|  |  |
| --- | --- |
| **Title** | Efficacy and safety of artemether-lumefantrine and dihydroartemisinin-piperaquine for the treatment of uncomplicated *Plasmodium falciparum* malaria in Alikadam Upazila and Lama Upazila of Bandarban district and Baghaichari Upazila of Rangamati districts, Bangladesh. |
| **Study site(s)** | Site 1: Alikadam Upazila of Bandarban  Treatment tested: Artemether-lumefantrine and dihydroartemisinin-piperaquine  Site 2: Lama Upazila of Bandarban  Treatment tested: Artemether-lumefantrine dihydroartemisinin-piperaquine  Site 3: Baghaichari Upazila of Rangamati  Treatment tested: Artemether-lumefantrine dihydroartemisinin-piperaquine  *(Add more sites as needed)* |
| **Protocol submission date** | 10/11/2022 |
| **Protocol number** | Unique protocol number/version 1 |
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| **Planned study dates** | From January to December/2023 |
| **Sponsor** | Ministry of Health and Family Welfare, Bangladesh  Complete postal address: Bangladesh Secretariat, MoH&FW-1000  Tel: 88-02-9559216  Email: [sasadmin2@mohfw.gov.bd](mailto:sasadmin2@mohfw.gov.bd) |

SYnopsis

Title: Efficacy and safety of artemether-lumefantrine and dihydroartemisinin-piperaquine for the treatment of uncomplicated *Plasmodium falciparum* malaria in Alikadam Upazila and Lama Upazila of Bandarban district and Baghaichari Upazila of Rangamati districts, Bangladesh.

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

Objective: To assess the efficacy and safety of artemether-lumefantrine and dihydroartemisinin-piperaquine for the treatment of uncomplicated *P. falciparum* malariainfections.

Study Sites: Alikadam Upazila of Bandarban district, Lama Upazila of Bandarban district and Baghaichari Upazila of Rangamati district.

Study Period: 1 January 2023 to 31 December 2023.

Study Design:This surveillance study is two arm prospective study.

Patient population: Febrile patients aged more than 6 months with confirmed uncomplicated *P. falciparum* infection.

Exclusion: pregnancy, breast feeding mother, young girls aged 12-18 years old and contraindication to Artemether-Lumefantrine.

Sample Size: A total of 360 patients (180 patients for each drug combination to be tested) will be enrolled from 3 upazilas, 120 patients of each upazila (60 patients for each drug combination).

Treatment(s) and follow-up: Clinical and parasitological parameters will be monitored over a 28-day follow-up period for artemether-lumefantrine and 42-day follow up period for dihydroartemisinin-piperaquine to evaluate drug efficacy of both the drug combinations.

Primary endpoints: The proportion of patients with early treatment failure, late clinical failure, late parasitological failure or an adequate clinical and parasitological response as indicators 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 (K13) for Artemisinin resistance

1. Background

Bangladesh has demonstrated significant progress in reducing the malaria caseload over the years except fluctuations in terms of upsurges in 2014 and again in 2019. Overall, with significant decline in the number of confirmed malaria cases in 2019 (17,225), 2020 (6,130) and 2021 (7,294) relative to 2015 (39,719) [57%, 85%, and 82% respectively reduction], the country appears to be on track towards reducing disease burden gradually moving towards achievement of the vision of malaria elimination.

Currently in Bangladesh diagnosis of uncomplicated falciparum and vivax malaria is confirmed by blood slide examination or Rapid Diagnostic test (RDT). Artemether + Lumefantrine combination (ACT) for uncomplicated falciparum malaria is given after confirming the diagnosis and treatment starts immediately. The calculated dose of ACT for adult and children are given below:

## For Falciparum malaria:

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Drug | Day | No of Dose | Time | 5-<15 Kg | 15-<25 Kg | 25-<35 Kg | >35- Kg |
| Artemether +Lumefantrine combination (ACT) | Day-1 | 1st | 0 hour | 1 | 2 | 3 | 4 |
| 2nd | 8 hour | 1 | 2 | 3 | 4 |
| Day-2 | 3rd | 24 hour | 1 | 2 | 3 | 4 |
| 4th | 36 hour | 1 | 2 | 3 | 4 |
| Day-3 | 5th | 48 hour | 1 | 2 | 3 | 4 |
| 6th | 60 hour | 1 | 2 | 3 | 4 |

Tab Primaquine (0.25mg/kg) is given with the first dose of ACT. The diagnosis and treatment is being provided free of charge to everyone. DOT is not included in national treatment guideline for Malaria.

Alternative WHO recommended ACTs: dihydroartemisinin-piperaquine**,** artesunate-mefloquine, artesunate-amodiaquine.

Doses schedule for dihydroartemisinin-piperaquine for *P. falciparum* malaria:

|  |  |
| --- | --- |
| Body weight (kg) | Dihydroartemisinin + piperaquine dose (mg) given daily for 3 days |
| 5 to <8 | 20 + 160 |
| 8 to <11 | 30 + 240 |
| 11 to <17 | 40 + 320 |
| 17 to <25 | 60 + 480 |
| 25 to <36 | 80 + 640 |
| 36 to <60 | 120 + 960 |
| 60 to <80 | 160 + 1280 |
| >80 | 200 + 1600 |

Tab Primaquine (0.25mg/kg) is given with the first dose of ACT.

The drugs are provided free of charge to any patients coming to any health care facility.

A study was conducted from March 2018 to March 2019 in three sentinel sites for drug resistance monitoring of currently used antimalarials (AL) in Bangladesh. The sites were Nykhongchori Upazilla Health Complex of Bandarban Hill District, Ramgarh Upazila Health Complex of Khagrachari district and Alikadam Upazilla Health Complex (included later on) of Bandarban district, situated in the high-risk multi-drug resistant malaria areas of Bangladesh bordering to India and Myanmar. A total of 82 subjects were recruited of which 65 subjects were in Nykhonchori, 12 were in Ramgarh and 05 were in Alikadam. Out of the total 82 subjects, all subjects showed Adequate Clinical and Parasitological Response (ACPR). All of them were symptomatic with fever or history of fever (100%). There were no adverse and serious adverse events recorded out of the total subjects recruited.

Another study was conducted during the malaria transmission season from May to September 2011 with the actual data collection from November 2011 to May 2012 in three sentinel sites for drug resistance monitoring of Artemether-Lumefantrine in Bangladesh. The sites were Kaptai Upazilla Health Complex of Rangamati Hill District**,** Matiranga Upazila Health Complex of Khagrachhari district and Roangchory Upazilla Health Complex of Bandarban district, situated in the high-risk multi-drug resistant malaria areas of Bangladesh. The population consisted of patients aged above 6 months diagnosed with uncomplicated *P. falciparum* malaria attending the health complexes. This study tested Artemether-Lumefantrine among 60 cases recruited from each UHC. All of them were symptomatic with fever or history of fever (100%). All cases in the three centers had completed the study follow up duration of 28 days. There was no serious adverse event in any of the cases and the drug was well tolerated. There was no failure in any site.

Ramu upazila under Cox’sbazar district was the site for the TRAC study where no artemisinin resistance was found (Year 2019).

Another antimalarial drug efficacy trial was conducted in Teknaf Upazila of Cox’s Bazar district, Lama Upazila of Bandarban district and Kalmakanda Upazila of Netrakona district in Bangladesh from January 2013 to July 2014. Patients were treated with 3 day-regimen of artemether-lumefantrine. Clinical and parasitological parameters were monitored over a 28-day follow-up period to evaluate drug efficacy. A total of 46 subjects were recruited in 3 sentinel sites of which 32 subjects were from Lama, 10 were from Teknaf and 4 were from Kalmakanda. Out of the total, 44 subjects showed adequate clinical and parasitological response (ACPR), 1 showed late clinical failure (LCF) and one withdrew from the study. There were no adverse and serious adverse events recorded out of the total subjects recruited. All the samples were positive for *P. falciparum*. Polymorphisms have been observed in GLURP, MSP1 and MSP2 alleles in one failure case. Based on genotyping PCR it seems that the patient has acquired new infection from day14.

After 2019, no study was conducted to see the efficacy of antimalarials in use in Bangladesh due to COVID 19 pandemic. Now this is the right time to conduct the study to assess efficacy of artemether-lumefantrine – the first line antimalarial and the alternative second line drug dihydroartemisinin-piperaquine for the treatment of uncomplicated *P. falciparum* malaria. The results of this study will be used to assist the Ministry of Health and Family Welfare, Bangladesh in assessing the current national treatment guidelines for uncomplicated *P. falciparum* malaria and to update the policy if necessary.

2. Objectives

The general objective of this study is to assess the therapeutic efficacy and safety of artemether-lumefantrine and dihydroartemisinin-piperaquine for the treatment of uncomplicated *Plasmodium falciparum* malaria in Alikadam Upazila of Bandarban district, Lama Upazila of Bandarban district and Baghaichari Upazila of Rangamati districts, Bangladesh.

The primary objectives are:

* to measure the clinical and parasitological efficacy of artemether-lumefantrine in patients aged more than 6 months, suffering from uncomplicated falciparum malaria, by determining the proportion with early treatment failure, late clinical failure, late parasitological failure or an adequate clinical and parasitological response as indicators of efficacy;
* to differentiate recrudescence from new infection by polymerase chain reaction (PCR) analysis.

The secondary objectives are:

* to evaluate the incidence of adverse events; and
* to determine the polymorphism of molecular markers (K13) for Artemisinin resistance.

3. Investigational Plan

3.1 Study design

This surveillance study is a two-arm prospective evaluation of clinical and parasitological responses to directly observed treatment for uncomplicated malaria.[[1]](#footnote-2),[[2]](#footnote-3) People with uncomplicated malaria who meet the study inclusion criteria will be enrolled, treated on site either with artemether-lumefantrine or dihydroartemisinin-piperaquine(artemether-lumefantrine and dihydroartemisinin-piperaquine will be used for enrolling and treating every alternate patient)and monitored for 28 days for artemether-lumefantrine and 42 days for dihydroartemisinin-piperaquine. The follow-up will consist of a fixed schedule of check-up visits and corresponding clinical and laboratory examinations. On the basis of the results of these assessments, the patients will be classified as having therapeutic failure (early or late) or an adequate response. The proportion of patients experiencing therapeutic failure during the follow-up period will be used to estimate the efficacy of the study drugs. PCR analysis will be used to distinguish between a true recrudescence due to treatment failure and episodes of reinfection.

3.2 Study sites

The study will be conducted in three sentinel sites – 1) Alikadam Upazila of Bandarban district, 2) Lama Upazila of Bandarban district, and 3) Baghaichari Upazila of Rangamati district. All the study sites are situated in the Chittagong Hill Tract districts with highest malaria transmission.

Site 1: Alikadam Upazila of Bandarban

Treatment to be tested: Artemether-lumefantrine and dihydroartemisinin-piperaquine

Alikadam has a population of about 75,357. The upazila health complex is accessible by road. Some parts of the upazila are hard to reach.

Site 2: Lama Upazila of Bandarban

Treatment to be tested: Artemether-lumefantrine and dihydroartemisinin-piperaquine

Lama has a population of about 158,137. The upazila health complex is accessible by road. Some parts of the upazila are hard to reach.

Site 3: Baghaichari Upazila of Rangamati

Treatment to be tested: Artemether-lumefantrine and dihydroartemisinin-piperaquine

Baghaichari has a population of about 127,115. The upazila health complex is accessible by road. Some parts of the upazila are hard to reach.

All the sites are hilly areas with forest and forest fringe. Alikadam constitute part of the borders between Bangladesh and India. Malaria is endemic in these areas throughout the year with peaks around rainy season (May to October).

Malaria case data from 2017-2022 (up to August)

**Alikadam**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Year** | **UM** | **SM** | **VM** | **Total** | **Death** |
| 2017 | 4586 | 21 | 666 | 5273 | 1 |
| 2018 | 1294 | 8 | 253 | 1555 | 0 |
| 2019 | 2080 | 22 | 296 | 2398 | 2 |
| 2020 | 1026 | 5 | 180 | 1211 | 2 |
| 2021 | 1328 | 8 | 343 | 1679 | 1 |
| 2022 (Up to August) | 2628 | 5 | 554 | 3187 | 0 |

**Baghaichari**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Year** | **UM** | **SM** | **VM** | **Total** | **Death** |
| 2017 | 1561 | 0 | 125 | 1686 | 0 |
| 2018 | 768 | 3 | 53 | 824 | 0 |
| 2019 | 1565 | 0 | 59 | 1624 | 0 |
| 2020 | 366 | 0 | 6 | 372 | 0 |
| 2021 | 545 | 0 | 19 | 564 | 0 |
| 2022 (Up to August) | 508 | 0 | 36 | 544 | 0 |

**Lama**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Year** | **UM** | **SM** | **VM** | **Total** | **Death** |
| 2017 | 2215 | 112 | 545 | 2872 | 0 |
| 2018 | 822 | 47 | 241 | 1110 | 0 |
| 2019 | 1509 | 79 | 358 | 1946 | 0 |
| 2020 | 721 | 18 | 342 | 1081 | 0 |
| 2021 | 777 | 24 | 543 | 1344 | 1 |
| 2022 (Up to August) | 1959 | 69 | 1277 | 3305 | 0 |

Cases of severe malaria cases are being managed at the upazila level hospital and in rare occasion patients with multi-organ involvement are referred to Chittagong Medical College Hospital or Cox’s Bazar Medical College Hospital (Cox’s bazar Medical College Hospital for Ramu). Parenteral Artesunate are used for the treatment of severe malaria according to the national guidelines.

