Title	***Efficacy and safety of artemether-lumefantrine for the treatment of uncomplicated Plasmodium falciparum malaria, and chloroquine for the treatment of Plasmodium vivax in the Philippines***.
Protocol submission date	19 July 2016
Protocol number	2003-25-03
Participating institutions	Rural Health Unit Bataraza, Palawan, Philippines Rural Health Unit Brooke's Point, Palawan, Philippines Rural Health Unit Rizal, Palawan, Philippines
Study dates	May 2013 – December 2018
Sponsor	Government of the Philippines

Contents

SYNOPSIS

Title: Efficacy and safety of Artemether-Lumefantrine for the treatment of uncomplicated *Plasmodium falciparum* malaria and chloroquine for the treatment of *Plasmodium vivax* malaria in the Philippines.

Purpose: To assess the efficacy of the current first line of treatment policy.

Objectives:

a) To assess the safety and efficacy of Artemether-lumefantrine for the treatment of uncomplicated *P. falciparum* infections in the Philippines.
b) To assess the efficacy of Chloroquine for the treatment of *P. vivax* infections in the Philippines.

Study Sites:

a) Rural Health Unit, Bataraza, Palawan
b) Rural Health Unit, Brooke's Point, Palawan
c) Rural Health Unit, Rizal, Palawan

Study Period: January 2018 – December 2018

Study Design: one-arm, prospective study

Patient Population: Febrile patients aged > 6 months to 59 years old, with confirmed uncomplicated *P. falciparum* infection only or *P. vivax* infection only, and non- pregnant and/or breastfeeding for female.

Sample Size: A minimum of 50 and maximum of 75 patients will be enrolled for both *Plasmodium falciparum* and *Plasmodium vivax* malaria.

Treatments and follow-up: Clinical and parasitological parameters will be monitored over a 28/34 day follow-up period to evaluate drug efficacy.

Primary endpoints: The proportion of patients with early treatment failure, late clinical failure, late parasitological failure or an adequate clinical and parasitological response as indicator of efficacy. Recrudescence will be distinguished from re-infection by polymerase chain reaction (PCR) analysis.

Secondary endpoints: The frequency and nature of adverse events.

Optional exploratory endpoints: to determine the polymorphism of molecular markers for name of the antimalarial drug(s) resistance.

1. BACKGROUND

In 2002, the Philippines changed its antimalarial drug policy to the combination treatment, CQ+SP as 1st-line treatment and artemether-lumefantrine as 2nd-line treatment. The DOH prescribed the use of artemether-lumefantrine (AL) combination as the second line drug, limiting its use only in the treatment of confirmed *Plasmodium falciparum,* until further study on its efficacy were done before making it as the first line treatment. Consequently, AL became the first-line drug for falciparum malaria in the 2009 revised drug policy. The DOH in the past 6 years (2002-2007) adopted the use of AL in the highly endemic areas of the country and conducted therapeutic efficacy studies (TES) in 3 sentinel sites: Kalinga-Isabela, Palawan and several Mindanao provinces, showing 97-100% efficacy. Whereas, CQ+SP showed variability and declining efficacy, results ranged from 70%-95% (CARAGA region). In Sultan Kudarat province, results in 2006-2007 showed 90% efficacy of CQ+SP and 96% for AL for falciparum malaria.

In the 2009 drug policy, chloroquine (CQ) remains as the primary treatment for *P. vivax* malaria, with primaquine as anti-relapse drug. Previous studies (1999-2005) elsewhere in the country have shown 100% efficacy of CQ or the CQ+PQ combination. However in 2013, recurrence of parasitemia was observed in one of 84 enrolled patients in Palawan. The last TES of AL as firstline drug of choice for falciparum malaria was made in 2015. This protocol will update this drug's efficacy for this parasite and of that P. vivax.

The results of this study will be used to assist the Department of Health of Philippines in assessing the current national treatment guidelines for uncomplicated P. falciparum and P. vivax malaria, and to update the policy if necessary.

2. OBJECTIVES

The general objective of this study is to assess the therapeutic efficacy and safety artemether-lumefantrine for the treatment of uncomplicated *P. falciparum* infections and of chloroquine for the treatment of uncomplicated *P. vivax* infections in the Philippines.

The primary objectives are:

- To measure the clinical and parasitological efficacy of artemether-lumefantrine (AL) among patients aged between > 6 months and 59 years old suffering from uncomplicated falciparum malaria, by determining the proportion of patients with Early Treatment Failure (ETF), Late Clinical Failure (LTF), Late Parasitological Failure (LPF), or with an Adequate Clinical and Parasitological Response (ACPR) as indicators of efficacy;
- To measure the clinical and parasitological efficacy of Chloroquine among patients aged between > 6 months and 59 years old suffering from uncomplicated vivax malaria, by determining the proportion of patients with Early Treatment Failure (ETF), Late Clinical Failure (LTF), Late Parasitological Failure (LPF), or with an Adequate Clinical and Parasitological Response (ACPR) as indicators of efficacy;
- To differentiate recrudescences from new infections by the Polymerase Chain Reaction (PCR) analysis;

The secondary objectives are:

- To evaluate the incidence of adverse events;
- To formulate recommendations to enable the Department of Health to make informed decisions about the possible need for updating of the current national antimalarial treatment guidelines.

The exploratory objective:

To determine the polymorphism of molecular markers for artemether-lumifantrine and chloroquine resistance.

3. INVESTIGATIONAL PLAN

3.1. Study Design

The design of this surveillance study is a one-arm, prospective evaluation of the clinical and parasitological response to directly observed treatment for uncomplicated falciparum malaria and vivax malaria. Individuals with uncomplicated malaria who meet the study inclusion criteria will be enrolled, treated on site with AL and monitored for a period of 28 days if they have falciparum malaria, and with chloroquine if with vivax malaria for a period of 34 days. The follow-up will consist of a fixed schedule of check-up visits and corresponding clinical and laboratory examinations. Study patients will be classified as therapeutic failures (early or late) or adequate responders based on the results of these assessments. The proportion of patients experiencing therapeutic failure during the follow-up period will be used to estimate the efficacy of the study drug(s). Polymerase Chain Reaction (PCR) analysis will help distinguish between a true recrudescence due to treatment failure and episodes of reinfection.

3.2. Study site

The study site will be conducted in the Rural Health Units in the municipalities of Rizal, Brooke's Point, and Bataraza, Palawan. Several factors influenced the selection of sites were: adequate numbers of patients with symptomatic, uncomplicated *P. falciparum* or *P. vivax* malaria; willingness and availability of the selected health care facility staff to participate in the surveillance study and to support the work with laboratory space; access of patients to the health facility for weekly follow-ups; availability of the Municipality Health Officer (MHO), the nurse and a trained Medical Technologist to take responsibility for conducting the study, and security.

