.g. doxycycline, azithromycin). If these are required the participants will be kept in the study and this will be noted as a protocol deviation. Anti-emetics should not be prescribed as a prophylaxis if no nausea or vomiting is present.

Antimalarials for symptomatic, confirmed malaria infections will be prescribed as described above. Any medication, other than the study medication taken during the study will be recorded in the CRF.

8. SAFETY REPORTING

This trial will use drugs that have either been registered or evaluated extensively. To add to the evidence base for safety of AL as prophylaxis, we will record and review all Adverse Events (AEs) and Serious Adverse Events (SAEs) that are reported to occur in the study.

A symptom questionnaire will be performed on enrolment and at each subsequent follow-up visit to the health care center, to aid in the identification of adverse events. In addition, enrolled individuals will be encouraged to promptly report any unexpected symptoms or illnesses between follow-up visits to the study team.

The investigator is responsible for the detection and documentation of events meeting the criteria and definition of an adverse event (AE) or serious adverse event (SAE), as provided in this protocol.

All SAEs and AEs will be promptly documented from the moment of drug administration in the study to discontinuation of the participant from study participation. Any events occurring between screening and drug administration will be considered as baseline, preexisting conditions.

All adverse events must be recorded in the AE/SAE CRF. To avoid colloquial expressions, the adverse event should be reported in standard medical terminology. Whenever possible, the adverse event should be evaluated and reported as a diagnosis rather than as individual signs or symptoms. If a definitive diagnosis is not possible, the individual symptoms and signs should be recorded. Whenever possible, the aetiology of the abnormal findings will be documented on the CRF. Any additional relevant laboratory results obtained by the Investigator during the course of this study will be recorded on the CRF.

If the event meets the criteria for “serious”, the SAE must be reported to the PAL-Cambodia safety team within 24 hours from the time that the event was identified. If further data is required, additional documentation can be submitted. All SAEs must be followed until resolution, or until the SAE is deemed permanent or leads to death.

Samples will be shipped for PCR to a molecular laboratory where they will be analysed in batches. Following quality control results will be available approximately 3-6 months from the time of collection. The list of positive tests will be returned to the field sites. If a participant is found to have a plasmodium infection, and has not already received antimalarial treatment subsequent to the sample being collected, then these individuals will be contacted by a local health worker, and if a participant reports fever or illness they will offered appropriate diagnosis and treatment.

8.1 Definitions

8.1.1. Adverse Event (AE)

An AE is any undesirable event or clinical deterioration that occurs to a study participant during the course of the study; that is, from the time of administration of study drugs until study ends (i.e., until the follow up visit) whether or not that event is considered related to the study drugs, or to a concomitant drug or procedure: e.g.

- any unfavourable and unintended symptom
- physical sign
- abnormal laboratory result
- an illness

Any new clinical sign or clinical deterioration that occurs between signing the consent form and the administration of study drugs is not an AE. This information will be recorded in the medical records, as a pre-existing condition.

8.1.2 Serious Adverse Event

A serious adverse event is an AE that:

- results in death
- is life-threatening i.e. the participant was at risk of death at the time of the AE

- requires in participant hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- Any other significant medical condition

All of the above criteria apply to the case as a whole and should not be confused with the outcomes of individual reactions/events. More than one of the above criteria can be applicable to the one event. Important medical events that may not be immediately life-threatening or result in death or hospitalisation may be considered an SAE when, based upon appropriate medical judgment, they may jeopardise the participant or require medical or surgical intervention to prevent one of the outcomes listed in the definition above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in hospitalisation, or development of drug dependency or drug abuse.

8.2 Reporting Procedures for Serious Adverse Events

All SAEs must be reported by the site investigator to the Study PI and PAL-Cambodia safety and medical monitor, within one day of his or her awareness of the SAE. The SAE report, should be emailed to the email paltrial@tropmedres.ac.

Further reports should be submitted, if required, until the SAE is resolved.

The site investigator must also report the SAEs to the local ethics committee in accordance with local requirements.

8.3 Evaluating Adverse Events and Serious Adverse Events

8.3.1 Assessment of Intensity

Each adverse event will be graded according to the Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 November 2017.