3.3 Timing and duration of the study

The study will be conducted from 1 January to 31 December 2023.

3.4 Study population

The study population will consist of patients with uncomplicated *P. falciparum* malaria attending the study upazila health comlexes who are aged more than 6 months. 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 the age of majority. Children aged 12 years to 18 years will be required to consent for participation by signing an informed assent form.

Children below 6 months will be excluded as this drug combination is not indicated in this age group.

Those unable to or unwilling to take pregnancy test or to use contraception (for married women of child-bearing age), minors (below 18 years of age) who have achieved menarche and unmarried women will be excluded from both studies. In Bangladesh it is not socially acceptable to offer or ask an unmarried woman to take contraceptive and to do pregnancy test. In case of married woman, it depends on her (sometimes husbands) decision whether to take pregnancy test or contraceptives.

3.5 Inclusion criteria

* age more than 6 months;
* mono-infection with *P. falciparum* detected by microscopy;
* parasitaemia of 1000/µl – 100,000 asexual forms;
* presence of tympanic temperature ≥ 37.5 °C or history of fever during the past 48 h;
* ability to swallow oral 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 guardian in the case of children aged less than 18 years;
* informed assent from any minor participant aged from 12 to 18 years; and
* consent for pregnancy testing from female of child-bearing potential and from their parent or guardian if under the age of majority years.

3.6 Exclusion criteria

* presence of general danger signs in children aged under 5 years or signs of severe falciparum malaria according to the definitions of WHO (Appendix 1);
* weight under 5 kg;
* any mixed or mono-infection with other *Plasmodium* species detected by microscopy;
* presence of severe malnutrition defined as a child aged 6-60 months who has symmetrical edema involving at least the feet and/or has a mid-upper arm circumference < 115 mm)
* presence of febrile conditions due to diseases other than malaria (e.g. measles, acute lower respiratory tract infection, severe diarrhea with dehydration) or other known underlying chronic or severe diseases (e.g. cardiac, renal and hepatic diseases, HIV/AIDS);
* regular medication, which may interfere with antimalarial pharmacokinetics;
* history of hypersensitivity reactions or contraindications to any of the medicine(s) being tested or used as alternative treatment(s);
* a positive pregnancy test or breastfeeding; and
* unable to or unwilling to take pregnancy test or to use contraception for married women of child-bearing age.
* minors (below 18 years of age) who have achieved menarche will be excluded from the study.
* Unmarried women

3.7 Loss to follow-up

Loss to follow-up occurs when, despite all reasonable efforts, an enrolled patient does not attend the scheduled visits and cannot be found. No treatment outcome will be assigned to these patients. Every effort must be made to schedule a follow-up visit for patients who fail to return to the study site, especially during but also after administration of the study drug. These patients will be classified as lost to follow-up and censored or excluded from the analysis. Patients who are lost to follow-up but who subsequently return to the study site before day 28 (for artemether-lumefantrine)/42 (for dihydroartemisinin-piperaquine) will not be turned away and will be encouraged to return for check-up visits. The principal investigator will decide whether the patient is to be definitely withdrawn from the study and classified as lost to follow-up on the basis of his or her history and behaviour, or is to be maintained in the study for the final evaluation.

3.8 Patient discontinuation or protocol violation

Study patients who meet any of the following criteria will be classified as withdrawn.

* withdrawal of consent. A patient may withdraw consent at any time, without prejudice for further follow-up or treatment at the study site.
* failure to complete treatment, due to:
* persistent vomiting of the treatment. A patient who vomits the study medication twice will be withdrawn from the study and given rescue treatment.
* failure to attend the scheduled visits during the first three days; or
* serious adverse events necessitating termination of treatment before the full course is completed. A patient can be discontinued from the study if the principal investigator decides so due to an adverse event. In this case, information on the adverse event and symptomatic treatment given must be recorded on a case report form. If the adverse event is severe, the principal investigator must notify immediately (latest within 72 hours) and follow the reporting procedures described in section 5.3.
* enrolment violation:
* severe malaria developed within 24 hours after beginning of the treatment; or
* erroneous inclusion of a patient who does not meet the inclusion criteria.
* voluntary protocol violation: self- or third-party administration of antimalarial drug (or antibiotics with antimalarial activity) (Appendix 2);
* involuntary protocol violation:
* occurrence during follow-up of concomitant disease that would interfere with a clear classification of the treatment outcome;
* detection of mono-infection with another malaria species during follow-up; or
* misclassification of a patient due to a laboratory error (parasitaemia), leading to administration of rescue treatment.

Patients who are withdrawn will nevertheless be followed up until recovery or the end of follow-up, if possible; however, no treatment outcome will be assigned to these patients, and they will be censored or excluded from the analysis. The reasons for discontinuation or protocol violation will be recorded on the case report form.

Pregnancy detected during the course of follow-up does not constitute a reason for withdrawal but the event must be recorded and managed as described in section 5.3.

4. Treatment

4.1 Antimalarial treatment

Artemether-lumefantrine will be administered – 6 doses over 3 days. Dihydroartemisinin-piperaquine will be administered daily for 3 days (total 3 doses). The correct drug dosage will be determined from the dosing chart (Appendix 3). Each dose will be provided with food (a glass of milk).

**Artemether:** Artemisinin and its derivatives are safe and remarkably well tolerated. There have been reports of mild gastrointestinal disturbances, dizziness, tinnitus, reticulocytopenia, neutropenia, elevated liver enzymes, and electrocardiographic abnormalities. Neurotoxicity has been reported in animal studies, particularly with very high dose of intramuscular Artemether. Clinical neurophysiological and pathological studies in humans have not shown similar findings with therapeutic use of these compounds.

**Lumefantrine:** oral bioavailability is variable and is highly dependent on administration with fatty foods. Absorption increases by 108% after a meal and is lower in patients with acute malaria than in convalescing patients. The manufacturer of artemether-lumefantrine recommends avoiding the following: grapefruit juice, anti-arrhythmics such as amiodarone, disopyramide, flecainide, procainamide and quinidine, antibacterials such as macrolides and quinolones; all antidepressants; antifungals such as imidazoless and triazoles; terfenadine; other antimalarials; all antipsychotic drugs; and beta blockers, such as metoprolol and sotalol. However, there is no evidence that co-administration with these drugs would be harmful.

**Dihydroartemisinin-piperaquine phosphate** is a fixed dose of tablet formula with 320 mg Piperaquine phosphate and 40 mg dihydroartemisinin. The dosing schedule is given below:

Tablets containing 40 mg dihydroartemisinin and 320 mg piperaquine phosphate.

|  |  |  |  |
| --- | --- | --- | --- |
| **Body weight (kg)** | **No. of tablets at approximate timing of dosing** | | |
| **Day 0** | **Day 1** | **Day 2** |
| 5 to <8 | ½ tablet | ½ tablet | ½ tablet |
| 8 to <11 | ¾ tablet | ¾ tablet | ¾ tablet |
| 11 to <17 | 1 tablet | 1 tablet | 1 tablet |
| 17 to <25 | 1½ tablet | 1½ tablet | 1½ tablet |
| 25 to <36 | 2 tablets | 2 tablets | 2 tablets |
| 36 to <60 | 3 tablets | 3 tablets | 3 tablets |
| 60 to <80 | 4 tablets | 4 tablets | 4 tablets |
| >80 | 5 tablets | 5 tablets | 5 tablets |

All patients will be given Primaquine with first dose of artemether-lumefantrine/DHA-PPQ according to dose schedule recommended by Bangladesh National Treatment Guideline (as provided above).

Study drugs will be obtained from National Malaria Elimination Programme (or GF) which is WHO pre-qualified. All antimalarial drug(s) will be stored in a cool dry environment.

All doses of medicine will be administered under the supervision of a qualified member of the staff designated by the principal investigator. The study patients will be observed for 30 minutes after medicine administration for adverse reactions or vomiting. Any patient who vomits during this observation period will be re-treated with the same dose of medicine and observed for an additional 30 min. If the patient vomits again, he or she will be withdrawn and offered rescue therapy.

Except for those who live nearby, patients will be admitted at the Upazila Health Complexes for three days to complete the treatment. For those living nearby, the first dose will be given while the patient is still in the health facility. The patient will be asked to come back for the subsequent doses. Alternate approaches may be undertaken upon discussion with principal investigator and team members.

4.2 Concomitant treatment and medication that should not be used

Fever over 38 °C can be treated with paracetamol or acetaminophen. Parents or guardians will be instructed in the use of tepid sponging, more specifically for children under 5 years of age.

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

Adverse events requiring treatment should be treated according to the best available local practice. If there is 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 medicine, the name of the medicine, the dosage and the date and time of administration must be recorded on the case report form.

The use of herbal remedies during the study should be avoided, and participants should be encouraged to return to the study site for treatment if they feel unwell. If any herbal remedies are taken during the study, this should be captured on the case report form, under ‘study medication administration’.

4.3 Rescue treatment

If a patient vomits twice, he or she will receive parenteral therapy with injection artesunate 2.4 mg/kg body weight at 0 hour, 12 hours, 24 hours and then 24 hourly until the patients can take orally followed by full course of artemether-lumefantrine as per national malaria treatment guidelines. The patient will be withdrawn from the study.

Any patient with signs of severe or complicated malaria will be hospitalized and will receive parenteral therapy with injection artesunate 2.4 mg/kg body weight at 0 hour, 12 hours, 24 hours and then 24 hourly until the patients can take orally followed by full course of artesunate and mefloquine combination for 3 days (see appendix 3) and relevant supportive treatment according to national treatment guidelines.

Women who are found to be pregnant at enrolment will be treated according to national treatment guidelines.

If a patient meets one of the criteria for therapeutic failure, he or she will receive artesunate and mefloquine combination for 3 days according to current national recommendations (see appendix 3). If the patient is re-infected with another malaria species, he or she will receive antimalarial drug(s) or drug combination, according to current national recommendations.

5. Evaluation criteria

The study end-point is the classification assigned to a patient. Valid study end-points include: treatment failure, completion of the follow-up period without treatment failure (adequate clinical and parasitological response), loss to follow-up, withdrawal from study including protocol violation. At all times, the well-being of the patient will take priority over his or her continuation in the study.

5.1 Efficacy and safety evaluation

### 5.1.1 Classification of treatment outcomes

Treatment outcomes will be classified on the basis of an assessment of the parasitological and clinical outcomes of antimalarial treatment according to the latest WHO guidelines.[[3]](#footnote-4) Thus, all patients will be classified as having early treatment failure, late clinical failure, late parasitological failure or an adequate clinical and parasitological response, as defined in Appendix 4.

As parasitological cure is the goal of antimalarial therapy, all study patients who show treatment failure will be given rescue treatment. Follow-up will continue until recovery. The outcome of the rescue treatment in these patients does not need to be recorded systematically for the purpose of the surveillance study.

### 5.1.2 Safety end-points

The incidence of any adverse event will be documented. All patients will be asked routinely about previous symptoms and about symptoms that have emerged since the previous follow-up visit. When clinically indicated, patients will be evaluated and treated appropriately. All adverse events, drug-related or not, will be recorded on the case report form. Serious adverse events (see definitions in 5.3) must be reported to the sponsor.

5.2 Clinical evaluation

All patients will be evaluated clinically as described below.

### 5.2.1 Physical examination

A standard physical examination will be performed at baseline (day 0 before dosing) and on days 1, 2, 3, 7, 14, 21, 28 for both arm and additionally on day 35 and 42 for dihydroartemisinin-piperaquine (total 8 times for artemether-lumefantrine and 10 times for dyhydroatemisin-piperaquine). A complete medical history, including prior and concomitant medication, demographic information and contact details will be recorded at baseline.

The circumference of the left mid-upper arm will be measured, at the mid-point between the elbow and the shoulder, and will be recorded to the nearest 0.2 cm.

Oedema will be assessed by thumb pressure for 3 s on the dorsal surface of both feet.

### 5.2.2 Body weight

Body weight will be recorded on day 0 to the nearest kilogram on a Salter scale or on a hanging scale for young children. The scales will be properly calibrated. The reliability of the scales will be verified before the study begins and checked at regular intervals. Patients should not wear excessive clothing while being weighed as this can overestimate their true weight. All young children should only wear undergarments while being weighed. The screening weight will be used to satisfy the inclusion or exclusion for nutrition status as well as to calculate the dose (number of tablets) to be administered.

### 5.2.3 Body temperature

Axilla temperature will be measured at baseline (day 0 before dosing) and on days 1, 2, 3, 7, 14, 21, 28 for both arm and additionally on day 35 and 42 for dihydroartemisinin-piperaquine (total 8 times for artemether-lumefantrine and 10 times for dyhydroatemisin-piperaquine). Temperature will be measured with a thermometer that has a precision of 0.1 °C. Temperature will also be measured as clinically indicated. If the result is < 36.0 °C, the measurement will be repeated. The same route should be used throughout the study.

