**Evaluating the efficacy of Chloroquine compared to Artemisinin Combination Therapy for the treatment of *Plasmodium vivax* infections**

DRAFT GENERIC PROTOCOL

vs 1.0

|  |  |
| --- | --- |
| **Title** | **Evaluating the efficacy of Chloroquine compared to Artemisinin Combination Therapy for the treatment of *Plasmodium vivax* infections** |
| **Protocol Number** | *--to be added--* |
| **Methodology** | Randomized controlled open labelled trial |
| **Study Duration** | Each patient will be followed for 42 days |
| **Country** | *--to be added--* |
| **Study Centres** | *--to be added--* |
| **Primary Objective** | To assess the therapeutic efficacy of Chloroquine (CQ) compared to Artemisinin Combination Therapy (ACT) for the treatment of *P. vivax* infections. |
| **Secondary Objective** | To quantify the prevalence and severity of G6D deficiency in patients presenting with *P. vivax* |
| **Number of subjects** | *--to be added--* |
| **Inclusion Criteria** | * Mono infection of *P. vivax* at the screening slide * Age >6 months * Weight ≥ 5.0 kg * Axillary temperature ≥ 37.5º C or tympanic temperature >38º C or history of fever during the previous 48 hours * Patient or caregiver consent to enrolment and agree to sampling and return visits |
| **Exclusion Criteria** | * Female participant who is pregnant or lactating * Inability to tolerate oral treatment. * Signs/symptoms indicative of severe/complicated malaria or warning signs requiring parenteral treatment * Known hypersensitivity or allergy to the study drugs |
| **Study design** | This study is designed as a randomized open label clinical trial to evaluate clinical and parasitological responses after treatment of uncomplicated *P. vivax* malaria infection. Patients with *P. vivax* infections, meeting the study criteria will be enrolled into the trial, randomized to one of the treatment arms and followed up for 42 days. All drug administration will be directly observed. Active follow up will be done on a weekly basis. |
| **Duration of administration** | CQ for 3 days  ACT for 3 days |
| **Endpoints** | Recurrent parasitaemia within 42 days follow up (treatment failure) or Adequate Clinical and Parasitological Response (ACPR) |
| **Date of first patient enrolled** | *--to be added--* |

Contents

[1. Background 3](#_Toc379462581)

[2. Trial Objective(s) 3](#_Toc379462582)

[3. Investigational Plan 3](#_Toc379462583)

[3.1 Study Design 3](#_Toc379462584)

[3.2 Study Site 4](#_Toc379462585)

[3.3 Duration of Study 4](#_Toc379462586)

[3.4 Trial Population 4](#_Toc379462587)

[3.5 Inclusion criteria 4](#_Toc379462588)

[3.6 Exclusion criteria 4](#_Toc379462589)

[3.7 Randomisation and Treatment Allocation 5](#_Toc379462590)

[3.8 Study treatment 5](#_Toc379462591)

[3.9 Trial Procedures 6](#_Toc379462592)

[4. Quality assurance 8](#_Toc379462593)

[5. Assessment of variables and statistical methodology 8](#_Toc379462594)

[5.1 Sample size determination 8](#_Toc379462595)

[5.2 Efficacy Endpoints 8](#_Toc379462596)

[5.3 Definitions of Failure 9](#_Toc379462597)

[5.4 Recurrent Parasitaemia 9](#_Toc379462598)

[5.5 Data Entry and Protection 10](#_Toc379462599)

[5.6 Statistical Analytical Plan 10](#_Toc379462600)

[5.7 Safety and tolerability 11](#_Toc379462601)

[6. Ethical Issues 11](#_Toc379462602)

[ANNEX I 14](#_Toc379462603)

[ANNEX II 15](#_Toc379462604)

[ANNEX III 16](#_Toc379462605)

[ANNEX IV 17](#_Toc379462606)

[ANNEX V 18](#_Toc379462607)

[ANNEX VI 19](#_Toc379462608)

[ANNEX VII 20](#_Toc379462609)

[ANNEX VIII 22](#_Toc379462610)

[ANNEX IX 24](#_Toc379462611)

[ANNEX X 25](#_Toc379462612)

[ANNEX XI 26](#_Toc379462613)