3.3. Timing and duration of study

The study will be conducted during the malaria transmission season, from January 2018 to December 2018.

3.4. Study population

The study population will consists of patients aged between > 6 months to 59 years old diagnosed with uncomplicated falciparum and vivax malaria attending the study health clinic, and having given, or whose parents or legal guardians have given an informed consent for study inclusion and assent in children as appropriate. All adult patients who are 18 years, age of majority in this country, will sign an informed consent form for participation. Parents or guardians will give informed consent on behalf of children who have not reached 18 years of age. Children aged 12 to 17 years old will be required to consent for participation by signing an informed assent form.

3.5. Inclusion criteria

- Above 6 months old to 59 years old;
- Mono-infection with *P. falciparum* or *P. vivax,* with parasitemia of:
    - *P. falciparum:* 1000–100 000 asexual forms per µl[1];
    - *P. vivax* : ≥ 250 per µl
- Axillary temperature ≥37.5 °C or oral/rectal temperature of ≥38 °C[2];
- Ability to swallow medication;
- Ability and willingness to comply with the study protocol for the duration of the study and to comply with the study visit schedule;
- Informed consent from the patient or from a parent or legal guardian in the case of children less
- than 18 years old;
- Informed assent from any minor participant aged 12 – 17 years; and
- Consent for pregnancy testing from female of child-bearing potential and from their parent or guardian if under 18 years old.

3.6. Exclusion criteria

- Presence of general danger signs among children <5 years old or other signs of severe and complicated falciparum malaria according to WHO definitions (*see Annex 1*);
- Weight under 5 kg;
- Mixed *Plasmodium* species detected by microscopy;
- Presence of severe malnutrition (defined as a child whose weight-for-height is below –3 standard deviation or less than 70% of the median of the NCHS/WHO normalized reference values, or who has symmetrical oedema involving at least the feet or who has a Mid Upper Arm Circumference [MUAC] <110 mm);
- Presence of febrile conditions due to diseases other than malaria (measles, acute lower tract respiratory infection, severe diarrhea with dehydration, etc.), or other known underlying chronic or severe diseases (e.g. cardiac, renal, hepatic diseases, HIV/AIDS);
- Regular medication, which may interfere with antimalarial pharmacokinetics;

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[1] In areas of low-to-moderate transmission, the cut-off point is set between 1000 and 100 000 asexual forms per µl.

[2] When enrolment proves difficult, in particular in areas of low-to-moderate transmission, proven fever or a history of fever within the previous 24 h is acceptable.

- History of hypersensitivity reactions or contraindications to any of the drug(s) being tested or used as alternative treatment;
- Positive pregnancy test or breastfeeding; and
- Unable to or unwilling to take pregnancy test or to use contraception for women or child-bearing age and who are sexually active.

3.7. Loss to follow-up

Loss to follow-up occurs when, despite all reasonable efforts within 48 hrs period of the visit, an enrolled patient that does not attend the scheduled visits cannot be found. No treatment outcome will be assigned to these patients. These patients will be classified as lost to follow-up and excluded from the per protocol analysis. Patients who are lost to follow-up, but who subsequently come back to the study site before day 28 for participants with Plasmodium falciparum and before day 34 for Plasmodium vivax participants, will not be turned away and will also be encouraged to return for check-up visits. Nevertheless, these patients will also be classified as lost to follow-up. Every effort must be made to schedule a follow-up visit for patients who fail to return to the study site especially during or but also after administration of the study drug.

3.8. Patient discontinuation or protocol violation

Study patients meeting any of the following criteria classified as withdrawn.

- Withdrawal of consent

A patient may withdraw consent at any time, without prejudice for further follow up or treatment by the study site.

- Failure to complete the treatment due to either:
  - Persistent vomiting of the treatment. A patient who vomits twice study medication will be withdrawn from the study and given rescue treatment.
  - Failure to attend the scheduled visits during the first 3 days;
  - Serious adverse events necessitating termination of the treatment before the full course of the treatment is completed. A patient can be discontinued from the study if the principal investigator decides that a patient should be withdrawn for safety reasons due to an adverse event of such a nature or intensity to recommend withdrawal from the study. In this case, information concerning the adverse event and symptomatic treatment given must be recorded on the case record form (CRF). If the adverse event is serious, the principal investigator must notify the sponsor or its designee immediately and the reporting procedures described in the safety section must be followed.

- Enrolment Violation
  - Severe malaria on day 0;
  - Erroneous inclusion of patient who does not meet the inclusion criteria.

- Voluntary protocol violation
  - Self or third party administration of antimalarial (or antibiotics with antimalarial activity) (*see Annex 2*)

- Involuntary protocol violation
  - Severe malaria occurring on Day 0
  - Occurrence during the follow-up of concomitant disease that would interfere with a clear classification of the treatment outcome
  - Detection of another malaria species during the follow-up
  - Erroneous inclusion of a patient who do not meet the inclusion criteria
  - Misclassification of a patient due to a laboratory error (parasitaemia) leading to the administration of the rescue treatment

Patients who are withdrawn will nevertheless be follow-up until day 28 for Plasmodium falciparum and until day 34 for Plasmodium vivax or until recovery, if possible. However, no treatment outcome will be assigned to these patients and excluded from the per protocol analysis. The reason for discontinuation or protocol violation will always be recorded on the CRF.

4. TREATMENT

4.1. Antimalarial treatment

P. falciparum: artemether-lumefantrine will be administered for 3 days according to body weight (Days 0, 1 and 2). Correct drug dosage will be determined using the dosing chart (*in accordance with national treatment guidelines, details provided in Annex 3*). Primaquine 0.75 mg/kg body weight single dose will be given on Day 3 (*in accordance with national treatment guidelines, details provided in Annex 3*).

P. vivax: chloroquine will be administered according to body weight at a total dose of 25mg base/kg over 3 days (10mg base/kg on Day 0; 10 mg base/kg on Day 1 and 5 mg base/kg on Day 2). Correct drug dosage will be determined using the dosing chart (*in accordance with national treatment guidelines, details provided in Annex 3*). Primaquine will be withheld for 28 days. It will be given after Day 28 follow-up, at 0.25 mg base/kg per day for 14 days.

Tablets of AL (Coartem™ 20/120 mg per tablet artemether/lumefantrine); chloroquine (250 mg base/tablet and primaquine (15 mg base per tablet) as well as other anti-malarial drugs for rescue treatment will be sourced from the Department of Health.