The quality of the temperature-taking technique and the thermometers should be assessed regularly. Thermometers should be tested in a water-bath of known temperature before the study begins and at regular intervals thereafter.

### 5.2.4 Microscopic blood examination

Thick and thin blood films for parasite counts will be obtained and examined at screening on day 0 to confirm adherence to the inclusion and exclusion criteria. Thick blood films will be also examined on days 1, 2, 3, 7, 14, 21, 28 for both arm and additionally on day 35 and 42 for dihydroartemisinin-piperaquine (total 7 times for artemether-lumefantrine and 9 times for dyhydroatemisin-piperaquine) or on any other day if the patient returns spontaneously and parasitological reassessment is required. Specimens will be labelled anonymously. The screening number or the patient study number, the date and the day of follow-up will be recorded either on the frosted edge of the slide or on the glass with a permanent glass pen.

A fresh Giemsa stain dilution will be prepared at least once a day and possibly more often, depending on the number of slides to be processed. Giemsa-stained thick and thin blood films will be examined at a magnification of 1000× to identify the parasite species and to determine the parasite density.

At screening, three blood slides per patient will be obtained: two thick blood smears and one thin blood smear for species confirmation if needed. One thick blood smear with the screening number will then be stained rapidly (10% Giemsa for 10–15 min) for initial screening, while the others will be retained. If the patient is subsequently enrolled, the second slide will be stained more carefully (e.g. 2.5–3% Giemsa for 45–60 min), and slower staining will also be used for all slides obtained at follow-up visits.

The thick blood smear for initial screening will be used to count the numbers of asexual parasites and white blood cells in a limited number of microscopic fields. The adequate parasitaemia for enrolment is at least one parasite for every six white blood cells, corresponding to approximately 1000 asexual parasites per microlitre, for low-to-moderate transmission areas.

The second blood smear with the study number 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).

|  |  |  |
| --- | --- | --- |
|  | Parasite density (per µl) = number of parasites counted × (6000) |  |
|  | 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 genotype analysis will be conducted. This is based on the extensive genetic diversity among the malaria parasite genes *msp1*, *msp2* and *glurp*.[[4]](#footnote-5) The genotypic profiles of pre- and post-parasite strains are compared.

In order to minimize discomfort to the patient due to repeated finger pricks, two to three drops of blood will be collected on filter paper Whatman filter paper 2 during screening and each time blood smears are required according to the protocol on and after day 7.

Specimens will be labelled anonymously (patient study number, date and day of follow-up), kept in individual plastic bags with desiccant pouches and protected from light, humidity and extreme temperature until analysed. When these conditions cannot be achieved, for example in extremely humid environments where air-conditioning is not available, storage in a refrigerator or freezer may be considered, but great care must be taken to protect samples from frost and moisture. The PCR will be done in Pasteur Institute, Cambodia/ICDDR’B. Paired filter papers will be used for parasite DNA extraction and genotyping only in cases of treatment failure. All filter papers will be destroyed immediately after the PCR analyses have been completed. 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 will be asked to take a urine pregnancy test before enrolment in the study, because inclusion of pregnant women will be risky as they need to be admitted in the hospital for the first 3 days and there will be scheduled follow up visits. They will also be asked to take a urine pregnancy test on day 28 (for both arm)/36 (for dihydroartemisinin-piperaquine group) or on early withdrawal from the study.

Female participants of child-bearing age should avoid pregnancy for the duration of the study. Barrier contraceptive devices will be recommended by the investigator 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

Haemoglobin will be determined on days 0, 14, 28 (for both arm) and additional on day 42 for dihydroartemisinin group by the acid-hematin method using the Hemo Q machine.

### 5.2.8 Molecular markers for antimalarial drug resistance

Two to three drops of blood will be collected on filter paper Whatman filter paper 2 on day 0 and day of failure to study the polymorphism or copy number of K13, which are considered as markers of resistance to artemisinin. This will be done in laboratory of Pasteur Institute, Cambodia/ICDDR’B. Specimens will be labelled anonymously (patient 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.

5.3 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 or its designee, regardless of whether the principal investigator considers the events to be related to the investigated medicine.

The investigator will collect information on any women who become pregnant while participating in this study and will record the information on the appropriate form. The pregnant woman will also be followed to determine the outcome of the pregnancy. Generally, follow-up will be no longer than 6–8 weeks after the estimated delivery date. Any premature termination of pregnancy will be reported. While pregnancy itself is not considered an adverse event or a serious adverse event, any complication of pregnancy or elective termination for medical reasons will be recorded as an adverse event or a serious adverse event. A spontaneous abortion is always considered a serious adverse event and will be reported as such.

6. Study assessment

6.1 Screening and enrolment

All patients who meet the basic enrolment criteria (age, fever or history of fever, symptoms of malaria, absence of danger signs in children in relation to malaria - child unable to drink or breastfeed, vomiting everything, recent history of convulsions, lethargic or unconscious state, unable to sit or stand, difficulty in breathing -,absence of signs of severe malaria, absence of severe malnutrition, pregnancy) during screening will be assigned a consecutive number and evaluated in greater depth by clinical staff. In children, care will be taken to detect early signs of febrile diseases other than malaria, as their presence will necessitate exclusion from the evaluation. The most frequent confounding condition is a lower respiratory tract infection: cough or difficult breathing, together with fast breathing, is an indicator for exclusion. Fast breathing is defined as a respiratory frequency > 50/min in infants under 12 months of age and > 40/min 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 should be treated for both malaria (if they have parasitaemia) and the other infection, as appropriate.

The screening record form (Appendix 5) will be used to record the general information and the clinical observations on each patient being screened. If the patient meets the clinical criteria, he or she will be examined for parasitaemia. Once the patient meets all the enrolment criteria, he or she or a parent or guardian will be asked for consent to participate in the study. Children between 12 years and age of majority will also need to provide their assent to participate. Then the patient will be assigned to either artemether lumefantrine group or to dihydroartemisinin piperaquine group. The first patient will be enrolled for artemether lumefantrine group and second one will be in dihydroartemisinin piperaquine group in each site and so on (alternating each group) until the sample size is reached.

6.2 Follow-up

Patients who meet all the enrolment criteria will be given a personal identification number (patient study number) and will receive treatment only after the study has been fully explained to them and they have willingly provided informed consent. Any person who decides not to participate in the study will be examined, treated and followed-up by the health facility staff according to the standard of care established by the Ministry of Health.

The basic follow-up schedule is summarized in Appendix 6. A case report form (Appendix 7) and a serious adverse event report form (Appendix 8) will be used to record the general information and clinical observations on each patient enrolled into the study. The appointment schedule will be clearly explained, and a follow-up card with the patient study number will be provided.

The day a patient is enrolled and receives the first dose of medicine is designated ‘day 0’. All antimalarial treatment will be given by a study team member under supervision. Enrolled patients will be observed for at least 30 min after treatment to ensure that they do not vomit the medicine. If vomiting occurs within 30 min of treatment, the full treatment dose will be repeated. Ancillary treatment, such as antipyretics, will be provided if necessary to patients by the study team and documented on the case report form. 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, patients are required to undergo regular clinical reassessment. Blood films for parasite counts will be made on days 1, 2, 3 and 7 and then weekly for the remainder of the follow-up period, i.e. on days 14, 21 and 28 for both arm and 35 and 42 for dihydroartemisinin piperaquine arm. Patient, or parents or guardians will be advised to return on any day during the follow-up period if symptoms return and not to wait for the next scheduled visit day. In particular, parents or guardians should be instructed to bring children to the centre at any time if they show any sign of danger (unable to drink or breastfeed, vomiting everything, presenting with convulsions, lethargic or unconscious, unable to sit or stand, presenting with difficult breathing), if they are still sick or if there is any cause for worry. Clinical reassessment will be sufficiently thorough to ensure patient safety and will include assessment not only for potential treatment failure but also for potential adverse reactions to the medicine. Additionally, blood films will be obtained whenever parasitological reassessment is requested by the clinical staff.

Because many medicines have to be given over several days, the initial visits are critical not only for assessing efficacy but also for ensuring patient safety; defaulters at this stage will not have received a complete course of treatment and 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. 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, and study team members familiar with the community will be responsible for home visits and means of transport for the patients.

The schedule of treatment and follow-up examinations given in this protocol must be followed to ensure data integrity. Patients who fail to return on days 1 and 2 and miss one dose of the treatment will be withdrawn from the study definitively. After day 3, patients who fail to return on day 7 but are present on day 6 or 8 (likewise days 13/15, days 20/22, days 27/29, days 34/36 and days 41/43 may still be included in the analysis. Deviation from the protocol of more than 1 day should, however, be avoided (see also section 3.7).

7. Data management

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

After the study has been completed, data will be entered into a database by double independent data entry, according to WHO standard procedures.[[5]](#footnote-6) The study data will be stored in a computer database, maintaining confidentiality.

The principal investigator is responsible for keeping all screening forms, case report forms and the completed subject identification code list in a secure location (patient screening and enrolment logbook).

8. Statistical methods

8.1 Minimum sample size

As the treatment failure rate to artemether-lumefantrine in the area is 5% has been chosen. At a confidence level of 95% and a precision around the estimate of 5%, a minimum of 50 patients must be included. With a 20% increase to allow loss to follow-up and withdrawals during the 28-day/42-day follow-up period, 60 patients should be included in the study per site.

8.2 Analysis of data

The WHO Excel data entry will be used for data management and analysis. Data will be analysed by two methods: the Kaplan-Meier method and per-protocol analysis. In addition to the reasons for withdrawal listed in section 3.8, patients will be censored or excluded 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* or *P. vivax.*

The final analysis will include:

* a description of all patients screened and the distribution of reasons for non-inclusion in the study;
* a description of all the patients included in the study;
* the proportion of adverse events and serious adverse events in all the patients included in the study;
* the proportion of patients lost to follow-up or withdrawn, with 95% confidence intervals and a list of reasons for withdrawal;
* the cumulative incidence of success and failure rates at day 28, PCR-uncorrected and PCR-corrected; and
* the proportion of early treatment failure, late clinical failure, late parasitological failure and adequate clinical and parasitological response at day 28, with 95% confidence intervals, PCR-uncorrected and PCR-corrected.

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

8.3 Dissemination of results

At the end of the study, the principal investigator will submit a report on the study and its main outcome. This report will be shared with the national malaria control programme and the Ministry of Health and Family Welfare and will allow to formulate recommendations and to enable the Ministry of Health and Family Welfare to make informed decisions about whether the current national antimalarial treatment guidelines should be updated. The patient data will be included in the WHO global database.

The study outcome will be disseminated among the health professionals and social representatives through a meeting held at local health complex, it will also be presented at policy makers’ level in Dhaka, a scientific paper will be written and submitted to relevant journal for publication.

8.4 Amendments to the protocol

After the protocol has been accepted, no change may be made without the agreement of the principal investigator, the sponsor(s) and the institutional review boards.

9. Ethical considerations

9.1 Approval by the national ethical committee

Before the study, official approval to conduct the study will be obtained from Bangladesh Medical Research Council. Before commencement of patient enrolment, the study key information will be posted on clinical trial registry: [www.ANZCTR](http://www.ANZCTR) before commencement of patient enrolment.

9.2 Informed consent

Patients will be included in the study only if they or parents or guardians of children give informed consent. The consent request, available in English and translated into Bengali, will be read entirely to the patient or parent or guardian. Details about the study and its benefits and potential risks will be explained. Once any questions have been answered, a signature will be requested on the document (Appendix 10). If the patient or parent or guardian is illiterate, a literate witness must sign; if possible, the signatory will be selected by the prospective participant and will have no connection to the research team. The principal investigator must also obtain and document the assent of children aged from 12 year and age of majority, but their assent should be accompanied by the consent of a parent or guardian. A child aged from 12 year and age of majority who does not agree to participate will not be enrolled in the study and will be referred to the health facility staff to be treated according to the standard of care established by the Ministry of Health and Family Welfare. Written consent statement for the pregnancy test and the need for contraception are also required for female participants of child-bearing age.

9.3 Confidentiality

All information on patients will remain confidential and be shared only by the study team. Unique identifiers will be used for computer-based data entry and blood samples. In all cases, the principal investigator will ensure that all screening forms, the case report forms and the completed subject identification code list (patient screening and enrolment logbook) are kept in locked files.

9.4 Health-care services

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

When prospective or actual participants are found to have diseases unrelated to malaria, the principal investigator should advise them or parents or guardians to obtain, or refer them for, medical care.

Any patient who decides not to participate or who cannot be enrolled into the study because he or she does not meet all inclusion criteria will not be enrolled. He or she will be referred to the health facility staff and be treated for malaria (if they have parasitaemia) with artemether-lumefantrine 6 doses for 3 days as per national guidelines and/or the other diseases. Such people will be treated and followed-up according to the standard of care established by the Ministry of Health and Family Welfare. The principal investigator will ensure that this antimalarial drug is available at the health centre. Patients with severe conditions will be referred to the nearest health facility where they can receive appropriate care.