# Background

*Plasmodium vivax* is a major public health burden, causing an estimated 72 to 390 million clinical cases of malaria each year. Vivax malaria is recognised as an important cause of morbidity particularly in young children interfering with education and development. It causes abortion and intrauterine growth retardation and in recent years severe and fatal disease has been reported increasingly. Chloroquine has been the primary treatment for blood stages of vivax malaria for almost 60 years, however evidence is gathering for its declining efficacy across much of the vivax endemic world. Understanding the extent and regional distribution of Chloroquine Resistant (CQR) vivax malaria is critical to optimize treatment guidelines, and reduce the risk of recurrent malaria. In many areas Artemisinin Combination Therapy (ACT) has already been adopted for the treatment of *P. falciparum* and mixed infections. A unified treatment policy of *P. falciparum* and *P. vivax* in regions where both species are present has practical implications that can improve malaria control strategies. Clinical trials are needed to quantify the degree of Chloroquine susceptibility and where this is declining the efficacy of suitable alternative treatment regimens.

# 2. Trial Objective(s)

The primary objective of the comparative trial is to assess the therapeutic efficacy of Chloroquine (CQ) compared to Artemisinin Combination Therapy (ACT) for the treatment of *P. vivax* infections.

The secondary objective is to assess prevalence as well as degree of severity of G6PD deficiency among the enrolled patient population.

**Specific Aims**

* To determine the comparative therapeutic efficacy of CQ and ACT against *P. vivax*.
* To determine the tolerability and adverse reactions of CQ and ACT.
* To assess gametocyte carriage following treatment with CQ and ACT after infection with *P. vivax*.

# 3. Investigational Plan

### 3.1 Study Design

This study is designed as a randomized open label clinical trial to evaluate clinical and parasitological responses after treatment of *P. vivax* malaria infection. Symptomatic patients with *P. vivax* mono-infections, meeting the study criteria will be enrolled into the trial, randomized to one of the treatment arms and followed up for 42 days. All drug administration will be directly observed. Active follow up will be done on a weekly basis.

### 3.2 Study Site

*--Add details about the study site--*

### 3.3 Duration of Study

Individual patients will be followed for 42 days after the after initial treatment (minimum 28 days if 42 days are not possible). The total study period will depend on the speed of recruitment.

Anticipated time required for patient enrolment: *X* months

Duration of individual patient's participation: 42 days (or 28 minimum)

Total duration of trial: *X* months

### 3.4 Trial Population

The target population includes patients in whom schizontocidal treatment is needed – symptomatic malaria cases presenting to a healthcare post. Older patients may have a degree of immunity, which may improve efficacy. Young children are at greatest risk and should therefore be included if possible. Confirming the relationship of efficacy in different ages is important.

### 3.5 Inclusion criteria

1. Mono-infection of *P. vivax*

*--Chloroquine can no longer be included for almost any site for P. falciparum, for comparison of ACTs, consider including mixed infections--*

1. Age >6 months
2. Weight ≥ 5.0 kg
3. One of the following: Axillary temperature ≥ 37.5º C or tympanic temperature >38º C or history of fever during the previous 48 hours
4. Patient or caregiver consent to enrolment and agree to sampling and return visits

### 3.6 Exclusion criteria

1. General danger signs or symptoms of severe malaria (Annex II)

2. Signs or symptoms of severe malnutrition, defined as weight-for-age ≤ 3 standard deviations below the mean (NCHS/WHO normalized reference values) (Annex VI)

3. Slide confirmed infection with any other *Plasmodium species* (incl. mixed infections)

4. Anaemia, defined as Hb <7g/dl

5. Known hypersensitivity to any of the drugs being evaluated

6. Presence of fever due to illness other than malaria

7. History of serious and/or chronic medical condition (cardiac, renal, hepatic diseases, sickle cell disease, HIV/AIDS)

8. Pregnancy or breastfeeding

9. Regular use of medication that may interfere with antimalarial pharmacokinetics

### 

### 3.7 Randomisation and Treatment Allocation

*-Define randomization method-*

Once the patient has a confirmed diagnosis of malaria, has fulfilled all the inclusion criteria, has none of the exclusion criteria and has given written informed consent to participate, he/she will be allocated the next code of the study.