All doses of drugs will be administered under supervision by qualified staff member of the team designated by the principal investigator. Study patients will be observed for 30 minutes after drug administration for adverse reactions or vomiting. Any patient who vomits during this observation period will be retreated with the same dose of drug and observed for an additional 30 minutes. If the patient vomits again he/she will be withdrawn and offered rescue therapy. The study patients will be required to return to RHU for each dosing dosing day.

4.2. Concomitant treatments and forbidden medication

Treatment of fever over 38 ℃ is permitted with paracetamol or acetaminophen. Parents/guardians will be instructed in the use of tepid sponging for children <5 years old.

Prior treatment with antimalarial drugs will not be considered as an exclusion criterion. But, during the follow-up, if infections other than malaria require the administration of drugs with antimalarial activity, the patient will be withdrawn from the study. Patients given tetracycline as eye ointment will not be excluded (*see Annex 2*). Similarly, patients will be withdrawn from the study in case of self-medication or if an antimalarial drug or antibiotics with antimalarial activity is administered by a third party.

Adverse events requiring treatment may be treated according to local practice. Should there be a clinical indication for any additional medication during the course of the study including medication given to treat an adverse event related to the study drug, the name of the drug, the dosage, and the date and time of administration must be recorded in the CRF.

The use of herbal remedies during the course of the study should be avoided and subjects should be encouraged to return to the study site for treatment if they are feeling unwell in the first instance. However, if any herbal remedies are taken during the study, this should be captured in the CRF, in the section Study Medication Administration.

4.3. Rescue treatment

If the patient vomits twice the treatment he/she will receive parenteral therapy with quinine at 10mg/kg bw every 8 hours for 2-3 days, followed by AL for 3 days when he/she can tolerate oral meds, and he/she will be withdrawn from the study.

With any sign of severe Pf or Pv malaria, the study patient will be hospitalized and receive parenteral therapy with Quinine at 10mg/kg bw every 8 hours for 2-3 days, followed by AL for 3 days, as well as relevant supportive treatments.

If a patient meets one of the criteria for therapeutic failure, he/she will receive oral Quinine at 10mg/kg bw every 8 hours for 7 days, in combination with tetracycline (250 mg QID x 7 days), clindamycin (10 mg/kg BID x 7 days) or doxycycline (3 mg/kg OD x 7 days) for Pf patients or AL for 3 days + Primaquine for 14 days for Pv patients, according to the current national recommendations. If the patient is re-infected with another malaria species he/she will receive treatment according to the current national recommendations.

5. Evaluation criteria

Valid end-points of the study include completion of the follow-up period without treatment failure, treatment failure, loss to follow-up, and withdrawal from study (voluntary or involuntary, and voluntary or involuntary protocol violation). At all times, the well-being of the study patient will take priority over the continuation of the involvement of that patient in the study.

5.1. Efficacy and safety evaluation

5.1.1. Classification of treatment outcomes

The classification of treatment outcomes will be based on an assessment of the parasitological and clinical outcome of antimalarial treatment according to the latest guidelines of WHO. Accordingly, all patients will be classified as having an Early Treatment Failure, a Late Clinical Failure, a Late Parasitological Failure, or an Adequate Clinical and Parasitological Response, as defined in Annex 4.

As parasitological cure is the goal of antimalarial therapy, all study subjects who present with a treatment failure will be treated with the rescue treatment and dropped from further follow-up.

5.1.2. Safety endpoints

Incidence of any adverse event will be documented. All patients will be routinely asked about old symptoms and new symptoms emerging since previous visit during the follow-up. Where clinically indicated, patients will be evaluated and treated appropriately. All adverse events will be recorded on the CRF. Serious adverse events must be reported to the co-investigator and principal investigator.

5.2. Clinical evaluations

Clinical evaluations will be undertaken in all patients using the following parameters:

5.2.1. Physical Examination

A standard physical examination will be performed at baseline (day 0 pre-dose) as well as on days 1, 2, 3, 7, 14, 21, 28. A complete medical history, demography and location of contact address and details will be taken at baseline.

5.2.2. Weighing and presence of edema

Body weight will be recorded at day 0. Weight will be measured at to the nearest kg on a Salter scale or some other hanging scale for weighing young children properly calibrated with only undergarments kept on the patient. The screening weight will be used to satisfy the inclusion/exclusion for nutrition status as well as to calculate the dose (number of tablets) to be administered. The reliability of scales will be verified using known standard weights prior to commencement of study and will be checked at regular intervals.

MUAC will be measured on the left arm, at the mid-point between the elbow and the shoulder and will be recorded to the nearest 0.2 cm. Edema will be assessed by thumb pressure for 3 seconds on the dorsal part of both feet.

5.2.3. Measurement of body temperature

Axillary temperature will be performed at baseline (day 0 pre-dose) as well as on days 1, 2, 3, 7, 14, 21,and 28**.** Temperature will be measured using a thermometer with a precision of 0.1°C. Temperature will additionally be measured as clinically indicated. If the result is <36.0°C, the measurement will be repeated.

Quality of temperature-taking technique and thermometers should be regularly tested in a water-bath of known temperature prior to study commencement and at regular intervals during study.

5.2.4. Microscopic blood examination

A pair of Giemsa-stained thick and thin blood films will be obtained from each patient and examined at a magnification of 1000x to identify parasite species and to determine the level of parasitemia at screening on day 0 to confirm inclusion/exclusion criteria. Thick and thin blood films will be also examined on days 1, 2, 3, 7, 14, 21 and 28 or on any other day if the patient spontaneously returns and parasitological reassessment is required. Specimens will be labelled anonymously (study number, day of follow-up, date taken). The other pair of blood film will be kept in a separate box as back-up blood films. The study number of the patient, the date and day of follow-up will be recorded on the frosted edge of the slide.

Giemsa stain solution will be freshly prepared at least once a day depending on the number of blood films being processed. Giemsa-stained thick and thin blood films will be examined at a magnification of 1000x to identify parasite species (for both *Pf* and *Pv*) and determine parasite density.

The second blood smear (Days 0, 1, 2, 3, 7, 14, 21, and 28,) will be used to calculate the parasite density, by counting the number of asexual parasites in a set number of white blood cells (typically 200) with a hand tally counter. Once a field has been started, it must be counted to completion; the final number of white blood cells will therefore rarely be exactly 200. If more than 500 parasites have been counted before 200 white blood cells have been reached, the count will be stopped after the reading of the last field has been completed. Parasite density, expressed as the number of asexual parasites per µl of blood, will be calculated by dividing the number of asexual parasites by the number of white blood cells counted and then multiplying by an assumed white blood cell density (typically 6000 per µl).

$$\text{Parasite density}/\mu l = \frac{\text{number of parasites counted x } 6000}{\text{number of leukocytes counted}}$$

The same technique will be used to establish the parasite count on each subsequent blood film. When the number of asexual parasites is less than 100 per 200 white blood cells in follow-up smears, counting will be done against at least 500 white blood cells (i.e. to completion of the field in which the 500th white blood cell is counted).