If a patient is withdrawn from the study before he or she has completed the full course of the treatment, the physician must make all necessary arrangements to provide the patient with the full dose of the medicine being tested or with a full course of medication being tested or with a full course of other drugs recommended in the national policy.

9.5 Reimbursement and compensation

Subjects shall be reimbursed for their transport to attend all visits to the health centre. Insecticide treated nets will be provided to participants. No other gifts or payments will be made. Modest wage loss (600 BDT per day will be provided to the participant or the guardian/husband accompanying in case of minors and woman.

9.6 Community

Currently most of the cases of UM are treated at the study sites by the community based government or non-government health workers. Community engagement meetings 2 for each site will be conducted to appraise the community about the study.

9.7 Data safety monitoring board (DSMB)

Medical Monitor: Prof Dr. Robed Amin, Director, NCDC, DGHS, Mohakhali, Dhaka will be the medical monitor of the study. He will independently monitor the quality implementation and reporting of the study. He will provide special attention regarding the admission of the recruited patients in the hospital for the initial 3 days (where applicable) for correct dosing of the drugs, assessment and timely collection blood smears. He will visit the sentinel sites every alternate month to see the activities and make a report to PI and all CIs regarding gaps and lapses (if any) and recommendations.

10. Budget

Therapeutic Efficacy Study of Artemether+ Lumifantrin and dihydroartemisinin piperaquine in the three Sentinel Sites.

Duration: 06 month

Venue- Upazila Health Complex, 3 Sentinel Sites: Alikadam and Lama, Bandarban Hill Tract Districts and Baghaichari of Rangamati Hill Tract District

| **Budget Head** | **Particulars** | **No of** | **Payment** | **No of** | **Budget BDT** |
| --- | --- | --- | --- | --- | --- |
| **Person** | **Rate** | **M/D/T** |
| DSA | A1. Principal Investigator (30% of total time per month) |  |  |  |  |
| (1st Class) | 1 | 0 | 0 | - |
|  | A2. Co-investigators (30% of total time per month) |  |  |  | - |
|  | (1st Class) (only 1 Co-PI and 1 CI will be paid) | 2 | BDT 12,000/month | 12 months | 288,000 |
|  | A3. Medical Monitor: |  |  |  | - |
|  | A3.1. Per diem (2 days per visit as non- local) | 1 | BDT 2,100x2 daysx3 sites | 5 times | 63,000 |
|  | A3.2. Travel Allowance  A.3.2.1. Travel: Dhaka to Chittagong and back (by air).  Chittagong to Lama and Alikadam and back by road:  Chittagong to Baghaichari, Rangamati and back | 1 | 10,000  10,000  10,000 | 5 times | 150,000 |
|  | A4. Research Assistants – Medical Officer (30% of total time per month) |  |  |  | - |
|  | (1st Class) | 3 | 8,000/month | 12 months | 288,000 |
|  | A5. Medical technologist – lab (30% of total time per month) |  |  |  |  |
|  | (3rd Class) | 3 | 6,000/month | 12 months | 216,000 |
|  | A6. Medical technologist – lab (quality control) |  |  |  |  |
|  | (3rd Class) | 1 | 6,000/month | 6 months | 36,000 |
|  | A7. Senior staff nurse (30% of total time per month) |  |  |  |  |
|  | (2nd Class) | 6 | 6,000/month | 12 months | 432,000 |
|  | A8. Field staff |  |  |  |  |
|  | (3rd Class) | 3 | 2,000/month | 12 months | 72,000 |
|  | A9. Monitoring and supervision by Civil Surgeon (10% of total time per month) |  |  |  | - |
|  | (1st Class) | 3 | 5,000/month | 6 months | 90,000 |
|  | A10. Monitoring and supervision by Upazila Health and family Planning Officer (10% of total time per month) |  |  |  |  |
|  | (1st Class) | 3 | 5,000/month | 6 months | 90,000 |
|  | **C. Travel by PI** |  |  |  | - |
|  | C1. Travel: Dhaka to Chittagong and back (by air) to cover all three sites.  Chittagong to Lama and Alikadam and back by road:  Chittagong to Baghaichari, Rangamati and back | 1  1  1 | 10,000  10,000  10,000 | 3 times  3 times  3 times | 30,000  30,000  30,000 |
|  | C2. Per diem | 1 | 2,100 x 5 days | 3 times | 31,500 |
|  | **D. Travel by Co-PI and CI** |  |  |  |  |
|  | D1. Travel: Dhaka to Chittagong and back (by air).  Chittagong to Lama and Alikadam and back by road:  Chittagong to Baghaichari, Rangamati and back | 5  5  5 | 10,000  10,000  10,000 | 6 times  6 times  6 times | 300,000  300,000  300,000 |
| D2. Per diem | 5 | 2,100 x 5 days | 6 times | 315,000 |
| Training | Training of the team members on the TES protocol including roles and responsibilities (detail attached) |  |  | 1 time | 392,000 |
| Stationaries | E. Stationery for source documents |  |  |  |  |
| Pen, Pad, Folder, questionnaire, treatment sheet etc | 1 | 20,000 | 1 | 20,000 |
| Supplies & Equip | F. Supplies and equipment (Whatman filter paper, Blood slides, reagent, blood slide box, cotton, antiseptic, lancet, digital thermometer, milk etc) |  |  |  | - |
|  | 3 | 50,000 | 1 | 150,000 |
| TA for Patient | G. Patient hospitalization and travel cost: 180 patients: 3000/per patient | 180  180 | 3,000  4,200 | 1 | 540,000  756,000 |
| Data Entry | K. Data entry, analysis and report writing | 1 | 40,000 | 1 | 40,000 |
| Dissemination | J. Dissemination (organizing workshop at the study sites, presentation in a seminar/workshop, publication) | 1 | 70,000 | 1 | 70,000 |
|  | Photocopy & Others |  |  |  | 3,000 |
| **Total** | | | | | **5,032,500** |

11. Curriculum vitae of the principal investigator (need to be included)

|  |  |
| --- | --- |
| Family name (surname): Islam | First name: Md. Nazmul |
| Place of birth: Comilla | Date of birth: 01-04-1967 |
| Current nationality: Bangladeshi | |
| Academic qualifications and dates:   1. Secondary School Certificate: 1982 (Comilla Board) 2. Higher Secondary Certificate: 1984 (Comilla Board) 3. MBBS: 1991 (Chittagong Medical College, Chittagong University) 4. MPH: 1998 (NIPSOM) 5. MS: 2011 (Otolaryngology, Dhaka University | |
| Posts held (type of post, institution, dates chronologically starting with current appointment):   1. Director, Disease Control and Line Director, CDC, DGHS, Mohakhali, Dhaka-1212. From January 2021 to till date 2. Line Director (Medical Education and Health Manpower Development), DGHS, Mohakhali, Dhaka-1212. From March 2019 to January 2021 3. Professor of ENT in Dhaka Medical College, Associate Professor, Assistant Professor and Medical Officer since April 1994. | |
| Selected relevant publications (maximum 5):   1. **Islam, M. N**., Lodh, D., Siddiqui, M. M., Ahsan, S., Debnath, B., & Khan, A. (2016). Surgical management of thyroid diseases in Dhaka Medical College Hospital. Bangladesh Medical Journal, 44(3), 157-159. <https://doi.org/10.3329/bmj.v44i3.27376> 2. **Islam, M. N.**, Lodh, D., Siddiqui, M. M., Mannan, M., & Khan, A. M. (2016). Pilomatrixoma in Periocular Tissues: A Case Report from Bangladesh. Journal of Science Foundation, 13(1), 21-24. <https://doi.org/10.3329/jsf.v13i1.27830> 3. **Islam, M. N.,** Lodh, D., Siddiqui, M. M., Khan, A., & Meherunnesa, K. (2016). Clinicopathological Study on Hypopharyngeal Carcinoma in Dhaka Medical College Hospital. Bangladesh Journal of Otorhinolaryngology, 21(2), 85-89. <https://doi.org/10.3329/bjo.v21i2.27645> 4. Alam, A., Talukder, D., Aich, M., Harun, M., Rumi, S., & **Islam, M. (2013)**. Non-epithelial tumors of the nose, nasopharynx and paranasal sinuses - a clinicopathological study. Journal of Dhaka Medical College, 21(1), 41-45. 5. Arefin, M. K., Arafat, M. S., Talukder, D. C., Rumi, S. N. F., **Islam, M. N**., Rahman, S. H.,   ... & Islam, M. A. (2021). ‘POLIDON’ Approach—A Novel Solution for the ENT & Skull Base Surgeons in COVID-19 era. *Indian Journal of Otolaryngology and Head & Neck Surgery*, *73*(1), 111-115.   1. Arefin, M. K., Uddin, M., Haque, M. M., Azam, M., Arafat, M. S., Islam, M., ... **Islam, M. N.,** Fakir, M. A. Y. & Uddin, A. K. M. (2020). 'Polidon' Approach-A Novel Approach of Mastoidectomy in COVID-19 Pandemic. *Online Journal of Otolaryngology & Rhinology.* ISSN: 2688-8238 2. Arefin, M. K., Uddin, M. B., Islam, M. Z., Arafat, M. S., Talukder, D. C., Rumi, S. N. F., **Islam, M. N**., ... & Uddin, B. G. D. M. N. (2020). Novel technique of tracheostomy in the era of novel coronavirus. *International Journal of Innovative Science and Research Technology*, *5*(5), 1149-1154. 3. Arefin, M. K., Islam, M. Z., & Shawrave, M. S. A., Rahman, A. K. M. F., **Islam, M.N**., Rumi, S.N. F., & Fakir, M. A. Y. (2020). The role of Povidone Iodine mouthwash & nasal spray or drop or inhalation for protection of health care professionals as well as patients and reduction of cross infection during current COVID-19 pandemic situation. *International Journal of Science and Research.* ISSN: 2319-7064 4. Arefin, M. K., Khan**,** A. F. M., Fakir, M. A. Y., **Islam, M.N**., Lodh, D., Shahin, M. M. H. (2018). Wegener's Granulomatosis: A Case Report. *The Beacon Medical Journal*, 1(1), 33. 5. Ahmed, H., Uddin, A., **Islam, M. N.,** Khan, M. A., Zaki, H., Hossain, T., Biswas, C., & Rabbani, M. G. (2016). Pattern of psychiatric morbidity among female patients who attended private consultation chambers in Dhaka city. Bangladesh Medical Journal, 45(1), 14-19. https://doi.org/10.3329/bmj.v45i1.28959 | |

Appendix 1. Definition of severe falciparum malaria[[6]](#footnote-7)

**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**

Appendix 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;
* primaquine (for *P. vivax*)
* 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, rash, nausea, vomiting.

* Artesunate-pyronaridine

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

* Dihydroartemisinin-piperaquine

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

Chloroquine: unpleasant taste, pruritus, headache, various skin eruptions and gastrointestinal disturbances, such as nausea, vomiting and diarrhea, rarely central nervous system toxicity including, convulsions and mental changes may occur. Chronic use (>5 years continuous use as prophylaxis) may lead to eye disorders, including keratopathy and retinopathy. Other uncommon effects include myopathy, reduced hearing, photosensitivity and loss of hair. Blood disorders, such as aplastic anaemia, are extremely uncommon.

Appendix 3. Dosing chart of Artemether-lumefantrine

Tablets containing 20 mg artemether and 120 mg lumefantrine

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Drug | Day | No of Dose | Time | 5-<15 Kg | 15-<25 Kg | 25-<35 Kg | >35- Kg |
| Artemether +Lumefantrine | Day-1 | 1st | 0 hour | 1 | 2 | 3 | 4 |
| 2nd | 8 hour | 1 | 2 | 3 | 4 |
| Day-2 | 3rd | 24 hour | 1 | 2 | 3 | 4 |
| 4th | 36 hour | 1 | 2 | 3 | 4 |
| Day-3 | 5th | 48 hour | 1 | 2 | 3 | 4 |
| 6th | 60 hour | 1 | 2 | 3 | 4 |

Tab Primaquine (0.25mg/kg) is given with the first dose of ACT.

Dosing of DHA-PPQ (Tablets containing 40 mg dihydroartemisinin and 320 mg piperaquine phosphate).

|  |  |  |  |
| --- | --- | --- | --- |
| **Body weight (kg)** | **No. of tablets at approximate timing of dosing** | | |
| **Day 0** | **Day 1** | **Day 2** |
| 5 to <8 | ½ tablet | ½ tablet | ½ tablet |
| 8 to <11 | ¾ tablet | ¾ tablet | ¾ tablet |
| 11 to <17 | 1 tablet | 1 tablet | 1 tablet |
| 17 to <25 | 1½ tablet | 1½ tablet | 1½ tablet |
| 25 to <36 | 2 tablets | 2 tablets | 2 tablets |
| 36 to <60 | 3 tablets | 3 tablets | 3 tablets |
| 60 to <80 | 4 tablets | 4 tablets | 4 tablets |
| >80 | 5 tablets | 5 tablets | 5 tablets |

Tab Primaquine (0.25mg/kg) is given with the first dose of ACT.