If an adverse event is not listed in the CTCAE table, the Investigator will assess the severity using the following guidelines:

1 = Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

2 = Moderate; minimal, local or noninvasive intervention indicated; limiting age appropriate instrumental ADL*

3 = Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL**

4 = Life-Threatening consequences; urgent intervention indicated

5 = Death related to AE

Activities of Daily Living (ADL)

*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

**Self care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

8.3.2 Clarification of the difference in meaning between ‘severe’ and ‘serious’

The term “severe” is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This is not the same as “serious”, which is based on the outcome or criteria defined under the serious adverse event definition. An event can be considered serious without being severe if it conforms to the seriousness criteria, similarly severe events that do not conform to the criteria are not necessarily serious. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

8.3.3 Assessment of relatedness

The investigator is obligated to assess the relationship between study drug and the occurrence of each AE/SAE using the following categories of relatedness:

- Definite: clear-cut temporal association
- Probable: clear-cut temporal association, with improvement upon drug withdrawal, and not reasonably explained by the participant's known clinical state or other aetiology.
- Possible: less clear temporal association; other aetiologies are possible. (Other possible aetiologies should be recorded on the CRF).
- Not related: no temporal association with the study drug; assessed as related to other aetiologies such as concomitant medications or conditions, or participant's known clinical state.

The investigator will provide the assessment of causality as per the AE/SAE data collection tool.

8.3.4 Outcome

The investigator will follow-up the AE and SAE until resolution or until no further medically relevant information can be expected. AE and SAE outcome will be classified as follows:

- Continuing/ongoing
- Resolved
- Resolved with sequelae
- Permanent
- Fatal

9 STATISTICAL CONSIDERATIONS

9.1 Sample size justification

The target population for this study will be adult Cambodians who work and sleep in the forest (farmers, collect forest goods, hunting, etc.). 2,200 study participant episodes are required in each arm to have sufficient power to detect a statistically significant difference between the treatment arm and a control arm. The estimate of the required sample size is complicated by the scarce data on *P. falciparum* incidence in forest workers. We estimate the required sample size based on our study in forest rangers in Vietnam in 2016 (13) combined with an estimate of the time spent in the forest from ongoing studies in northeast Cambodia. In Viet Nam, we found that 1 forest ranger became infected per 500 person-nights spent in the forest. We estimate conservatively that during each episode, each participant will spend at least 10 days in a high-risk zone. We will need 20 infectious bites per study-arm: 2x20=40 (i.e. irrespective of protection afforded per arm). Risk days/nights needed: 40x500= 20,000. Each participant episode contributes 10 risk days/nights: 20,000/10 = 2,000 episodes required. The assumed loss to follow-up could be as high as 10% =200. Therefore, the total sample required is 2,000+200=2,200 study participant episodes.

Formally, we anticipate that the risk of being Pf positive without receiving prophylaxis will be around 5%. A total of 1,605 participant-episodes per arm are enough to detect a difference of at least 40% in the proportion of episodes with a Pf positive result as defined by the 28-day PCR parasite positivity rate i.e. from 5% positivity in participants without receiving antimalarial prophylaxis (i.e. multivitamin) to 3% positivity in participants receiving artemether-lumefantrine prophylaxis. This has been estimated with 80% power and 5% significance level. However, we also anticipate that we will likely observe multiple episodes being recruited into the study that can reduce power of the study if not accounted for. To compensate for the multiple episodes and any losses to follow up, we plan to recruit approximately 600 (i.e. 595) additional episodes in each group on top of the required 1605 single episodes. This gives an additional 27% episodes to account for the multiple episodes and losses to follow up. Thus, the overall sample size will be 4,400 episodes (i.e. 2,200 episodes in the treatment arm and 2,200 episodes in the control arm).The sample size calculations have been performed in Stata version 15.

9.2 Statistical Analyses

Analysis of other endpoints will be described in a Statistical Analysis Plan. A brief overview is given below.

9.2.1 Proportions

These will be compared using chi squared or Fisher's exact test, as appropriate. Crude proportions will be calculated with the exact 95% confidence intervals (CI), where relevant.

9.2.2 Continuous data

These will be summarised by medians (IQR, ranges) and means (standard deviations, 95% CIs), as appropriate, and will include the parasite counts and laboratory parameters. Comparisons of continuous data will be assessed using the paired/unpaired t tests or the sign rank/Mann Whitney U tests, as appropriate.

9.2.3 Safety analysis

Safety analyses will be based on the whole population that get administered the study drug. Safety and tolerability of ACT versus multivitamin will be assessed by comparing the frequency (%) of adverse events and serious adverse events, with particular attention to abdominal pain, appetite perturbation, using the Fisher's exact test. Safety data will be presented in tabular and/or graphical format and summarised descriptively. Any clinically relevant abnormalities or values of potential clinically concern will be described. Participants will be analysed according to an intention to treat and a per protocol method where appropriate.

9.2.4 Adverse events

Adverse events will be graded according to Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 November 2017.

All adverse event summaries will refer to treatment emergent adverse events, i.e. adverse events that newly started or increased in intensity after the study drug administration. AE summaries will be generated for all AEs that occurred after study drug administration, until the end of the study.