A blood slide will be considered negative when examination of 1000 white blood cells or 100 fields containing at least 10 white blood cells per field reveals no asexual parasites. The presence of gametocytes on an enrolment or follow-up slide will be recorded, but this information will not contribute to basic evaluation.

In addition, 100 fields of the second thick film at day 0 will be examined to exclude mixed infections; in case of any doubt, the thin film will be examined for confirmation. If examination of the thin film is not conclusive, the patient will be excluded from the analysis after complete treatment and follow-up.

To detect the presence of gametocyte, at least 1000 white blood cells should be counted.

Two qualified microscopists will read all the slides independently, and parasite densities will be calculated by averaging the two counts. Blood smears with discordant results (differences between the

two microscopists in species diagnosis, in parasite density of > 50% or in the presence of parasites) will be re-examined by a third, independent microscopist, and parasite density will be calculated by averaging the two closest counts.

5.2.5. Genotyping of malaria parasites

In order to differentiate a recrudescence (same parasite strain) from a newly acquired infection (different parasite strain), a genotypic analysis based on the extensive genetic diversity displayed by the malaria parasite genes, msp1, msp2 and glurp will be performed. Genotypic profiles of the pre- and post parasite strains will be compared.

Two to three drops of blood will be collected on a filter paper Whatmann3 from each patient on Day 0 and on any succeeding scheduled or un-scheduled follow-up visit where the repeat blood film shows the presence of asexual parasitemia *(see Annex – WHO classification of response to treatment*).

The filter paper will be labeled anonymously (study number, Day 0 and Day of treatment failure, if any and date taken), kept in individual plastic bags with desiccant pouches and protected from light, humidity and extreme temperature until analyzed. When such room temperature conditions are not possible, for example in extremely humid environments where air-conditioning is not available, storage in a refrigerator will be considered, but great care will be taken to protect samples from frost and moisture. The PCR technique used will…….. be done in RITM molecular biology laboratory. Paired filter papers will be used for parasite DNA extraction and genotyping. All filter papers will be destroyed immediately after the PCR analyses have been completed, otherwise kept in safe locations for further research with patient's consent. The sponsor will provide instructions to the principal investigator regarding shipment or destruction procedures of biological specimen collected during the study.

5.2.6. Pregnancy test.

Female patients of child-bearing age (≥ 12 years), defined as those who menstruate and who are sexually active, will be asked to take a urine pregnancy test before enrolment in the study, because name of the antimalarial drug(s) or drug combination(s) is contraindicated during the first trimester. They will also be asked to take a urine pregnancy test on day 28 or on early withdrawal from the study.

Female participants of child-bearing age, defined as those who menstruate and who are sexually active should avoid pregnancy, preferably by using barrier contraceptive devices for the duration of the study. Appropriate contraceptive method (condom, pills) will be provided by the Public Health Nurse or study team at the time informed consent is obtained, with appropriate counselling about the risks of becoming pregnant and exposing the fetus to the study medicines.

5.2.7. Haematological assessment

Hemoglobin will be determined at Day 0, Day 3, Day 7, Day 14 (optional) follow-up among patients enrolled in the Pf study and on Day 0, Day 3, Day 7, Day 14 (optional), Day 28, Day 31, and Day 34 among enrolled Pv patients using the Hemacue method, requiring 60 ul from a finger-prick blood sample.

5.2.8. Chloroquine blood assays for vivax patients

100 ul finger prick blood samples for determining blood chloroquine levels will be collected from P. vivax patients at Day 0, Day 3, Day 7, Day 14, Day 21, Day 28 and day of treatment failure, if any. This will be blotted on filter papers (chromatography paper 31ETCHR®, Whatman), and kept in individual plastic bags with desiccant pouches and sealed, protected from light, humidity and extreme temperature. Specimens will be labelled (Study number, day of follow-up, and day of treatment failure, if any, and date taken) anonymously. These will be stored in appropriate conditions and later sent to RITM laboratory for processing and assay.

5.2.9 Molecular markers for antimalarial drug resistance

Two to three drops of blood will be collected on filter paper on day 0 and day of failure to study the polymorphism, parasite DNA extraction and genotyping which are considered as markers of resistance to name of the antimalarial drug(s) or metabolite(s). The PCR technique used will…….. and be done in RITM molecular biology laboratory. Specimens will be labelled anonymously (study number, day of follow-up, date), kept in individual plastic bags with desiccant pouches and protected from light, humidity and extreme temperature until analysed.

5.2.10 Storage of unused samples

All samples will be destroyed immediately after the analyses have been completed, otherwise kept in safe locations for further research with patient's consent.

5.3. Safety assessment

Safety will be assessed by recording the nature and incidence of adverse events and serious adverse events. Adverse events will be assessed by direct questioning. An adverse event is defined as any unfavourable, unintended sign, symptom, syndrome or disease that develops or worsens with the use of a medicinal product, regardless of whether it is related to the medicinal product. All adverse events must be recorded on the case report form.

A serious adverse event is defined as any untoward medical occurrence that at any dose:

- results in death, is life threatening;
- requires hospitalization or prolongation of hospitalization;
- results in a persistent or significant disability or incapacity; or
- is a congenital anomaly or birth defect.

'Life-threatening' means that the person was at immediate risk for death; it does not refer to an adverse event that might have caused death if it were more severe. 'Persistent or significant disability or incapacity' means that a person's ability to carry out normal life functions is substantially disrupted.

All serious adverse events occurring during the study must be recorded and reported by the principal investigator to the sponsor, regardless of whether the principal investigator considers the events to be related to the investigated medicine.

6. STUDY ASSESSMENTS

6.1. Screening and enrolment procedures

All patients meeting the basic enrolment criteria (age, fever or history of fever, presence of symptoms of malaria, absence of signs of severe malaria, absence of severe malnutrition, pregnancy, etc) during the screening procedure will be assigned a consecutive screening number and evaluated in greater depth by clinical staff. Special care will be taken to detect the presence or early signs of febrile diseases other than malaria, as these will probably necessitate exclusion of the patient from the evaluation. Among paediatric populations, the most frequent confounding condition is lower respiratory tract infections: cough or difficult breathing, together with fast breathing, is an indicator for identifying and excluding patients suffering from such conditions. Fast breathing is defined as a respiratory frequency >50/minute in infants under 12 months of age and >40/minute in children aged 12–59 months. Other relatively common febrile conditions are otitis media, tonsillitis, measles and abscesses. Patients with these conditions will not be enrolled, but obviously need to be treated both for malaria (if they have parasitaemia) and the other infection as appropriate.