1 tablet contains 50 mg Artesunate and 250 mg Mefloquine base. Artesunate dose 4 mg/kg once a day for 3 days and Mefloquine 8.3 mg/kg/day for 3 days

|  |  |
| --- | --- |
| **Body weight (kg)** | **Artesunate + Mefloquine dose in mg (given daily for 3 days** |
| 4.5 to <9 | 25+55 |
| 9 to <18 | 50+110 |
| 18 to <36 | 100+220 |
| ≥36 | 200+440 |

Appendix 4. Classification of treatment outcomes[[7]](#footnote-8)

**Early treatment failure**

* danger signs or severe malaria on day 1, 2 or 3 in the presence of parasitaemia;
* parasitaemia on day 2 higher than on day 0, 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**

**Late clinical failure**

* danger signs or severe malaria in the presence of parasitaemia on any day between day 4 and day 28 in patients who did not previously meet any of the criteria of early treatment failure;
* presence of parasitaemia on any day between day 4 and day 28 with axillary temperature   
  ≥ 37.5 ºC or history of fever in patients who did not previously meet any of the criteria of early treatment failure.

**Late parasitological failure**

* presence of parasitaemia on any day between day 7 and day 28 with axillary temperature   
  < 37.5 ºC in patients who did not previously meet any of the criteria of early treatment failure or late clinical failure.

**Adequate clinical and parasitological response**

* absence of parasitaemia on day 28, irrespective of axillary temperature, in patients who did not previously meet any of the criteria of early treatment failure, late clinical failure or late parasitological failure.

Appendix 5. Case screening form

**.**

**.**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Case screening form** | | | | | |
| Health centre name: | | | | Study number: | |
| Locality: | | | | Patient screening number: | |
| District: | | | | Date of visit: dd/mmm/yyyy | |
| Province: | | | |  | |
| **Demographic data** | | | | | |
| Date of birth: dd/mmm/yyyy | | | 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 yes, patient is not eligible)** | | | | | |
| Provide the date of the last menstrual period: dd/mmm/yyyy | | | | | |
| **Pre-treatment temperature** | | | | | |
| History of fever in previous 24 h?  Yes  No | | | | | |
| Temperature:       ºC  Axillary  Tympanic  Rectal  Oral | | | | | |
| **Blood analysis** | | | | | |
| Parasitology | | | | | |
| Approximate number of *P. falciparum* asexual parasites:  Presence of 1–100 parasites/3–6 white blood cells?  Yes  No **(If no, patient is not eligible)** | | | | | |
| Presence of *P. falciparum* gametocytes?  Yes  No | | | | | |
| Were species other than *P. falciparum* present?  Yes  No **(If yes, patient is not eligible)** | | | | | |
| If yes which species:  *P. vivax*  *P. ovale*  *P. malariae* | | | | | |
| Has blood sample for PCR been collected?  Yes  No | | | | | |
| Haematology | |  | | | |
| Haemoglobin:       g/dl | | Haematocrit:       % | | | |
| **Urinary analysis (pregnancy test for female patients)** | | | | | |
| Result of pregnancy test:  Positive  Negative **(If positive, patient is not eligible)** | | | | | |
| **Inclusion criteria** | | | | | |
| * age between       months/years and       months/years; * mono-infection with *P. falciparum* confirmed by positive blood smear (i.e. no mixed infection); * parasitaemia between       and      /µl of asexual forms; * measured temperature (depending on method of measurement) or history of fever within previous 24 h; * ability to swallow oral medication; * ability and willingness to comply with the study protocol for the duration of the study and to comply with the study visit schedule. | | | | | |
| Does the patient meet all the inclusion criteria?  Yes  No **(If no, patient is not eligible)** | | | | | |
| **Case screening form (page 2)** | | | | | |
| **Exclusion criteria** | | | | | |
| * presence of general danger signs in children aged under 12 years or signs of severe falciparum malaria according to the definitions of WHO (Appendix 1); * female 12 years and age of majority; * weight < 5 kg; * haemoglobin < 8g/dl; * mixed or mono-infection with another *Plasmodium* species detected by microscopy; * severe malnutrition (defined as per protocol); * febrile conditions caused by diseases other than malaria or other known underlying chronic or severe diseases; * regular medication which interferes with antimalarial pharmacokinetics; * history of hypersensitivity reactions or contraindications to the medicine tested; * glucose-6-phosphate dehydrogenase deficiency for patient treated with primaquine (only applicable for vivax studies); * positive pregnancy test or breastfeeding; * unable to or unwilling to take pregnancy test or to use contraception for women of child-bearing age (defined as age > 12 years and sexually active). | | | | | |
| Does the patient meet any of the exclusion criteria?  Yes  No **(If yes, the patient is not eligible)** | | | | | |
| If yes, please specify the reason for exclusion: | | | | | |
| **Patient informed consent and assent** | | | | | |
| Consent form signed:  Yes  No **(If no, the patient is not eligible)** | | | | | Patient study number:  Date: dd/mmm/yyyy |
| Assent form signed:  Yes  No **(If no, the patient is not eligible)**  Enrolled:  Yes  No  If yes,to:  AL  DAPQ | | | | |

Appendix 6. Schedule of follow-up activities

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | Day | | | | | | | | | | |
| 0 | 1 | 2 | 3 | 7 | 14 | 21 | 28 | 35 | 42 | Any other |
| **Procedure** |  |  |  |  |  |  |  |  |  |  |  |
| 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 parasite count | X | X | X | X | X | X | X | X | X | X | (X) |
| Urine sample | X |  |  |  |  |  |  |  |  |  |  |
| Blood for:  genotyping  haemoglobin or haematocrit  molecular markers | X  X  X |  |  |  | (X)  (X) | (X)  X  (X) | (X)  (X) | (X)  X  (X) | (X)  (X) | (X)  X  (X) | (X)  (X) |
| Treatment |  |  |  |  |  |  |  |  |  |  |  |
| Medicine to be tested | X | (X) | (X) |  |  |  |  |  |  |  |  |
| Rescue treatment |  | (X) | (X) | (X) | (X) | (X) | (X) | (X) | (X) | (X) | (X) |

Parentheses denote conditional or optional activities. For example, treatment would be given on days 1 and 2 only for 3-day dosing. On day 1, the patient should be examined for parasitaemia if he or she has any danger signs or if parasite clearance needs to be calculated. 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 taken routinely or at the request of the clinical staff.

**Day 0**

**Screening**

* clinical assessment, including measurement of weight and height; referral in cases of severe malaria or danger signs;
* measurement of temperature;
* parasitological assessment;
* pregnancy test (if necessary);
* informed consent and assent.

**Enrolment**

* treatment, first dose;
* blood sampling for genotyping.

**Optional**

* urinary test to detect antimalarial drugs;
* haemoglobin/haematocrit;
* molecular markers of drug resistance;
* in vitro test;
* antimalarial drug blood concentration.

**Day 1**

* clinical assessment; referral in cases of severe malaria or danger signs;
* measurement of temperature;
* parasitological assessment in cases of severe malaria or danger signs or if parasite clearance needs to be calculated;
* treatment, second dose or alternative treatment in case of severe malaria.

**Day 2**

* clinical assessment; referral in cases of severe malaria or danger signs;
* measurement of axillary temperature;
* 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 or any other day**

* clinical assessment; referral in cases of severe malaria or danger signs;
* measurement of axillary temperature;
* parasitological assessment;
* alternative treatment in cases of treatment failure;
* pregnancy test at the end of follow-up (if necessary);
* blood sampling for genotyping to distinguish between recrudescence and reinfection in cases of treatment failure after day 7.

**Optional (on or after day 7)**

* haemoglobin/haematocrit;
* blood sampling for antimalarial blood concentration and molecular markers for drug resistance.

Appendix 7. Case report forms

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Case report form: follow-up day 0** | | | | | | | | | |
| Health centre name: | | | | | | | Study number: | | |
| Locality: | | | | | | | Patient study number: | | |
| District: | | | | | | | Date of visit: dd/mmm/yyyy | | |
| Province: | | | | | | |  | | |
| **Demographic data** | | | | | | | | | |
| Date of birth: dd/mmm/yyyy | | | | | or estimated age:       in:  months or  years | | | | |
| Height (cm): | | Weight (kg): | | | Height (cm): | | | | |
| If female, is the patient pregnant?  Yes  No  Not sure **(If yes, patient is not eligible)** | | | | | | | | | |
| Provide the date of the last menstrual period: dd/mmm/yyyy | | | | | | | | | |
| **Pre-treatment temperature** | | | | | | | | | |
| History of fever in previous 24 h?  Yes  No | | | | | | | | | |
| Temperature:       ºC  Axillary  Tympanic  Rectal  Oral | | | | | | | | | |
| **Thick blood smears for** ***P. falciparum*: quantitative parasite counts and qualitative gametocyte counts** | | | | | | | | | |
| Average number of asexual *P. falciparum* parasites/μl: | | | | | | | | | |
| Presence of *P. falciparum* gametocytes?  Yes  No | | | | | | | | | |
| Were species other than *P. falciparum* present?  Yes  No **(If yes, patient is not eligible)** | | | | | | | | | |
| If yes which species  *P. vivax*  *P. ovale*  *P. malariae* | | | | | | | | | |
| Has blood sample for PCR been collected?  Yes  No | | | | | | | | | |
| **Urinary test for antimalarial drugs** | | | | | | | | | |
| Test used: | | | | Test result:  Positive  Negative | | | | | |
| Test used: | | | | Test result:  Positive  Negative | | | | | |
| **Prior medication** | | | | | | | | | |
| All prior medication, including natural remedies and homeopathic medicines, taken within the previous 14 days should be reported in this section. | | | | | | | | | |
| Has the patient taken any prior antimalarial medication?  Yes  No. If yes, please specify below. Either the date of stopping or the ‘ongoing’ box should be checked. | | | | | | | | | |
| Medicine name (generic name) | Dates | | Ongoing  (Yes = ) | | | Total daily dose and unit | | Route of administration | Indication for use |
|  | Start: dd/mmm/yyyy | |  | | |  | |  |  |
| Stop: dd/mmm/yyyy | |
|  | Start: dd/mmm/yyyy | |  | | |  | |  |  |
| Stop: dd/mmm/yyyy | |

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Case report form: follow-up day 0 (page 2)** | | | | | |
| **Medication administration** | | | | | |
| Name(s) of antimalarial drug(s) | | Time of dose (hh:min) | Number of tablets | Did the patient vomit? | Time of vomiting (hh:min) |
|  | |  |  | Yes  No |  |
|  | |  |  | Yes  No |  |
| Name(s) of other medicine(s) |  | | | | |
|  | |  |  | Yes  No |  |
|  | |  |  | Yes  No |  |

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Case report form: follow-up day 1** | | | | |
| Study number: | | | | |
| Patient study number: | | | | |
| Date of visit : dd/mmm/yyyy | | | | |
| **Clinical status** | | | | |
| Presence of danger signs or signs of severe or complicated malaria?  Yes  No  If yes, perform thick blood smear | | | | |
| Temperature:       ºC  Axillary  Tympanic  Rectal  Oral | | | | |
| **Thick blood smears for estimation of *P. falciparum* parasite counts** | | | | |
| Average number of asexual *P. falciparum* parasites/μl: | | | | |
| Presence of *P. falciparum* gametocytes?  Yes  No | | | | |
| Were species other than *P. falciparum* present?  Yes  No | | | | |
| If yes which species  *P. vivax*  *P. ovale*  *P. malariae* | | | | |
| **Adverse events** | | | | |
| Presence of an adverse event?  Yes  No | | | | |
| If yes, name the adverse event: | | | | |
| Is it a serious adverse event?  Yes  No. If yes, inform the sponsor and other relevant institutions | | | | |
| **Medication administration** | | | | |
| Name(s) of antimalarial drug(s) | Time of dose (hh:min) | Number of tablets | Did the patient vomit? | Time of vomiting (hh:min) |
|  |  |  | Yes  No |  |
|  |  |  | Yes  No |  |
| Name(s) of other medicine(s) |  | | | |
|  |  |  | Yes  No |  |
|  |  |  | Yes  No |  |

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Case report form: follow-up day 2** | | | | |
| Study number: | | | | |
| Patient study number: | | | | |
| Date of visit : dd/mmm/yyyy | | | | |
| **Clinical status** | | | | |
| Presence of danger signs or signs of severe or complicated malaria?  Yes  No | | | | |
| Temperature:       ºC  Axillary  Tympanic  Rectal  Oral | | | | |
| **Thick blood smears for estimation of *P. falciparum* parasite counts** | | | | |
| Average number of asexual *P. falciparum* parasites/μl: | | | | |
| Presence of *P. falciparum* gametocytes?  Yes  No | | | | |
| Were species other than *P. falciparum* present?  Yes  No | | | | |
| If yes which species  *P. vivax*  *P. ovale*  *P. malariae* | | | | |
| **Adverse events** | | | | |
| Presence of an adverse event?  Yes  No No | | | | |
| If yes, name the adverse event: | | | | |
| Is it a serious adverse event?  Yes  No. If yes, inform the sponsor and other relevant institutions | | | | |
| **Medication administration** | | | | |
| Name(s) of antimalarial drug(s) | Time of dose (hh:min) | Number of tablets | Did the patient vomit? | Time of vomiting (hh:min) |
|  |  |  | Yes  No |  |
|  |  |  | Yes  No |  |
| Name(s) of other medicine(s) |  | | | |
|  |  |  | Yes  No |  |
|  |  |  | Yes  No |  |