Randomization will be carried out in groups of 20, and each code given a sealed opaque envelope which will contain that patient’s treatment group and which will only be opened when a patient has been allocated a study code number.

Once the patient has been enrolled and given his/her subject number, the participant is considered in the study whether or not the protocol is followed correctly thereafter i.e. included in the analyses on an intention to treat basis. The intake of all doses of the study drug will be supervised.

### 3.8 Study treatment

Patients will be assigned to receive either CQ or an ACT. All doses will be given under supervision. Patients will be observed for 60 minutes after treatment for adverse reactions or vomiting. The exact time of tablet administration will be recorded. Those patients vomiting their medication within the first 30 minutes will receive a repeat full dose; those vomiting from 30-60 minutes will receive half dose.

Dosing for CQ is detailed in Annex V.

**Rescue Medication.** If deterioration of the medical condition occurs, indicating failure to respond, then rescue medication should be initiated according to the investigator's clinical judgement.

This treatment will be administered orally unless the patient has persistent vomiting, in which case he/she will be referred to the nearest hospital for IV treatment.

The exact rescue regimen and route of administration must be recorded in the Case Record Form (CRF) on the concomitant medication page under "Anti-malarial medication", together with the start and end dates of the rescue medication.

**Radical cure**. Primaquine treatment will be delayed until the end of the follow up and then given as recommended by the national guidelines. The rationale for this is that early primaquine has schizontocidal activity and will mask early indication of reduced drug susceptibility of Chloroquine or ACT.

**Concomitant Treatment.** At trial start, any anti-malarial medication which was given in the last 4 weeks should be documented in the CRF under recent episodes of malaria.

Patients who are taking regular medication at trial entry for conditions other than malaria, e.g. asthma, hypertension, need to have this documented under "Other previous/current medication (in the past 30 days)" and should continue to take their medication in the normal way. Any new additional medications taken during the 42 day trial period for whatever reason must be documented on the concomitant medication page (e.g. antibiotics for inter-current infection, anti-emetics, anti-pyretics etc.). Each new medication needs to be documented only once.

Patients who prematurely discontinue trial medication, or who fail to respond to trial medication and receive other anti-malarial therapy should have this documented with start and end date on the concomitant medication page under "Anti‑malarial medication". Drugs with antimalarial activity should be avoided (Annex III).

### 3.9 Trial Procedures

See also Annex VII

**3.9.1 Enrolment**

**At enrolment a standard physical examination** and symptom questionnaire, including medical history, demographic information will be performed (day 0 pre-dosing).

**A urine pregnancy test** will be conducted on all women aged 13-49 during the screening process.

**On admission** a finger prick for blood smear will be performed. If the smear is positive for *P. vivax* then a venous sample will be requested from all patients; 5ml of whole blood will be taken from those agreeing to be venesected and collected into sterile vacutainer tubes containing potassium EDTA.

**3.9.1 Visit Procedures**

Patients will be monitored daily during the first week by blood microscopy until aparasitaemic. Patient will then be asked to attend the clinic weekly (or visited by a home visitor) where temperature measurements will be taken and blood microscopy performed.

At each visit a symptom questionnaire will be completed, vital signs recorded, and any adverse event documented. A finger prick sample will also be collected for blood film +/- measurement of haemoglobin concentration.

On day 7 a second bleed (250 µl capillary blood or 5ml venous blood) will be collected for measurement of drug concentration.

If any parasitaemia is detected during follow up then a further sample (250 µl capillary blood or 5ml venous blood), will be collected prior to retreatment.

Patients are advised to return on any day during the follow-up period if symptoms consistent with malaria occur (i.e. fever). In particular, parents or guardians are instructed to bring children to the study centre at any time if they show any sign of danger (unable to drink or breastfeed, severe vomiting, convulsions, lethargic or unconscious, unable to sit or stand, difficulty to breath), if fever persists or in case of general and severe other sickness.

#### 3.9.3 Laboratory Evaluation

The schedule of sample collection is outlined in Annex IV.