The screening record form will be used to record the general information and the clinical observations of each patient under screening. If the patient meets the clinical criteria, he/she will be examined for parasitaemia. Once the patients meets all the enrolment criteria (*see section above*), he/she or the

parent/guardian will be asked for consent to participate in the study. Children between 12-17 years old will also need to provide their assent to participate.

6.2. Follow-up procedure

Patients meeting all enrolment criteria will be given a personal identification number and receive treatment only after they have had the study fully explained to them and have willingly provided their informed consent. Any subject who decides not to participate in the study will be examined and treated by the health facility staff as usual. They will be treated and followed-up according to the standard of care established by the Department of Health.

The basic follow-up schedule is summarized in *Annex 6*. A Case Report Form (CRF) (*Annex 7*) will be used to record the general information and clinical observations for each patient enrolled into the study. The appointment scheduled will be clearly explained and a follow-up card mentioning the personal identification number will be handed out.

The day that the patient is enrolled and receives the first dose of drugs is designated as "day 0". All antimalarial treatment will be given by a study team member under supervision. Enrolled patients will be observed for at least 30 minutes after treatment to ensure that they do not vomit the medicine. If vomiting occurs within 30 minutes of treatment, the full treatment dose will be repeated. Ancillary treatments, such as antipyretics, may be required and will be provided to patients by the study team and documented on the CRF. Patients with persistent vomiting (i.e. necessitating more than a single repeat dose) will be excluded from the study and immediately referred to the health facility staff for appropriate management.

Thereafter, the schedule calls for clinical reassessments and blood films for malaria (parasites and parasite count) to be made on days 1, 2, 3, 7, 14, 21, and 28. Patients will always be advised to return on any day during the follow-up period if symptoms return and not to wait for scheduled visit day. Clinical reassessments will be sufficiently thorough to ensure patient safety and will include assessments not only for potential treatment failure but also for potential adverse reactions to the treatment drug. Additionally, blood films will be obtained whenever parasitological reassessment is requested by the clinical staff for reasons of patient safety.

AL drugs require multiple-day dosing and the initial visits are critical not only for the efficacy assessment but also for patient safety; defaulters at this stage who will not have received a complete course of treatment may be at risk for clinical deterioration. All reasonable efforts will be made to find defaulters to ensure complete treatment. Similarly, the ultimate success of the study rests on minimizing loss to follow-up. Subjects treated with AL will be asked to return on the same days but they will need to be seen twice on Days 0, 1 and 2 because of the twice daily dosing. It is imperative that this second dose be observed therefore either the study participant returns to the health center or a health worker (BHW or midwife) connected to the study visits the person at their home, or they are admitted at the district hospital during the 3-day treatment, whichever is applicable. For subjects treated with CQ, Primaquine is withheld until Day 28 follow-up. It is important that a health worker will follow-up the patinets in their homes to give the daily dose of Primaquine for 14 days by Direct Observed Treatment (DOTs). Since only ambulatory patients with uncomplicated malaria and drugs with well-known safety profiles are being assessed as part of this protocol, there is no need for daily follow-up through the course of the study. Subjects and parents/guardians (in the case of children) will be encouraged to return to the clinic for further clinical and parasitological assessment (repeat blood smears) and/or treatment at any time during follow-up at which the subject is perceived to be ill. A repeat Hgb count will also be done on Day 3, 7, 14 (optional), and 28, and additional Day 31 and 34 for Pv patients. The Barangay Health Worker (BHW) or the malaria field worker will specifically look for them in place of residence for follow-up on Days 3, 7, 14, 21 and 28 if they do not return.

While patients are encouraged to return on their own for scheduled follow-up visits, it is essential that provisions be made ahead of time for locating patients at home if they do not attend as requested. This

requires obtaining detailed directions to the home during enrolment, study team members familiar with the community responsible for home visits, and means of transportation. The schedule for treatment and follow-up examination given in this protocol must be followed rigorously to ensure data integrity. Patients who fail to return on day 1 and day 2 and miss one dose of the treatment are withdrawn from the study definitively. After day 3, patients who fail to return on day 7 but are present on day 8 (likewise days 14/15, days 21/22, and days 28/29) may still be included in the study group. Deviation from the protocol of more than 1 day cannot be allowed, both for the safety of the patient and for the relevance of the data.

Summary of Detailed Procedures for Patient Enrolment, Scheduled Follow-up Visits

Procedures	**Schedule of Screening, Recruitment and Enrolment Days, and Follow-up Visits**												
	D0	D1	D2	D3	D7	D14	D21	D28	D31	D34	D35 (optional)	D42 (optional	Un-scheduled day
Screening Procedures													
History taking	X												
Clinical Assessment Signs/symptoms (assess if no severe malaria danger signs)	X												
Recruitment and Enrolment Procedures													
If patient has satisfied the inclusion criteria and is a potential enrollee[3]	X												
Clinical Assessment													
Signs/symptoms (refer to next level of care in case of severe malaria/danger signs	X	X	X	X	X	X	X	X			X	X	(X)
Physical Examination													
Weight	X												
Axillary Temperature	X	X	X	X	X	X	X	X			X	X	(X)
Respiratory Rate	X	X	X	X	X	X	X	X			X	X	(X)
Laboratory Procedures													
Blood smear, including parasite count	X	X	X	X	X	X	X	X			X	X	(X)
Filter paper (PCR)	X	X	X	X	X	X	X	X			X	X	(X)
Filter paper for CQ assay (for Pv participants only)	X			X	X	X	X	X			X	X	(X)
Pregnancy test	X												
Haematological assessment (Pf)	X			X	X	(X)	(X)				X	X	(X)
Haematological assessment (Pv)	X			X	X	(X)		X	X	X			
Medicine													
For Pf participants: AL	X	X	X										
PQ				X									
For Pv participants: CQ	X	X	X										
PQ	To be given after Day 28 (see summary table below)												

[3] Using the information sheet as guide, explain to patient the study protocol. If patient has understood the the study protocol (procedures to be done on him/her during the study period, follow-up visits, etc) secure a written informed consent

Procedures	Schedule of Screening, Recruitment and Enrolment Days, and Follow-up Visits												
	D0	D1	D2	D3	D7	D14	D21	D28	D31	D34	D35 (optional)	D42 (optional	Un-scheduled day
Rescue treatment (refer to next level of care)													
Pf patient - QN + antibiotic	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)					(X)
Pv patient - AL	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)					

Note: Parenthesis denote conditional or optional activities

Medicine	Schedule of Primaquine treatment days* *Note: Give on Day 29													
Primaquine	D29	D30	D31	D32	D33	D34	D35	D36	D37	D38	D39	D40	D41	D42
	X	X	X	X	X	X	X	X	X	X	X	X	X	X

7. DATA MANAGEMENT

The principal investigator will ensure that the study protocol is strictly adhered to throughout, and that all data are collected and recorded correctly on the CRF. Laboratory and clinical data will be recorded on a daily basis in the CRF designed for the study. Data that are derived from source documents should be consistent with the source documents or the discrepancies should be explained. Any change or correction to a CRF should be dated, and explained and should not obscure the original entry. All CRF will be checked for completeness.