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Case report form:** **follow-up day 3** | | | | |
| Study number: | | | | |
| Patient study number: | | | | |
| Date of visit : dd/mmm/yyyy | | | | |
| **Clinical status** | | | | |
| Presence of danger signs or signs of severe or complicated malaria?  Yes  No | | | | |
| Temperature:       ºC  Axillary  Tympanic  Rectal  Oral | | | | |
| **Thick blood smears for estimation of** ***P. falciparum* parasite counts** | | | | |
| Average number of asexual *P. falciparum* parasites/μl: | | | | |
| Presence of *P. falciparum* gametocytes?  Yes  No | | | | |
| Were species other than *P. falciparum* present?  Yes  No | | | | |
| If yes which species  *P. vivax*  *P. ovale*  *P. malariae* | | | | |
| **Adverse events** | | | | |
| Presence of an adverse event?  Yes  No No | | | | |
| If yes, name the adverse event: | | | | |
| Is it a serious adverse event?  Yes  No. If yes, inform the sponsor and other relevant institutions | | | | |
| **Medication administration** | | | | |
| Name(s) of antimalarial drug(s) | Time of dose (hh:min) | Number of tablets | Did the patient vomit? | Time of vomiting (hh:min) |
|  |  |  | Yes  No |  |
|  |  |  | Yes  No |  |
| Name(s) of other medicine(s) |  | | | |
|  |  |  | Yes  No |  |
|  |  |  | Yes  No |  |

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Case report form: follow-up day 7** | | | | | |
| Study number: | | | | | |
| Patient study number: | | | | | |
| Date of visit : dd/mmm/yyyy | | | | | |
| **Clinical status** | | | | | |
| Presence of danger signs or signs of severe or complicated malaria?  Yes  No | | | | | |
| History of fever within previous 24 h?  Yes  No | | | | | |
| Temperature:       ºC  Axillary  Tympanic  Rectal  Oral | | | | | |
| **Thick blood smears for estimation of *P. falciparum* parasite counts** | | | | | |
| Average number of asexual *P. falciparum* parasites/μl: | | | | | |
| Presence of *P. falciparum* gametocytes?  Yes  No | | | | | |
| Were species other than *P. falciparum* present?  Yes  No | | | | | |
| If yes which species  *P. vivax*  *P. ovale*  *P. malariae* | | | | | |
| Has a blood sample for PCR been collected?  Yes  No | | | | | |
| **Adverse events** | | | | | |
| Presence of an adverse event?  Yes  No No | | | | | |
| If yes, name the adverse event: | | | | | |
| Is it a serious adverse event?  Yes  No. If yes, inform the sponsor and other relevant institutions. | | | | | |
| **Medication administration** | | | | | |
| Name(s) of antimalarial drug(s) | | Time of dose (hh:min) | Number of tablets | Did the patient vomit? | Time of vomiting (hh:min) |
|  | |  |  | Yes  No |  |
|  | |  |  | Yes  No |  |
| Name(s) of other medicine(s) |  | | | | |
|  | |  |  | Yes  No |  |
|  | |  |  | Yes  No |  |

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Case report form: follow-up day 14** | | | | |
| Study number: | | | | |
| Patient study number: | | | | |
| Date of visit : dd/mmm/yyyy | | | | |
| **Clinical status** | | | | |
| Presence of danger signs or signs of severe or complicated malaria?  Yes  No | | | | |
| History of fever within previous 24 h?  Yes  No | | | | |
| Temperature:       ºC  Axillary  Tympanic  Rectal  Oral | | | | |
| **Thick blood smears for estimation of *P. falciparum* parasite counts** | | | | |
| Average number of asexual *P. falciparum* parasites/μl: | | | | |
| Presence of *P. falciparum* gametocytes?  Yes  No | | | | |
| Were species other than *P. falciparum* present?  Yes  No | | | | |
| If yes which species  *P. vivax*  *P. ovale*  *P. malariae* | | | | |
| Has a blood sample for PCR been collected?  Yes  No | | | | |
| **Adverse events** | | | | |
| Presence of an adverse event?  Yes  No No | | | | |
| If yes, name the adverse event: | | | | |
| Is it a serious adverse event?  Yes  No. If yes, inform the sponsor and other relevant institutions. | | | | |
| **Medication administration** | | | | |
| Name(s) of antimalarial drug(s) | Time of dose (hh:min) | Number of tablets | Did the patient vomit? | Time of vomiting (hh:min) |
|  |  |  | Yes  No |  |
|  |  |  | Yes  No |  |
| Name(s) of other medicine(s) |  | | | |
|  |  |  | Yes  No |  |
|  |  |  | Yes  No |  |

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Case report form: follow-up day 21** | | | | |
| Study number: | | | | |
| Patient study number: | | | | |
| Date of visit: dd/mmm/yyyy | | | | |
| **Clinical status** | | | | |
| Presence of danger signs or signs of severe or complicated malaria?  Yes  No | | | | |
| History of fever within previous 24 h?  Yes  No | | | | |
| Temperature:       ºC  Axillary  Tympanic  Rectal  Oral | | | | |
| **Thick blood smears for estimation of *P. falciparum* parasite counts** | | | | |
| Average number of asexual *P. falciparum* parasites/μl: | | | | |
| Presence of *P. falciparum* gametocytes?  Yes  No | | | | |
| Were species other than *P. falciparum* present?  Yes  No | | | | |
| If yes which species  *P. vivax*  *P. ovale*  *P. malariae* | | | | |
| Has a blood sample for PCR been collected?  Yes  No | | | | |
| **Adverse events** | | | | |
| Presence of an adverse event?  Yes  No No | | | | |
| If yes, name the adverse event: | | | | |
| Is it a serious adverse event?  Yes  No. If yes, inform the sponsor and other relevant institutions. | | | | |
| **Medication administration** | | | | |
| Name(s) of antimalarial drug(s) | Time of dose (hh:min) | Number of tablets | Did the patient vomit? | Time of vomiting (hh:min) |
|  |  |  | Yes  No |  |
|  |  |  | Yes  No |  |
| Name(s) of other medicine(s) |  | | | |
|  |  |  | Yes  No |  |
|  |  |  | Yes  No |  |

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Case report form: follow-up day 35 (for DAPQ group)** | | | | |
| Study number: | | | | |
| Patient study number: | | | | |
| Date of visit: dd/mmm/yyyy | | | | |
| **Clinical status** | | | | |
| Presence of danger signs or signs of severe or complicated malaria?  Yes  No | | | | |
| History of fever within previous 24 h?  Yes  No | | | | |
| Temperature:       ºC  Axillary  Tympanic  Rectal  Oral | | | | |
| **Thick blood smears for estimation of *P. falciparum* parasite counts** | | | | |
| Average number of asexual *P. falciparum* parasites/μl: | | | | |
| Presence of *P. falciparum* gametocytes?  Yes  No | | | | |
| Were species other than *P. falciparum* present?  Yes  No | | | | |
| If yes which species  *P. vivax*  *P. ovale*  *P. malariae* | | | | |
| Has a blood sample for PCR been collected?  Yes  No | | | | |
| **Adverse events** | | | | |
| Presence of an adverse event?  Yes  No No | | | | |
| If yes, name the adverse event: | | | | |
| Is it a serious adverse event?  Yes  No. If yes, inform the sponsor and other relevant institutions. | | | | |
| **Medication administration** | | | | |
| Name(s) of antimalarial drug(s) | Time of dose (hh:min) | Number of tablets | Did the patient vomit? | Time of vomiting (hh:min) |
|  |  |  | Yes  No |  |
|  |  |  | Yes  No |  |
| Name(s) of other medicine(s) |  | | | |
|  |  |  | Yes  No |  |
|  |  |  | Yes  No |  |

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Case report form: day (any other day that is not part of regular follow-up)** | | | | |
| Study number: | | | | |
| Patient study number: | | | | |
| Date of visit : dd/mmm/yyyy | | | | |
| **Clinical status** | | | | |
| Presence of danger signs or signs of severe or complicated malaria?  Yes  No | | | | |
| History of fever within previous 24 h?  Yes  No | | | | |
| Temperature:       ºC  Axillary  Tympanic  Rectal  Oral | | | | |
| **Thick blood smears for estimation of *P. falciparum*****parasite counts** | | | | |
| Average number of asexual *P. falciparum* parasites/μl: | | | | |
| Presence of *P. falciparum* gametocytes?  Yes  No | | | | |
| Were species other than *P. falciparum* present?  Yes  No | | | | |
| If yes which species  *P. vivax*  *P. ovale*  *P. malariae* | | | | |
| Has a blood sample for PCR been collected?  Yes  No | | | | |
| **Adverse events** | | | | |
| Presence of an adverse event?  Yes  No No | | | | |
| If yes, name the adverse event: | | | | |
| Is it a serious adverse event?  Yes  No. If yes, inform the sponsor and other relevant institutions. | | | | |
| **Medication administration** | | | | |
| Name(s) of antimalarial drug(s) | Time of dose (hh:min) | Number of tablets | Did the patient vomit? | Time of vomiting (hh:min) |
|  |  |  | Yes  No |  |
|  |  |  | Yes  No |  |
| Name(s) of other medicine(s) |  | | | |
|  |  |  | Yes  No |  |
|  |  |  | Yes  No |  |

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Case report form: final day of follow-up (28/42)** | | | | | | | |
| Study number: | | | | | | | |
| Patient study number: | | | | | | | |
| Date of visit: dd/mmm/yyyy | | | | | | | |
| **Clinical status** | | | | | | | |
| Presence of danger signs or signs of severe or complicated malaria?  Yes  No | | | | | | | |
| History of fever within previous 24 h?  Yes  No | | | | | | | |
| Temperature:       ºC  Axillary  Tympanic  Rectal  Oral | | | | | | | |
| **Thick blood smears for estimation of *P****.* ***falciparum* parasite counts** | | | | | | | |
| Average number of asexual *P. falciparum* parasites/μl: | | | | | | | |
| Presence of *P. falciparum* gametocytes?  Yes  No | | | | | | | |
| Were species other than *P. falciparum* present?  Yes  No | | | | | | | |
| If yes which species  *P. vivax*  *P. ovale*  *P. malariae* | | | | | | | |
| Has a blood sample for PCR been collected?  Yes  No | | | | | | | |
| **Adverse events** | | | | | | | |
| Presence of an adverse event?  Yes  No No | | | | | | | |
| If yes, name the adverse event: | | | | | | | |
| Is it a serious adverse event?  Yes  No. If yes, inform the sponsor and other relevant institutions. | | | | | | | |
| **Medication administration** | | | | | | | |
| Name(s) of antimalarial drug(s) | Time of dose (hh:min) | | Number of tablets | | Did the patient vomit? | Time of vomiting (hh:min) | |
|  |  | |  | | Yes  No |  | |
|  |  | |  | | Yes  No |  | |
| Name(s) of other medicine(s) |  | | | | | | |
|  |  |  | | | Yes  No |  | |
|  |  |  | | | Yes  No |  | |
| **Urinary analysis (pregnancy test for female patients)** | | | | | | | |
| **Patients with a positive pregnancy test must be followed up for 6–8 weeks after delivery** | | | | | | | |
| Result of pregnancy test:  Positive  Negative | | | | Date of test: dd/mmm/yyyy | | | |
| If the patient is pregnant, follow-up of the pregnancy is required, including: clinical examination of the infant at birth and 6-8 weeks after birth. Please provide comments below. If needed fill in the serious adverse event report form: | | | | | | | |
| **Case report form: final day of follow-up (28/42) (page 2)** | | | | | | | |
| **Overall assessment** | | | | | | | |
| Outcome:  adequate clinical and parasitological response  early treatment failure  late clinical failure  late parasitological failure  lost to follow-up  withdrawn (complete section below: Reason for withdrawal) | | | | | | | |
| Outcome occurred on follow-up day:      (e.g. 1, 2, 3, 7, 14, …) | | | | | | | |
| PCR:  *P. falciparum* recrudescence  *P. falciparum* reinfection  other species  mixed with *P. falciparum* recrudescence  mixed with *P. falciparum* reinfection  unknown | | | | | | |  |
| PCR corrected results:  adequate clinical and parasitological response  early treatment failure  late clinical failure  late parasitological failure  lost to follow-up  withdrawn | | | | | | |  |
| Reason for withdrawal: | | | | | | | |
| Other comments: | | | | | | | |

Appendix 8. Serious adverse event report form

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Serious adverse event report form** | | | | | |
| Health centre name: | | | | Study number: | |
| Locality: | | | | Patient study number: | |
| District: | | | | Date of visit: dd/mmm/yyyy | |
| Province: | | | | Follow-up day: | |
| **Demographic data** | | | | | |
| Date of birth: dd/mmm/yyyy | | | or estimated age:       in:  months or  years | | |
| Height (cm): | Weight (kg): | | Height (cm): | | |
| If female, is the patient pregnant?  Yes  No  Not sure | | | | | |
| Provide the date of the last menstrual period: dd/mmm/yyyy | | | | | |
| **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/mmm/yyyy | | | | | |
| 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/mmm/yyyy | | | | | | | |
| **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 |
|  |  |  | | | dd/mmm/yyyy | dd/mmm/yyyy |  |
|  |  |  | | | dd/mmm/yyyy | dd/mmm/yyyy |  |
|  |  |  | | | dd/mmm/yyyy | dd/mmm/yyyy |  |
|  |  |  | | | dd/mmm/yyyy | dd/mmm/yyyy |  |
|  |  |  | | | dd/mmm/yyyy | dd/mmm/yyyy |  |
| **Reporting officer** | | | | | | | |
| Name: | | | | | | | |
| Qualification: | | | | | | | |
| Address: | | | | | | | |
| Phone: | | |  | | | | |
| Fax: | | |  | | | | |
| Email: | | | | | | | |
| Signature: | | | | Date: dd/mmm/yyyy | | | |

Appendix 9. 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>).