**Microscopy**: All baseline slides and any symptomatic patients will have their slide re-read by an expert microscopists. Blood smears with discordant results (differences between the two microscopists regarding species diagnosis, parasite density of > 50% or regarding the positivity in general) will be re-examined by a third, independent microscopist, and parasite density will be calculated by averaging the two closest counts. Slides for microscopy will be collected upon enrollment and on all follow up days as well as on any unscheduled visit days.

Please refer for more details to the WWARN toolkit for blood smear preparation and reading.

**Haemoglobin/Haemataocrit Concentration** will be measured during the screening process, on days 7, 28 and at any recurrence.

*--add details on methods used (e.g. Hemocue™)—*

**Molecular testing**:Parasite DNA will be collected at baseline, and the time of recurrent parasitaemia for molecular analysis. It is also possible to use PCR to confirm parasitaemia and detect subpatent clearance on days 1 to 3.

*--The volume of blood collected will depend on factors such as cold storage facilities (required for blood collected in tubes), costs, and ethical restrictions. As well as intended for distinct, molecular studies. The volume of blood should be recorded so that assessment of subpatent parasitaemia can be standardised.*

*--Blood collected by finger prick (collected onto filter paper blood spot (Whatmann 3M) or Microtainer) or venesection. EDTA is usually preferred for molecular analysis.  
--Define which tests will be done and add where the test will be done. It is recommended to use the consensus markers for genotyping from the Asia Pacific Malaria Elimination Network (APMEN) partners for better comparison across different sites[[1]](#footnote-1).*

**Measurement of Drug Concentration**: Blood collected on day 7 and day of recurrent parasitaemia to measure drug concentrations of CQ and the long acting partner drug of ACTs.

*--add where the test will be done. LiHep are preferred for drug concentrations, but plasma from EDTA or filter spots are also acceptable for some drugs (this needs confirmation with the Pharmacokinetics laboratory).*

**Details of G6PD testing**:

*--add how/where the test will be done.*

**Details of in Vitro testing**: Venous blood collected at day 0 or the day of recurrence will be used for ex vivo drug susceptibility testing.

*--add how/where the test will be done.*

#### 3.9.4 Discontinuation and Protocol Violation

Patients meeting any of the following criteria will be withdrawn from the study:

* Withdrawal of consent
* Failure to complete the treatment
* Vomiting of both initial and re-administration doses of treatment
* Severe side-effects necessitating hospitalization
* Progression to severe malaria (Annex II)
* Occurrence during the follow-up of concomitant disease that interferes with a clear classification of the treatment outcome
* Need for or receipt of blood transfusion
* Detection of another malaria species infection during the follow-up
* Antimalarial (or antibiotics with antimalarial activity) treatment administered by a third party or self-medication with antimalarial
* Erroneous inclusion of a patient outside of the inclusion/exclusion criteria
* Misclassification of a patient due to a laboratory error (parasitaemia) leading to the administration of the rescue treatment

# 4. Quality assurance

Site monitoring visits will be scheduled on a regular basis. During these visits, information recorded on the case report forms will be verified against source documents (e.g. laboratory records and clinic registers). After the CRFs are collated at the end of the trial, they will be reviewed for completeness and accuracy. The data are entered into a database, where specially designed computer checks are used to identify selected protocol violations and data errors. If necessary, requests for clarifications or corrections will be sent to the field site.

All blood films on admission will be read at the study site as well as by a senior microscopist at a coordinating centre. A random selection of 10% of all blood films analysed at the study site will also be collected and re-read by an independent observer.

# 5. Assessment of variables and statistical methodology

### 5.1 Sample size determination

*--adjust as needed, this depends on comparison of drugs, estimated efficacy and assumed lost to follow up rate--*

Estimated adjusted cure rates of >95% for ACT apply when drug administration is fully supervised. Assuming a similar efficacy a sample size of 200 patients in each arm will determine with 95% confidence the cure rate within ±3% units of the true cure rate (allowing for 30% loss to follow up). In addition this sample size will allow detecting (with 80% power and 90% confidence) a reduction in efficacy of Chloroquine greater than 9%.

### 5.2 Efficacy Endpoints

**Primary Endpoint:** The recurrence of *P. vivax* parasitaemia during the follow up

**Secondary Endpoints:**

* Proportion of patients with parasitaemia on day 1, 2 and 3
* Any recurrent parasitaemia irrespective of species
* Proportion of patients with anaemia (Hb<7g/dl) on day 7

### 5.3 Definitions of Failure

See also Annex I.