After the study has been completed, data will be entered onto a database using double independent data entry. The data will be stored in a computer database maintaining confidentiality in accordance with the national data legislation.

The principal investigator is responsible for keeping all the screening forms, the CRF and the completed subject identification code list in a secure location.

8. STATISTICAL METHODS

8.1. Minimum sample size

Treatment failure to AL in the area being 0-5 %, 5% has been chosen as the estimated therapeutic failure rate of the drug. At a confidence level of 95% and with a precision around the estimate of 10%, 18 patients will be needed. With a 20% increase to allow losses to follow-up and withdrawals during the 28-day follow-up period, 22 patients need to be included. But in order for the sample to be representative, a minimum of 50 *P. falciparum* and 50 *P.vivax* patients need to be included and maximum of 75 patients for both *P. falciparum and P. vivax* will be enrolled.

8.2. Analysis of data

The EPI-INFO 6.0 software from USA and Excel sheet program (designed from WHO HQ for monitoring *P. falciparum* and *P.vivax* resistance to antimalarial drugs) will be used for data entry, management and analysis. Data will be analysed by two methods: the Kaplan-Meier method and per-protocol analysis (including those who were withdrawn from the study or who were lost to follow-up). In addition to the reasons for withdrawal listed in section 3.8, patients will be considered withdrawn from the analysis if the PCR results are unclassifiable or if the results of PCR indicate that the failure is due to reinfection with *P. falciparum.*

The final analysis will include:

- The description of all the patients screened as well as the distribution of the reasons for non-inclusion in the study
- The description of all the patients included in the study

- The proportion and/or percentage of adverse events and serious adverse events for all the patients included in the study
- The proportion and/or percentage of patients who are lost to follow-up or withdrawn with 95% confidence intervals and a list of reasons for exclusion
- The proportion and/or percentage of ETF, LCF and LPF and ACPR on day 28 with 95% confidence intervals using both methods of analysis

Guidelines on calculating the cumulative success or failure rate, the proportion of adequate clinical and parasitological response and treatment failure are given in *Annex 9*.

8.3. Dissemination of results

At the end of the study, the principal investigator will submit a report on the study and the main outcome. This report will be shared with the National Malaria Program of Department of Health, Philippines and will allow to formulate recommendations and enable to make informed decisions about wheter the current national anti-malarial treatment guidelines should be updated.
The patient data will be included in the global database. The results will also be presented during the scientific meeting and also be dessiminated to the study sites.

8.4. Amendments to the protocol

Before the study, official approval to conduct the study will be obtained from RITM institutional review board. After the protocol has been accepted, no change may be made without the agreement of the principal investigator, the sponsor(s), and the IRBs.

9. ETHICAL CONSIDERATIONS

9.1. Approval by the national ethical committee

Prior to the study, official approval to conduct the study will be obtained from Research Institute for Tropical Medicine Institutional and Ethical Review Board.

9.2. Patient Information Sheet and Informed consent

Inclusion in the study will occur only if the patient or the parent/guardian of the child gives an informed consent and informed assent from any minor participant aged 12 – 17 years. The consent request, available in English and Tagalog, will be read entirely to the patient or the parents/guardians. The Patient Information Sheet, available in English and in Tagalog, showing the details about the trial and its benefits and potential risks will be explained, and after answering to any potential questions, signature on the document will be requested (*Annex10*). If the patient is illiterate, a literate witness must sign (if possible, this person will be selected by the participant and will have no connection to the research team). The principal investigator must also obtain the assent of children over the age of 12 years, but their assent should normally be completed by the permission of a parent or guardian.

9.3. Confidentiality

All information regarding the patients will remain confidential within the study team. Unique numerical identifiers will be used for the computer-based data entry and blood samples. In all cases, principal investigator will seek to ensure that screening forms, CRF and completed subject identification code list are kept in locked files.

9.4. Health care services

Free health care during the duration of the follow-up for illness related to malaria will be provided to the study patients regardless of treatment outcome; this includes any necessary expenses related with hospital admission and to adverse drug reactions, if required.

When prospective or actual subjects are found to have diseases unrelated to malaria, the principal investigator should advice them to obtain, or refer them for medical care.

Any subject who decides not to participate or cannot be enrolled in the study because they do not

meet the criteria, will be referred to the health facility staff. They will be treated with and followed-up according to the standard of care established by the Department of Health. The principal investigator must ensure that this antimalarial drug is available at the health centre. If a patient is withdrawn from the study before the full course of the treatment is completed, the physician must make all necessary arrangements to provide the patient with the full dose of the drug currently tested or with a full course of Quinine 10mg/kg bw every 8 hours for 7 days, as recommended by the national policy.

9.5 Reimbursement and Travel Compensation

Subject shall be reimbursed for their transport to attend all visits to the RHU. This will occur on each follow up visit and will cover expenses of transport for the next visit.

9.6. Community

At the end of the study, the community, through a meeting with the LGU, RHU staff and village health workers will be informed of the results of the study. The Malaria Awareness Day celebration, World Malaria Day and national Malaria Month are fora for information dissemination in lay terms.

10. TES MONITORING

Following recommendations of the just concluded 2nd Pacific Malaria Drug Resistance Network Meeting held in Manila, Philippines, this TES will be monitored by identified individuals from WHO Representative Office, Manila and WPRO. They will follow applicable procedures of the WHO-TDR clinical monitoring standard operating procedures (SOPs).[4]

11. REFERENCES

International ethical guidelines for biomedical research involving human subjects. Geneva, Council for International Organization of Medical Sciences, 2002.

Declaration of Helsinki. Ethical principles for medical research involving human subjects.

ICH Topic E8. Note for guidance on general considerations for clinical trials. London, European Agency for the Evaluation of Medicinal Products, 1997 (CPMP/ICH/291/95).