Appendix 10. Consent and assent forms[[8]](#footnote-9) (Translated into bengali)

**Example of an informed consent form for adults**

This informed consent form is for adults over 18 years of age who attend ------------------------- Upazila Health Complex, ---------------------------- district, who have been invited to participate in a study to evaluate the efficacy of Artemether-lumefantrine/dihydroartemisinin piperaquine for the treatment of uncomplicated falciparum malaria.

|  |  |  |
| --- | --- | --- |
| Name of principal investigator: |  | Prof Dr. Md. Nazmul Islam |
| Name of organization: |  | Director, Disease Control and Line Director, CDC |
| Name of sponsor: |  | Ministry of Health and Family Welfare, Bangladesh |
| Name of proposal and version: |  | Efficacy and safety of artemether-lumefantrine and dihydroartemisinin piperaquine for the treatment of uncomplicated *Plasmodium falciparum* malaria in Alikadam Upazila of Bandarban district, Lama Upazila of Bandarban district and Baghaichari Upazila of Rangamati districts, Bangladesh. Version 1 |

This informed consent form has two parts:

1. Information sheet (to share information about the study with you)
2. Certificate of consent (for signatures if you agree to take part)

You will be given a copy of the full informed consent form.

**Part I. Information sheet**

My name is Prof Dr. Md. Nazmul Islam and I work for the Ministry of Health and Family Welfare. We are doing a study on the treatment of malaria. Malaria is a dangerous disease; however, it can be treated with medicine. The purpose of this study is to verify that the medicine, called Artemether-lumefantrine (Coartem™) and Dihydroartemisinin piperaquine, are still effective for curing malaria.

We are inviting all adults and children aged more than 6 months living in this area to take part in this study.

I am going to give you information and invite you to participate in this study. Before you decide whether to participate, you can talk to anyone you feel comfortable with. There may be some words that you do not understand. Please ask me to stop as we go through the information, and I will take time to explain. If you have questions later, you can ask me, the study doctor or the staff.

Your participation in this study is entirely voluntary. It is your choice whether to participate or not. Whether you choose to participate or not, all the services you receive at this clinic will continue and nothing will change. If you choose not to participate in this project, we will offer the treatment that is routinely provided in this clinic for malaria: artemether-lumefantrine (Coartem™). You may change your mind later and stop participating even if you agreed earlier.

You will receive 6 doses (for artemether lumefantrine) or 3 doses (dihydroartemisinin piperaquine) of medicine over 3 days. The medicine, artemether-lumefantrine/dihydroartemisinin piperaquine, is recommended by the Ministry of Health and Family Welfare. As the parasites that cause malaria can become resistant to the medicine, the Ministry regularly does studies to make sure the medicine is still working. The medicine-artemether-lumefantrine is made by Novartis pharma AG, Basel Switzerland; it is produced with the trade name: Coartem™. Another medicine dihydroartemisinin piperaquine is made by --------- You should know that like other antimalarial medicines, it may cause some side-effects such as: loss of appetite, nausea, vomiting, abdominal pain, diarrhea, dizziness, headache, joint and muscle pain. These effects are usually minor and resolve quickly.

In the event we find that the medicine is not working, we will use what is called ‘rescue medicine’. This medicine is called artesunate-mefloquine is given over 3 days. You should know that this medicine, like other antimalarial medicines, may cause some side-effects such as: loss of appetite, nausea, vomiting, abdominal pain, diarrhea, dizziness, and temporary deafness. These side effects are usually minor and resolve quickly.

The study will take place over 28/42 days. During that time, you will have to come to the health facility for 1 hour each day for the first 3 days or remain hospitalized for first 3 days depending on the situation and then every week for 4/6 weeks according to the scheduled dates given to you. At the end of 4/6 weeks, the study will be finished. At each visit, you will be examined by a physician.

Today, we will take blood and urine for testing and you will receive the first dose of treatment.

On the

* 2nd visit: you will receive the 2nd dose of treatment plus a blood test;
* 3rd visit: you will receive the 3rd dose of treatment plus a blood test;
* 4th, 5th, 6th, 7th, 8th, 9th and 10th visits, you will have a blood test.

For the blood test, a small amount of blood, equivalent of 5 drops, will be taken from your fingertip. You may experience a bit of pain or fear when your finger is pricked. The pain should disappear within 1 day. The blood will be dropped onto a slide and a small piece of paper. The blood samples will only be used to study the malaria in your blood.

The examination of some of the blood samples will only be done after the study and it will not affect the success of the treatment. Nothing else will be done with your blood. The blood samples will be destroyed after the study when no more verification of the information collected is needed.

If you do not attend the scheduled visit, our health staff will visit you at home.

As already mentioned, this medicine may have some minor side effects. It is also possible that it may cause some problems that we are not aware of; however, we will follow you closely and keep track of these effects, if they arise, and of any other problems. We will give you a telephone number to call if you notice anything out of the ordinary or if you have concerns or questions. You can also come to this health facility at any time and ask to see (name of nurse, doctor). If you experience side-effects, we may use some other medicine, free of charge, which will help to reduce the symptoms or reactions, or we may stop one or more of the medicines. If this is necessary we will discuss it together. You will always be consulted before we move to the next step.

Your participation will help us to make sure the medicine is still working, and this will benefit society and future generations. If you decide to participate in this study, the malaria treatment and/or any illnesses related to malaria will be given at no charge to you. We will give you BDT 600 to pay for your travel expenses to the clinic for every visit and a bednet.

We will not share the identity of participants in the study with anyone. The information that we collect from this study will be kept confidential. Any information collected about you will have a number on it instead of your name. Only the study team members will know what your number is, and we will lock that information up.

We will share the knowledge that we get from this study with you before it is made available to the public. Confidential information will not be shared. There will be small meetings in the community, and these will be announced. Afterwards, we will publish the results and make them available so that other interested people may learn from our study.

This proposal has been reviewed and approved by Bangladesh Medical Research Council (BMRC). This is a committee that makes sure that study participants are protected from harm. If you wish to find about more about the institutional review board, you may contact (name, address, telephone number).

**Part II. Certificate of consent**

I have been invited to participate in a study of a medicine used to treat malaria.

I have read the above information, or it has been read to me. I have had the opportunity to ask questions, and any questions that I have asked have been answered to my satisfaction. I consent voluntarily to participate in this study.

|  |  |  |
| --- | --- | --- |
| Print name of participant: |  |  |
| Signature of participant: |  |  |
| Date: |  |  |
|  |  | dd/mmm/yyyy |

**Witness’ signature:** A witness’ signature and the patient’s thumbprint are required only if the patient is illiterate. In this case, a literate witness must sign. If possible, this person should be selected by the participant and should have no connection with the study team.

I have witnessed the accurate reading of the consent form to the potential participant, who has had the opportunity to ask questions. I confirm that the participant has given consent freely.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Print name of witness: |  |  |  | and thumbprint of participant: |
| Signature of witness: |  |  |  |  |
| Date: |  |  |  |  |
|  |  | dd/mmm/yyyy |  |  |

**Investigator’s signature:**

I have accurately read or witnessed the accurate reading of the consent form to the potential participant, who has had the opportunity to ask questions. I confirm that the participant has given consent freely.

|  |  |  |
| --- | --- | --- |
| Print name of investigator: |  |  |
| Signature of investigator: |  |  |
| Date: |  |  |
|  |  | dd/mmm/yyyy |

A copy of this informed consent form has been provided to the participant. \_\_\_\_\_ (initials of the principal investigator or assistant).

**Example of an informed consent form for parents or guardian of prospective children or minors participants**

This informed consent form is for parents or guardians of children aged from 12 to 18 year who attend ----------------------- Upazila Health Complex, ------------------------- district, who have been invited to participate in a study to evaluate the efficacy Artemether-lumefantrine/ dihydroartemisinin piperaquine for the treatment of uncomplicated falciparum malaria.

|  |  |  |
| --- | --- | --- |
| Name of principal investigator: |  | Prof Dr. Md. Nazmul Islam |
| Name of organization: |  | Director, Disease Control and Line Director, CDC |
| Name of sponsor: |  | Ministry of Health and Family Welfare, Bangladesh |
| Name of proposal and version: |  | Efficacy and safety of artemether-lumefantrine and dihydroartemisinin piperaquine for the treatment of uncomplicated *Plasmodium falciparum* malaria in Alikadam Upazila of Bandarban district, Lama Upazila of Bandarban district and Baghaichari Upazila of Rangamati districts, Bangladesh. Version 1 |

This informed consent form has two parts:

1. Information sheet (to share information about the study with you)
2. Certificate of consent (for signatures if you agree to take part)

You will be given a copy of the full informed consent form.

**Part I: Information sheet**

My name is Prof Dr. Md. Nazmul Islam, and I work for the Ministry of Health and Family Welfare. We are doing a study on the treatment of malaria. Malaria is a dangerous disease; however, it can be treated with medicine. The purpose of this study is to verify that the medicine, called (Coartem™), and Dihydroartemisinin piperaquine, are still effective for curing malaria.

We are inviting aged more than 6 months living in this area to take part in this study.

I am going to give you information and invite you to consent to have your child participate in this study. Before you decide whether you agree for your child to participate, you can talk to anyone you feel comfortable with. There may be some words that you do not understand. Please ask me to stop as we go through the information, and I will take time to explain. If you have questions later, you can ask me, the study doctor or the staff.

Your decision to have your child participate in this study is entirely voluntary. It is your choice whether to participate or not. Whether you choose to participate or not, all the services your child receives at this clinic will continue and nothing will change. If you choose your child should not participate in this project, we will offer the treatment that is routinely provided in this clinic for malaria: artemether-lumefantrine (Coartem™). You may change your mind later and stop participating even if you agreed earlier.

Your child will receive 6 doses (for artemether lumefantrine) or 3 doses (dihydroartemisinin piperaquine) of medicine over 3 days. The medicine, artemether-lumefantrine/dihydroartemisinin piperaquine, is recommended by the Ministry of Health and Family Welfare. As the parasites that cause malaria can become resistant to the medicine, the Ministry regularly does studies to make sure the medicine is still working. The medicine is made by Novartis pharma AG, Basel Switzerland; it is produced with the trade name: Coartem™. Another medicine dihydroartemisinin piperaquine is made by ---------You should know that like other antimalarial medicines, it may cause some side-effects such as: loss of appetite, nausea, vomiting, abdominal pain, diarrhea, dizziness, headache, joint and muscle pain. These effects are usually minor and resolve quickly.

In the event we find that the medicine is not working, we will use what is called ‘rescue medicine’. This medicine is called artesunate-mefloquine is given over 3 days. You should know that this medicine, like other antimalarial medicines, may cause some side-effects such as: loss of appetite, nausea, vomiting, abdominal pain, diarrhea, dizziness, and temporary deafness. These side effects are usually minor and resolve quickly.

The study will take place over 28/42 days. During that time, your child will have to come to the health facility for 1 hour each day for the first 3 days or remain hospitalized for first 3 days depending on the situation and then every week for 4/6 weeks according to the scheduled dates given to you. At the end of 4/6 weeks, the study will be finished. At each visit, your child will be examined by a physician. You may stay with your child during each of the visits and during the procedures.

Today, we will take blood and urine for testing and your child will receive the first dose of treatment.

On the

* 2nd visit: you will receive the 2nd dose of treatment plus a blood test;
* 3rd visit: you will receive the 3rd dose of treatment plus a blood test;
* 4th, 5th, 6th, 7th, 8th, 9th and 10th visits, you will have a blood test.

For the blood test, a small amount of blood, equivalent of 5 drops, will be taken from your child’s fingertip or heel. Your child may experience a bit of pain or fear when the finger or the heel is pricked. The pain should disappear within 1 day. The blood will be dropped onto a slide and a small piece of paper. The blood samples will only be used to study the malaria in your child’s blood.

The examination of some of the blood samples will only be done after the study and it will not affect the success of the treatment. Nothing else will be done with the blood. The blood samples will be destroyed after the study when no more verification of the information collected is needed.

If you do not attend the scheduled visit, our health staff will visit you at home.