10 DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

Direct access will be granted to authorised representatives from the sponsor and host institution, the regulatory authorities, and ethical committee (if applicable), to permit trial-related monitoring and inspections.

11 QUALITY CONTROL AND QUALITY ASSURANCE PROCEDURES

The study will be conducted in accordance with the current approved protocol, ICH GCP, any national regulations that may apply to this study and standard operating procedures. The WWARN will be engaged in assuring QA/QC of study execution in collaboration with the MORU Clinical Trials Support Group (CTSG). Their role will include but not be limited to monitoring adherence to SOPs for collection of laboratory specimens and quality checks (curation) of laboratory data according to standard methodologies.

11.1 Monitoring

Study sites may have in place a system for internal monitoring. In addition, regular external monitoring of all sites will be performed by the MORU CTSG according to ICH GCP and a Monitoring Plan. Data will be evaluated for compliance with the protocol and accuracy in relation to source documents. The monitors will check whether the clinical trial is conducted and data are generated, documented and reported in compliance with the protocol, GCP and the applicable regulatory requirements. Evaluation of on-site monitoring schemes, such as a reciprocal monitoring scheme, may be undertaken at selected sites by CTSG.

12 ETHICS

12.1 Declaration of Helsinki

The Investigator will ensure that this study is conducted in compliance with the current revision of the Declaration of Helsinki (Fortaleza 2013).

12.2 ICH Guidelines for Good Clinical Practice

The Investigators will ensure that this study is conducted according to any National Regulations and that it will follow the principles of the ICH Guidelines for Good Clinical Practice.

12.3 Approvals

The study protocol and its associated documents will be submitted to the Oxford Tropical Research Ethics Committee (OxTREC) and the appropriate local ethics committees for written approval.

The Investigator will submit and, where necessary, obtain approval from the above parties for all substantial amendments to the original approved documents.

12.4 Risks

This study will use drugs that have been studied thoroughly and their toxicities are well described. In general, they are all well tolerated. In the event of any serious or severe adverse event participants will be referred to the local Referral Hospital where best available care will be provided.

12.4.1 Risks of artemether-lumefantrine

The safety of artemether and lumfantrine for treatment of malaria has been evaluated in clinical trials and, post licensing, widespread use for treating malaria in hundreds of millions of patients per year. Reported AL side effects have generally been mild. Reported adverse reactions in clinical trials have been similar or lower in frequency and magnitude to other ACTs. The commonest (>=3%) reported adverse events in clinical studies with AL in adults were headache, anorexia, dizziness and asthenia. AL is not known to cause harmful prolongation of the QTc interval.[22].

12.4.2 Risks of multivitamin

The main side-effects of multivitamin are upset stomach, unpleasant taste or headache which are mild to moderate in nature. Very rarely, these may cause an allergic reaction.

12.4.3 Risk of phlebotomy & finger stick

The primary risks of phlebotomy include local discomfort, occasional bleeding or bruising of the skin at the site of needle puncture, and rarely haematoma or infection. Phlebotomy will be performed by suitably qualified and trained staff using appropriate hygiene measures including gloves and alcohol swabs to clean the skin.

12.4.4 Risk of GPS data

Due to the potential unique nature of the GPS tracking data, it may be possible to identify individuals from their tracks. This will be minimized by the GPS tracking data being kept separately from any personally identifiable information and linked to the data collected on the study CRF only through a unique study code. The GPS tracking data will also be stored anonymously on the tracking device during collection and moved to an encrypted hard drive upon completion of collection.

12.5 Benefits

There are no anticipated direct benefits to the participants in this study. However, knowledge gained from this study is expected to help to assess the efficacy and feasibility of prophylaxis to prevent malaria in forest workers, and to predict its efficacy in reducing overall transmission. The proposed study is a critical step for future use of chemoprophylaxis to protect forest workers in the GMS against malaria.

12.6 Alternatives to Study Participation

Participants are able to decline freely participation in this study. If so, they will receive standard care for their malaria (if applicable).

12.7 Incentives & Compensation

Study participants will be compensated for time lost from work as a result of trial activities, the cost of local transport to attend for the follow up visits and will receive a per diem to cover the costs of meals on those days. The amounts in monetary terms will be determined by CNM in accordance with local norms.

The study will pay for treatment for drug-related SAEs or other research-related injuries. The study cannot pay for long term care for disability resulting from complications of the illness.

12.8 Confidentiality

The trial staff will ensure that the participants' anonymity is maintained. The participants will be identified only by initials and a study number on the CRF and electronic databases. All documents will be stored securely and be accessible to trial staff and authorised personnel only.