**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 clinical failure**

* Danger signs or severe malaria in the presence of parasitaemia on any day between day 4 and day 42 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 42 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 42 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 42, 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.

### 5.4 Recurrent Parasitaemia

*P. vivax* infections that recur after drug treatment can have one of three aetiologies: either a recrudescence (same infection that was never cleared), reinfection with a different parasite or a relapse arising from dormant liver stage (hypnozoite).

Genotypic analysis can determine whether a recurrent parasitaemia is homologous to the initial infection. Recurrence of *P. vivax* genetically identical to the pre-treatment isolate can occur from either a true recrudescence of the initial infection or a relapse from hypnozoites generated from the prior blood stage infection; current molecular methods are unable to distinguish between these alternatives. However PCR adjusted efficacy can reduce the confounding effects of recurrent parasitaemias arising from new infection or relapse from a different strain.

Clinical studies of CQ sensitive parasites have demonstrated that if a total dose of 25mg/kg is well absorbed, then the first relapse should not be detectable for approximately 35 days following treatment, by which time the mean whole blood concentrations of CQ will have fallen to below 100ng/ml. Therefore, any *P. vivax* recurrence within 28 days raises suspicion of a CQR infection, although pharmacokinetic analysis is required to confirm adequate drug absorption and the ability of the parasite to grow in the presence of blood concentrations known to exceed the minimal inhibitory concentration (MIC) of a sensitive parasite. All patients with recurrence should have drug concentrations tested from filter paper or venous blood collected on the day of failure. Routine sampling of patients at day 7 can provide a useful surrogate of adequate absorption.

### 5.5 Data Entry and Protection

Data will be double entered into a custom-made database. Internal error checks and systematic error assessment will be developed to check for data entry discrepancies, invalid data ranges and overall consistency. All discrepancies will be resolved by reference to the original checked data collection forms.

Original data collection forms will be handled only by staff members and kept under locked storage until completely coded, checked and transported for data entry. Once data entry and cleaning are complete the original forms will be stored as long as appropriate.

### 5.6 Statistical Analytical Plan

The analysis of the 42 day cure rate will be performed both for the modified intention-to-treat (mITT) patient population (all randomised patients) and the evaluable patient population per protocol (PP). Patients are evaluable for the analysis of the 42 day cure rate if parasite counts are recorded up to Day 40 or the patient discontinues due to "unsatisfactory therapeutic effect" because of reappearance of parasites.

The mITT analysis also includes patients who discontinue before Day 40 due to reasons other than "unsatisfactory therapeutic effect" (e.g. this could include "adverse experience(s)" because of repeated vomiting). These patients will be counted in the mITT analysis as treatment failures regardless of their reason for discontinuation. Patients who had concomitant treatment with antibiotics which have an anti‑malarial effect will be excluded from the evaluable patients and included in the mITT.

Analyses will be performed using *–add software*-. For categorical variables percentages and corresponding 95% confidence intervals will be calculated using Wilson’s method. Proportions will be compared by calculating the 2 with Yates' correction or by Fisher's exact test as appropriate. Normally distributed continuous data will be compared by Student's t test and analysis of variance. Data not conforming to a normal distribution will be compared by the Mann-Whitney U test or Kruskal-Wallis analysis of variance. The association between 2 continuous variables will be assessed using Spearman’s rank correlation coefficient.

Parasite, fever and symptom clearance times and the resolution of other signs (anaemia [haematocrit <30%], hepatomegaly, splenomegaly), and the risk of treatment failure will all be evaluated by survival analysis calculated by Kaplan Meier method and compared by the Mantel-Haenszel log rank test.

### 5.7 Safety and tolerability

Safety and tolerability will be evaluated in detail on the basis of NIH/NCI Common Toxicity Criteria grades and deviations from laboratory normal ranges. Adverse experiences (AE) will be evaluated on the basis of their incidence, duration, severity and relationship to trial drug.

Safety and tolerability measurements will be summarised for the mITT patient population. The mITT population is defined for this purpose, as all randomised patients who received at least one dose of trial medication.