As already mentioned, this medicine may have some minor side effects. It is also possible that it may cause some problems that we are not aware of; however, we will follow your child closely and keep track of these effects, if they arise, and of any other problems. We will give you a telephone number to call if you notice anything out of the ordinary or if you have concerns or questions. You can also bring your child to this health facility at any time and ask to see (give name of nurse, doctor). If your child experiences side-effects, we may use some other medicine, free of charge, which will help to reduce the symptoms or reactions, or we may stop one or more of the medicines. If this is necessary we will discuss it together. You and your child will always be consulted before we move to the next step.

Your child’s participation will help us to make sure the medicine is still working, and this will benefit society and future generations. If you decide to participate in this study, the malaria treatment and/or any illnesses related to malaria will be given at no charge to you. We will give you BDT 600 to pay for your travel expenses to the clinic for every visit and a bednet.

We will not share the identity of participants in the study with anyone. The information that we collect from this study will be kept confidential. Any information collected about your child will have a number on it instead of your child’s name. Only the study team members will know what the number is, and we will lock that information up.

We will share the knowledge that we get from this study with you before it is made available to the public. Confidential information will not be shared. There will be small meetings in the community, and these will be announced. Afterwards, we will publish the results and make them available so that other interested people may learn from our study.

This proposal has been reviewed and approved by Bangladesh Medical Research Council (BMRC). This is a committee that makes sure that study participants are protected from harm. If you wish to find about more about the institutional review board, you may contact (name, address, telephone number).

**Part II: Certificate of consent**

I have been invited to have my child participate in a study of a medicine used to treat malaria.

I have read the above information, or it has been read to me. I have had the opportunity to ask questions, and any questions that I have asked have been answered to my satisfaction. I consent voluntarily to my child’s participation in this study.

|  |  |
| --- | --- |
| Print name of participant: |  |
| Print name of parent or guardian: |  |
| Signature of parent or guardian: |  |
| Date: |  |
|  | dd/mmm/yyyy |

**Witness’ signature:** A witness’ signature and the thumbprint of the participant’s parent or guardian are required only if the parent or guardian is illiterate. In this case, a literate witness must sign. If possible, this person should be selected by the participant’s parent or guardian and should have no connection with the study team.

I have witnessed the accurate reading of the consent form to the potential participant’s parent or guardian, who has had the opportunity to ask questions. I confirm that the participant’s parent or guardian has given consent freely.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Print name of witness: |  |  |  | and thumbprint of parent or guardian: |
| Signature of witness: |  |  |  |  |
| Date: |  |  |  |  |
|  |  | dd/mmm/yyyy |  |  |

**Investigator’s signature:**

I have accurately read or witnessed the accurate reading of the consent form to the potential participant’s parent or guardian, who has had the opportunity to ask questions. I confirm that the participant’s parent or guardian has given consent freely.

|  |  |  |
| --- | --- | --- |
| Print name of investigator: |  |  |
| Signature of investigator: |  |  |
| Date: |  |  |
|  |  | dd/mmm/yyyy |

A copy of this informed consent form has been provided to participant’s parent or guardian. \_\_\_\_\_ (initials of the principal investigator/assistant).

An informed assent form will \_\_\_\_\_ or will not \_\_\_\_\_ be completed.

**Example of an informed assent form**

This informed assent form is for children aged between 12 years and 18 years who attend -------------------------- Upazila Health Complex, ----------------------------- district and who have been invited to participate in a study designed to evaluate the efficacy of Artemether-lumefantrine/dihydroartemisinin piperaquine for the treatment of uncomplicated falciparum malaria.

|  |  |  |
| --- | --- | --- |
| Name of principal investigator: |  | Prof Dr. Md. Nazmul Islam |
| Name of organization: |  | Director, Disease Control and Line Director, CDC |
| Name of sponsor: |  | Ministry of Health and Family Welfare, Bangladesh |
| Name of proposal and version: |  | Efficacy and safety of artemether-lumefantrine and dihydroartemisinin piperaquine for the treatment of uncomplicated *Plasmodium falciparum* malaria in Alikadam Upazila of Bandarban district, Lama Upazila of Bandarban district and Baghaichari Upazila of Rangamati districts, Bangladesh. Version 1 |

This informed assent form has two parts:

1. Information sheet (to share information about the study with you)
2. Certificate of assent (for signatures if you agree to take part)

You will be given a copy of the full informed assent form.

**Part I. Information sheet**

My name is Prof Dr. Md. Nazmul Islam, and I work for the Ministry of Health and Family Welfare t. We are doing a study on the treatment of malaria. Malaria is a dangerous disease; however, it can be treated with medicine. The purpose of this study is to verify that the medicine, called Artemether-lumefantrine (Coartem™), and Dihydroartemisinin piperaquine, are still effective for curing malaria.

We are inviting all adults and children aged more than 6 months living in this area to take part in this study.

I am going to give you information and invite you to participate in this study. You can choose whether you want to participate. We have discussed this study with your parent(s) or guardian, and they know that we are also asking you for your agreement. If you decide to participate in the study, your parent(s) or guardian also have to agree. If you do not wish to take part in the study, you do not have to, even if your parents have agreed. It is your choice. If you decide not to participate, nothing will change; this is still your clinic. Even if you say ‘Yes’ now, you can change your mind later and it will still be okay. You may discuss anything in this form with your parents or friends or anyone else you feel comfortable talking to. There may be some words you do not understand or things that you want me to explain more because you are interested or concerned. Please ask me to stop at any time, and I will take time to explain.

**Interviewer:** I have checked with the child, and he or she understands that participation is voluntary. \_\_\_\_\_ (initials)

You will receive 6 doses (for artemether lumefantrine) or 3 doses (dihydroartemisinin piperaquine) of medicine over 3 days. The medicine, artemether-lumefantrine/dihydroartemisinin piperaquine, is recommended by the Ministry of Health and Family Welfare. The Ministry regularly conducts studies to make sure the medicine is still working. The medicine is made by Novartis pharma AG, Basel Switzerland; it is produced with the trade name Coartem™. Another medicine dihydroartemisinin piperaquine is made by ---------This medicine is known to be very effective, but you should know that it has some minor side-effects: loss of appetite, nausea, vomiting, abdominal pain, diarrhea, dizziness, headache, joint and muscle pain.

The study will take place over 28/42 days. During that time, you will have to come to the health facility for 1 hour each day for the first 3 days or remain hospitalized for first 3 days depending on the situation and then every week for 4/6 weeks according to the scheduled dates given to you. At the end of 4/6 weeks, the study will be finished. At each visit, you will be examined by a physician.

A small amount of blood equivalent of 5 drops, will be taken from your finger, today and once at each visit during the follow-up. You may experience a bit of pain or fear when your finger is pricked. The blood will be dropped onto a slide and a small piece of paper. The blood samples will be used to study the malaria in your blood.

The examination of some of the blood samples will be done after the study and it will not affect the success of the treatment. Nothing else will be done with your blood.

**Interviewer:** I have checked with the child, and he or she understands the procedures. \_\_\_\_\_ (initials)

The medicine can have some unwanted effects or some effects that we are not currently aware of; however, we will follow you closely and keep track of any unwanted effects, if they arise, or any other problems. If anything unusual happens to you, we need to know, and you should feel free to call us any time with your concerns or questions. If you get sick or have concerns or questions between scheduled visits to clinic, you should let me or the staff nurse know. You do not have to wait for a scheduled visit. We have also given your parents information about what to do if you are hurt or get sick during the study.

**Interviewer:** I have checked with the child, and he or she understands the risks and discomforts. \_\_\_\_\_ (initials)

Your participation will help us to make sure the medicine is still working, and this will benefit society and future generations. If you decide to participate in this study, the malaria treatment and/or any illnesses related to malaria will be given at no charge to you.

Because you live quite far from the clinic, we will give your parents or guardian enough money to pay for the trip here and back and a bednet.

**Interviewer:** I have checked with the child, and he or she understands the benefits. \_\_\_\_\_ (initials)

We will not tell other people that you are participating in this study, and we will not share information about you with anyone who does not work in the study. Information about you that will be collected from the study will be put away, and no one but the study team will be able to see it. Any information about you will have a number on it instead of your name. Only the study team will know what your number is, and we will lock that information up.

When we have finished the research, I will sit down with you and your parent or guardian and tell you about what we learnt. Afterwards, we will be telling more people, scientists and others, about the study and what we found. We will do this by writing and sharing reports and data and by going to meetings with people who are interested in the work we do.

You can ask me questions now or later. You can ask the nurse questions. I have written a number and address where you can reach us or, if you are nearby, you can come and see us. If you want to talk to someone else whom you know, like your teacher, doctor or auntie, that is okay too.

**Part II: Certificate of assent**

I have been invited to participate in a study of the efficacy of an antimalarial medicine. I have read this information (or had the information read to me), and I understand it. I have had my questions answered and know that I can ask questions later if I have them. I agree to take part in the study. \_\_\_\_\_ (initials)

or I do not wish to take part in the study and I have not signed the assent below. \_\_\_\_\_ (initials)

**Child’s signature (only if the child assents):**

|  |  |  |
| --- | --- | --- |
| Print name of child: |  |  |
| Signature of child: |  |  |
| Date: |  |  |
|  |  | dd/mmm/yyyy |

**Witness’ signature:** A witness’ signature and the child’s thumbprint are required only if the child is illiterate. In this case, a literate witness must sign. If possible, this person should be selected by the participant and should have no connection with the study team.

I have witnessed the accurate reading of the assent form to the potential participant, who has had the opportunity to ask questions. I confirm that the participant has given consent freely.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Print name of witness: |  |  |  | and thumbprint of the child or minor: |
| Signature of witness: |  |  |  |  |
| Date: |  |  |  |  |
|  |  | dd/mmm/yyyy |  |  |

**Investigator’s signature:**

I have accurately read or witnessed the accurate reading of the assent form to the potential participant, who has had the opportunity to ask questions. I confirm that the participant has given consent freely.

|  |  |
| --- | --- |
| Print name of investigator: |  |
| Signature of investigator: |  |
| Date: |  |
|  | dd/mmm/yyyy |

A copy of this informed assent form has been provided to the participant. \_\_\_\_\_ (initials of the principal investigator or assistant).

**Example of a consent statement for a pregnancy test**

I have been invited to participate in a study on the medicine used to treat malaria. I have been asked to supply a specimen of urine at the first visit and at day 28/42 or on the day of withdrawal from the study, all of which will be used for pregnancy testing. I understand that the results of the tests will be kept fully confidential and anonymous. I understand that I must avoid becoming pregnant during the study because the medicine I will be taking may be dangerous for my child. I have discussed the different methods of birth control with my doctor, and I have been recommended Barrier contraceptive devices. I understand that if the test is positive, I will not be eligible to participate in this study.

**Participant’s signature:**

I accept to be tested. \_\_\_\_\_ (participant’s initials) or

I do not want to be tested, and I have notsigned the consent form below. \_\_\_\_\_ (participant’s initials)

|  |  |  |
| --- | --- | --- |
| Print name of participant: |  |  |
| Signature of participant: |  |  |
| Date: |  |  |
|  |  | dd/mmm/yyyy |

**Witness’ signature:** A witness’ signature and the thumbprint of the participant are required only if the participant is illiterate. In this case, a literate witness must sign. If possible, this person should be selected by the participant and should have no connection with the study team.

I have witnessed the accurate reading of the consent form to the potential participant, who has had the opportunity to ask questions. I confirm that the participant has given consent freely.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Print name of witness: |  |  |  | and thumbprint of the participant: |
| Signature of witness: |  |  |  |  |
| Date: |  |  |  |  |
|  |  | dd/mmm/yyyy |  |  |

**Investigator’s signature:**

I have accurately read or witnessed the accurate reading of the consent form to the potential participant, who has had the opportunity to ask questions. I confirm that the participant has given consent freely.

|  |  |  |
| --- | --- | --- |
| Print name of investigator: |  |  |
| Signature of investigator: |  |  |
| Date: |  |  |
|  |  | dd/mmm/yyyy |

A copy of this consent statement has been provided to participant. \_\_\_\_\_ (initials of the principal investigator or assistant).

1. WHO. Assessment and monitoring of antimalarial drug efficacy for the treatment of uncomplicated falciparum malaria. Geneva, World Health Organization, 2003 (WHO/RBM/HTM/2003.50) (<http://www.who.int/malaria/resistance>). [↑](#footnote-ref-2)
2. WHO. Method for surveillance of antimalarial drug efficacy. Geneva, World Health Organization, 2009 (<http://www.who.int/malaria/resistance>). [↑](#footnote-ref-3)
3. 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>). [↑](#footnote-ref-4)
4. 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>). [↑](#footnote-ref-5)
5. WHO/GMP. Standardized data entry for therapeutic efficacy tests. Geneva, World Health Organization (<http://www.who.int/malaria/resistance>). [↑](#footnote-ref-6)
6. World Health Organization. Severe falciparum malaria. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, 2000, 94(Suppl. 1):1–90. [↑](#footnote-ref-7)
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>). [↑](#footnote-ref-8)
8. http://www.who.int/rpc/research\_ethics/en/ [↑](#footnote-ref-9)