Assessment and monitoring of antimalarial drug efficacy for the treatment of uncomplicated falciparum malaria. Geneva, World Health Organization, 2009.

[4]Necessary permission and approval will be sought from the concerned groups.

Annex 1. DEFINITION OF SEVERE FALCIPARUM MALARIA[6]

Severe manifestation of *P. falciparum* malaria in adults and children

Clinical manifestations

- prostration,
- impaired consciousness,
- respiratory distress (metabolic acidosis),
- multiple convulsions,
- circulatory collapse,
- pulmonary oedema (radiological),
- abnormal bleeding,
- jaundice,
- haemoglobinurea.

Laboratory findings

- severe anaemia (haemoglobin < 5 g/dl, haematocrit < 15%),
- hypoglycaemia (blood glucose < 2.2 mmol/l or 40 mg/dl),
- acidosis (plasma bicarbonate < 15 mmol/l),
- hyperlactataemia (venous lactic acid > 5 mmol/l),
- hyperparasitaemia (> 4% in non-immune patients),
- renal impairment (serum creatinine above normal range for age).

Classification of severe malaria in children

Group 1: children at increased risk for death

- prostration
- respiratory distress

Group 2: children at risk for clinical deterioration

- haemoglobin < 5 g/dl, haematocrit < 15%
- two or more convulsions within 24 h

Group 3: children with persistent vomiting

[6] World Health Organization. Severe falciparum malaria. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, 2000, 94(Suppl. 1):1–90.

Annex 2. MEDICATIONS (WITH ANTIMALARIAL ACTIVITY) THAT SHOULD NOT BE USED DURING THE STUDY PERIOD IN ADDITION TO THE STUDY DRUG(S)

- chloroquine, amodiaquine;
- quinine, quinidine;
- mefloquine, halofantrine, lumefantrine;
- artemisinin and its derivatives (artemether, arteether, artesunate, dihydroartemisinin);
- proguanil, chlorproguanil, pyrimethamine;
- sulfadoxine, sulfalene, sulfamethoxazole, dapsone;
- atovaquone;
- antibiotics: tetracycline*, doxycycline, erythromycin, azythromycin, clindamycin, rifampicin, trimethoprim;
- pentamidine.

* Tetracycline eye ointments can be used.

MAJOR SIDE-EFFECTS OF THE STUDY DRUGS

- Artemether-lumefantrine

Abdominal pain, asthenia, cough, diarrhoea, dizziness, fever, headache, joint and muscle pain, loss of appetite, rush, nausea, vomiting.

- Artesunate

Abdominal pain, diarrhoea, dizziness, nausea, vomiting.

- Artesunate-amodiaquine

abdominal pain, asthenia, cough, diarrhoea, dizziness, insomnia, loss of appetite, nausea, vomiting.

- Artesunate-mefloquine

Abdominal pain, asthenia, diarrhoea, dizziness, fever, headache, insomnia, joint and muscle pain, loss of appetite, palpitation, rush, nausea, vomiting.

- Artesunate-pyronaridine

Abdominal pain, diarrhoea, dizziness, headache, nausea, vomiting.

- Dihydroartemisinin-piperaquine

Asthenia, cough, diarrhoea, fever, loss of appetite, nausea, vomiting.

Annex 3. DRUG DOSAGE

Dose and schedule of Artemether-Lumefantrine (Coartem™) and Primaquine (PQ) in the Treatment of Uncomplicated Plasmosium falciparum Malaria Infection

Day of Treatment	**Artemether-Lumefantrine (AL) (1 tablet contains 20 mg artemether and 120 mg lumefantrine)**			
	(1) Use body weight in kgs as basis			
	5 - <15 kg	15 - <25 kg	25 - <35 kg	≥35 kg
	(2) If weight cannot be taken, use age as basis			
	(6 mos.– 3 y.o.)	(4- 8 y.o.)	(9-13 y.o.)	If (≥ 13 y.o.)
Day 1	1 tab	2 tabs	3 tabs	4 tabs
8 hrs after	1 tab	2 tabs	3 tabs	4 tabs
Day 2	1 tab BID	2 tabs BID	3 tabs BID	4 tabs BID
Day 3	1 tab BID	2 tabs BID	3 tabs BID	4 tabs BID

Day 4	**Primaquine (PQ) (1 tablet contains 15 mg base primaquine)**				
	(1) Use body weight in kgs as basis: use 0.75 mg-base/kg bw single dose				
	(2) If weight cannot be taken, use age as basis				
	< 1 y.o.	1-3 y.o.	4-6 y.o.	7-11 y.o.	≥ 12 y.o
	contra-indicated	½ Primaquine single dose	1 Primaquine tablet single dose	2 Primaquine tablets single dose	3 Primaquine tablets single dose

AL ***is preferably taken with high fat*** meal

Annex 4. CLASSIFICATION OF TREATMENT OUTCOMES[7]

Classification of treatment outcomes - WHO, 2005
Early Treatment Failure (ETF)
• Development of danger signs or severe malaria on day 1, day 2 or day 3 in the presence of parasitaemia; • Parasitaemia on day 2 higher than day 0 count irrespective of axillary temperature; • Parasitaemia on day 3 with axillary temperature ≥37.5 ºC; • Parasitaemia on day 3 ≥25% of count on day 0.
Late Treatment Failure (LTF)
Late Clinical Failure **(LCF)** • Development of danger signs or severe malaria on any day from day 4 to day 28 in the presence of parasitaemia, without previously meeting any of the criteria of Early Treatment Failure; • Presence of parasitaemia and axillary temperature ≥37.5 ºC (or history of fever in low/moderate transmission areas) on any day from day 4 to day 28, without previously meeting any of the criteria of Early Treatment Failure. ***Late Parasitological Failure*** **(LPF)** • Presence of parasitaemia on any day from day 7 to day 28 and axillary temperature <37.5 ºC, without previously meeting any of the criteria of Early Treatment Failure or Late Clinical Failure.
Adequate Clinical and Parasitological Response (ACPR)
• Absence of parasitaemia on day 28 irrespective of axillary temperature without previously meeting any of the criteria of Early Treatment Failure or Late Clinical Failure or Late Parasitological Failure.

[7] WHO. *Susceptibility of* Plasmodium falciparum *to antimalarial drugs. Report on global monitoring 1996–2004*. Geneva, World Health Organization, 2005 (WHO/HTM/MAL/2005.110) (http://www.who.int/malaria/resistance).