13 SAMPLE SHARING AND STORAGE

Samples collected will be used for the purpose of this study as stated in the protocol and stored for future use no longer than 10 years. Consent will be obtained from participants for sample storage and/or shipment of specific samples to collaborating institutions for investigations that cannot be performed locally. Any proposed plans to use samples other than for those investigations detailed in this protocol will be submitted to the relevant ethics committees prior to any testing. Material transfer agreements will be arranged and signed where appropriate/needed.

14 DATA HANDLING AND RECORD KEEPING

Study data will be recorded on Case Report Forms (CRF) at the study sites and stored in a secure database. Validation checks will be built into the study database to identify missing values, inconsistencies, or invalid data. Additionally, study data will be profiled using statistical software to check for outliers and errors not detected by the database. All tasks related to data management will be carried out in accordance with the study data management plan.

Data sharing

With participant′s consent, participant′s data and results from blood analyses may be shared with other researchers in the future, in an anonymized form.

15 SPONSORSHIP AND INSURANCE

The University of Oxford 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.

16 PUBLICATION POLICY

Any data published in the peer-reviewed medical literature will protect the identity of the participants. This trial will be registered in a web based protocol registration scheme. All those who have made a substantial contribution will be co-authors on publications. The sites have the right to publish their data individually and to include members of the sponsor's team who have made a significant contribution. There will also publications of pooled data which will be coordinated by the MORU group. All sites will have the opportunity to contribute to these publications.

All the research findings from the programme and from relevant research outside the Programme will be analysed and integrated, and through the WHO Global Malaria Programme will be disseminated to policy makers, National Malaria Control Programmes (NMCPs) and other researchers.

17. REFERENCES

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18 APPENDIX 1. SCHEDULE OF ASSESSMENTS

TEST/APPLICATION	SCREENING	D0	D1	D2	CCM*	D28-35	CCM*	D56-63	CCM*	D84-91	CCM* up to D112
Informed consent	X										
Demographics		X									
Risk history		X				X		X		X	
Travel history		X				X		X		X	
Medical and drug history		X									
Symptoms questionnaire		X				X		X		X	
Temperature		X									
Weight		X									
Randomisation and assign study ID		X									
AL/multivitamin doses to be given		X	X	X							
Plasmodium PCR		X				X		X		X	
Blood for storage (serology)		X									
Plasmodium genetic analysis (DBS)					X*		X*		X*		X*
*CCM = episode of confirmed clinical malaria between enrolment and follow-up											

19 APPENDIX 2. DOSING SCHEDULES

19.1 Artemether-lumefantrine

Artemether -lumefantrine dosing schedule										
One tablet AL contains 20 mg artemether and 120 mg lumefantrine (Coartem)										
	No. of tablets recommended at approximate timing of dosing									
	Day 1		Day 2		Day 3		Day 8		Weekly	
Weight: Kilogram	0h	8h	24h	36h	48h	60h	168h	176h	336h ...	344h ...
15 - <25	2	2	2	2	2	2	2	2	2	2
25 - <35	3	3	3	3	3	3	3	3	3	3
≥35	4	4	4	4	4	4	4	4	4	4
Alternative preparation: one tablet AL contains 80 mg artemether and 480 mg lumefantrine (Artefan)										
	No. of tablets recommended at approximate timing of dosing									
	Day 1		Day 2		Day 3		Day 8		Weekly	
Weight: Kilogram	0h	8h	24h	36h	48h	60h	168h	176h	336h ...	344h ...
≥35	1	1	1	1	1	1	1	1	1	1

19.2 Multivitamin

Multivitamin dosing schedule					
One tablet contains Vitamin -A : 5000 USP units Vitamin D: 400 USP Units Ascorbic acid: 75 mg Thiamine Mononitrate: 2 mg Riboflavin: 3 mg Niacin amide: 20 mg Or suitable equivalent alternative					
	No. of tablets recommended at approximate timing of dosing				
	Day 1	Day 2	Day 3	Day 8	Weekly
Weight: Kilogram	0h	24h	48h	168h	336h ...
≥15	1	1	1	1	1

20 APPENDIX 3. LIST OF STUDY SITES & PRINCIPAL INVESTIGATORS

CAMBODIA

CNM: Dr Huy Rekol (Principal investigator) Dr Siv Sovannaroth (Co-Principal Investigator)

MORU : Dr. Rupam Tripura (Local investigator), Dr. James Callery (Local investigator), Dr. Tom Peto (Local Investigator), Dr Lorenz von Seidlein (Local Investigator), Professor RJ Maude (Principal Investigator), MORU, Thailand.

Site office: **Stung Treng Referral Hospital/Siem Pang Health Center**, Stung Treng Province.

Site office: **Pursat Referral Hospital/Kravanh Health Center**, Pursat Province.

21 APPENDIX 4. AMENDMENT HISTORY

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made
Not applicable				