The incidence of adverse experiences will be tabulated by severity and trial period in which the AEs started (e.g. present at baseline (day 0), started after baseline). A separate summary for AEs which were felt to be related to trial drug by the investigator will be produced.

# 6. Ethical Issues

**Consent Process:** Study aim and procedures will be fully explained to participants and / or their caretakers. Written informed consent / assent will be collected prior to enrolment. If a participant or parent/guardian is illiterate, the consent form will be read to them and a thumbprint will be accepted as a legally effective signature. Right to withdraw at any time during the study participation will be explained. It will be emphasized that withdrawal will not result in any disadvantages.

*--Examples of Information sheet and consent forms can be found in Annex IIX, IX & X)—*

**Privacy of the individual:** Examinations will take place in a private room. Person specific data will be reported to the participant, treating medical staff and relevant study staff only.

**Confidentiality of data:** All collected personal data will be kept under lock and key away from the public and will at no time during or after the study period be made available to staff outside the core study team. Unique numerical identifiers will be used for data entry and blood samples. Decoding lists will be kept under lock and key under the direct responsibility of the principal investigator. Publications will only contain aggregate data.

**Notifying participant about their individual results:** On every visit participants or their legal guardians will be informed about the outcome of the malaria smear, haemoglobin level, and clinical assessments.

**Storage of specimens**

*--add as appropriate—*

ANNEXES

# ANNEX I

**Definition of Treatment Outcomes**

**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 42 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 42 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 42 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 42, 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.

# ANNEX II

**Signs or Symptoms Indicative of Severe Malaria**

* impaired consciousness, including unrousable coma (Blantyre Coma Score <5, GCS<15)
* prostration, i.e. generalized weakness so that the patient is unable to sit, stand or walk without assistance
* multiple convulsions: more than two episodes within 24h
* deep breathing and respiratory distress (acidotic breathing)
* acute pulmonary oedema and acute respiratory distress syndrome
* circulatory collapse or shock, systolic blood pressure
* < 80mm Hg in adults and < 50mm Hg in children
* acute kidney injury
* clinical jaundice plus evidence of other vital organ dysfunction
* Bleeding Disorder (Epistaxis, bleeding gums, frank haematuria)

For further reference see the Third Edition of the WHO publication “Management of severe malaria – A practical handbook”

<http://www.who.int/malaria/publications/atoz/9789241548526/en/index.html>

# ANNEX III

**Drugs with antimalarial activity that should not be used during the study**

* Chloroquine, amodiaquine
* quinine, quinidine
* Mefloquine, halofantrine, lumefantrine
* Artemisinin and its derivatives (artemether, arteether, artesunate, dihydroartemisinin)
* Proguanil, chlorproguanil, pyrimethamine
* Sulfadoxine, sulfalene, sulfamethoxazole, dapsone
* Primaquine
* Atovaquoneantibiotics: tetracycline\*, doxycycline, erythromycin, azythromycin, clindamycin, rifampicin, trimethoprim
* Pentamidine

\* Tetracycline eye ointments can be used.

# ANNEX IV

**Schedule of follow-up activities**

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **0** | **1** | **2** | **3** | **7** | **14** | **21** | **28** | **35** | **42** | **Day of recurrent parasitaemia** | **Any other additional visit** |
| Consent, Medical history, previous medication, Symptom physical exam | X |  |  |  |  |  |  |  |  |  |  |  |
| Pregnancy testing (females of child bearing age) | X |  |  |  |  |  |  |  |  |  |  |  |
| Treatment | X | X | X |  |  |  |  |  |  |  |  |  |
| Symptom Questionnaire and vital signs | X | X | X | X | X | X | X | X | X | X | X | X |
| Adverse Event Monitoring | X | X | X | X | X | X | X | X | X | X | X | X |
| Microscopy | X | X | X | X | X | X | X | X | X | X | X | X |
| Haemoglobin | X |  |  | X | X | X | X | X | X | X | X |  |
| Dried blood spot or venous blood for molecular testing | X |  |  |  |  |  |  |  |  |  | X |  |
| Dried blood spot or venous blood for drug concentration | X |  |  |  | X |  |  |  |  |  |  |  |
| G6PD testing | X |  |  |  |  |  |  |  |  |  |  |  |