Annex 5. CASE SCREENING LOG

Date of Screening	Screening Number	Name of Patient	Initial	Age	Gender	Address/ Contact No.	Enrolled (Y/N)	Date Enrolled	Specie	Patient ID No.	Remarks/ comment why not enrolled

Annex 6. SCHEDULE OF FOLLOW-UP ACTIVITIES

	D0	D1	D2	D3	D7	D14	D21	D28	D35 (optional)	D42 (optional)	Un-scheduled (fever)
PROCEDURES											
Clinical assessment	X	X	X	X	X	X	X	X	X	X	(X)
Temperature	X	X	X	X	X	X	X	X	X	X	(X)
Blood slide for parasites count	X	X	X	X	X	X	X	X	X	X	(X)
Urine sample for Pregnancy Test	X										
Hemoglobin	X			X	X	(X)					
Blood for PCR	X	X	X	X	X	X	X	X	(X)	(X)	(X)
TREATMENT											
AL	X	X	X								
Primaquine				X							
Rescue treatment		(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)

NOTES: Parentheses denote conditional or optional activities. For example, treatment on days 1 and 2 would occur only for drugs requiring 3-day dosing. On day 1, the patient should be examined for parasitaemia if she or he has any danger sign. Rescue treatment could be given on any day, provided that the patient meets the criteria for treatment failure. Extra days are any days other than regularly scheduled follow-up days when the patient returns to the facility because of recurrence of symptoms. On extra days, blood slides may be routinely taken or at the request of the clinical staff for reasons of patient safety.

Day 0:

Screening

Clinical assessment including measurement of weight and height — referral in case of severe malaria/danger signs
Measurement of axillary temperature
Respiratory rate
Parasitological assessment
Informed consent

Enrolment

Treatment, first dose
Blood sampling for PCR
Hemoglobin test

Day 1:

Clinical assessment – referral in case of severe malaria/danger signs
Measurement of axillary temperature
Respiratory rate
Parasitological assessment
Treatment, second dose or alternative treatment in case of early treatment failure

Day 2:

Clinical assessment – referral in case of severe malaria/danger signs
Measurement of axillary temperature
Respiratory rate
Parasitological assessment
Treatment, third dose or alternative treatment in case of early treatment failure

Day 3, Day 7, Day 14, Day 21 Day 28, Day 35 and Day 42 *(Optional)*

Clinical assessment — referral in case of severe malaria/danger signs
Measurement of axillary temperature
Respiratory rate
Parasitological assessment
Hemoglobin test: Day 3, Day 7, Day 14 *(optional)*
Alternative treatment in case of treatment failure
Blood sampling for PCR (any scheduled day in case of failure

Any other *unscheduled* day:

Clinical assessment — referral in case of severe malaria/danger signs
Measurement of axillary temperature
Parasitological assessment
Alternative treatment in case of treatment failure
blood sampling for PCR (in case of failure)

Appendix 7. SERIOUS ADVERSE EVENT REPORT FORM

SERIOUS ADVERSE EVENT FORM	
Health center name:_____ Study number: _____2003-25-03_____ Philippines Patient identity number: _____	Municipality:_____ Date of visit (dd-mm-yy): _____ Province: _____ Follow-up day: _____

Demographic data

Date of birth (dd-mm-yy): _____ or estimated age: _____ in: ☐ months or ☐ years

Height (cm): _____ Weight (kg): _____

Sex: ☐ Male ☐ Female

If female, is the patient pregnant? ☐ Yes ☐ No ☐ Not sure

If pregnant, provide the date of the last menstrual period (dd-mm-yy): _____

Serious adverse event

Type of event:	Severity	Relationship to the study drug
☐ Death	☐ Mild	☐ None
☐ Life-threatening	☐ Moderate	☐ Possible
☐ Hospitalization or prolongation of hospitalization	☐ Severe	☐ Probable
☐ Permanent disability	☐ Life-threatening	☐ Definite
☐ Congenital anomaly or birth defect		

Date of occurrence (dd-mm-yy): _____

Describe the serious adverse event (include all relevant laboratory results):

Describe how the reaction was treated:

Serious adverse event report form (page 2)

Comments (e.g. relevant medical history, drug allergies, previous exposure to similar drugs, other laboratory data, whether reaction abated after stopping the drug, whether reaction reappeared after reintroduction):

Outcome

☐ Recovered completely

☐ Not yet recovered

☐ Recovered with long-term consequences

If patient recovered, provide date of recovery (dd-mm-yy): _____

Medicines (*list the medicine suspected of causing the serious adverse event as well as all concomitant medicines*)

Brand name, batch number, manufacturer name (list suspected medicine first)	Daily dose	Route	Start date	End date	Indications for use

Reporting officer

Name: _____

Qualification: _____

Address: _____

Phone: _____

Fax:_____

Email: _____

Signature:_____ Date: _____

Appendix 8. GUIDELINES FOR ANALYSIS OF RESULTS

End-point for day X (X = 28 or 42)	PCR-uncorrected results	
	Cumulative success or failure rate (Kaplan-Meier analysis)	Proportion (per-protocol analysis)
Adequate clinical and parasitological response on day X	Success	Success
Early treatment failure	Failure	Failure
Late clinical failure before day 7	Failure	Failure
Late clinical failure or late parasitological failure on or after day 7	Failure	Failure
Other species infection	Censored day of infection	Excluded from analysis
Lost to follow-up	Censored last day of follow-up according to timetable	Excluded from analysis
Withdrawal and protocol violation	Censored last day of follow-up according to timetable before withdrawal or protocol violation	Excluded from analysis

End-point for day X (X = 28 or 42)	PCR-corrected results	
	Cumulative success or failure rate (Kaplan-Meier analysis)	Proportion (per-protocol analysis)
Adequate clinical and parasitological response at day X	Success	Success
Early treatment failure	Failure	Failure
Late clinical failure before day 7	Failure	Failure
Late clinical failure or late parasitological failure on or after day 7		
• falciparum recrudescence*	Failure	Failure
• falciparum reinfection*	Censored day of reinfection	Excluded from analysis
• other species mixed with falciparum recrudescence	Failure	Failure
• other species mixed with falciparum reinfection	Censored day of reinfection	Excluded from analysis
• other species infection	Censored day of infection	Excluded from analysis
• undetermined or missing PCR	Excluded from analysis	Excluded from analysis
Lost to follow-up	Censored last day of follow-up according to timetable	Excluded from analysis
Withdrawal and protocol violation	Censored last day of follow-up according to timetable before protocol violation or withdrawal	Excluded from analysis

* WHO. *Methods and techniques for clinical trials on antimalarial drug efficacy: genotyping to identify parasite populations*. Geneva, World Health Organization, 2008 (http://www.who.int/malaria/resistance).