# 

# ANNEX V

**Chloroquine Dosing Table (Tablets containing 150 mg Chloroquine base) for patients ≥20kg**

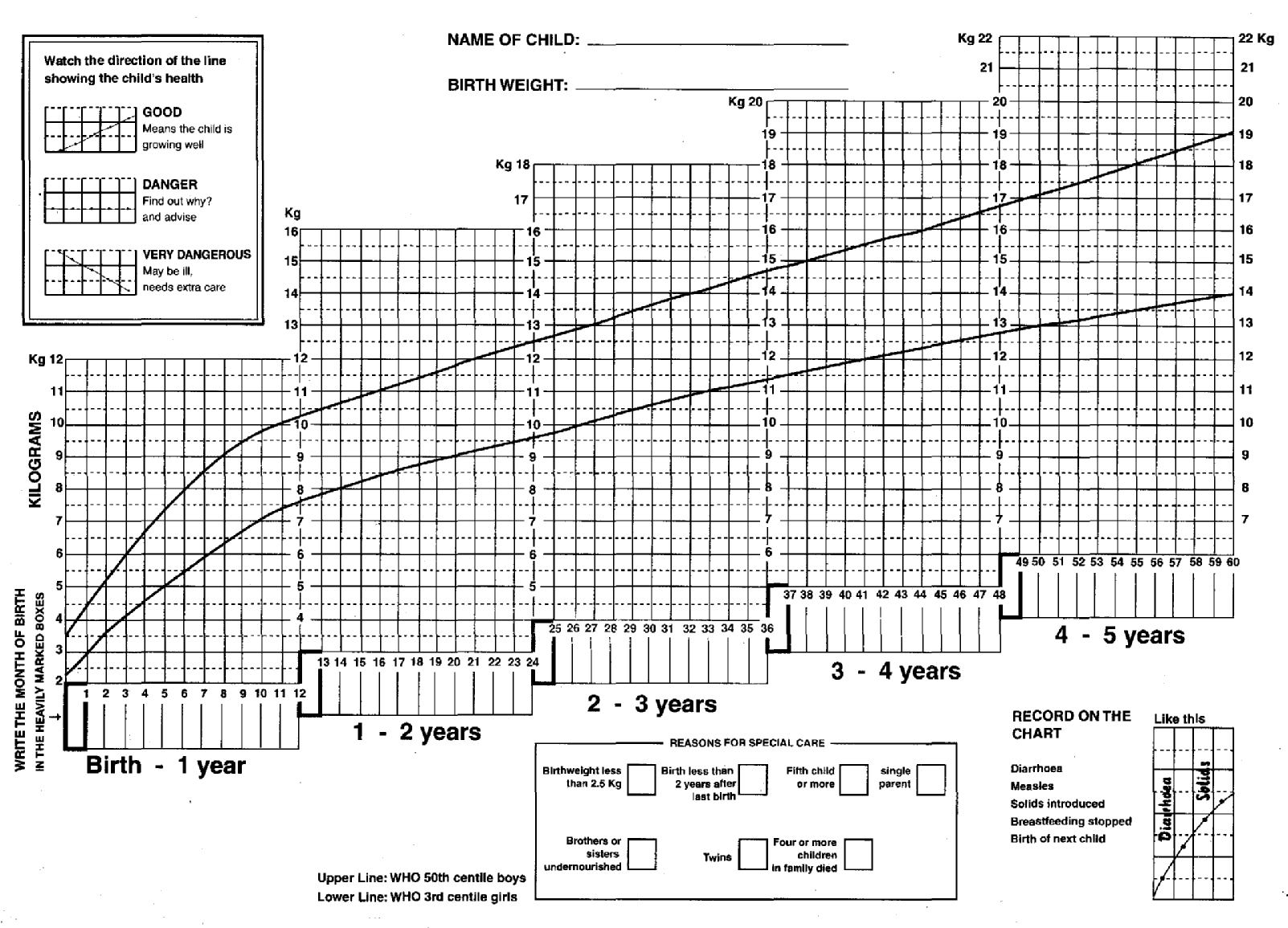
|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Weight**  **(kg)** | **Number of Tablets** | | | **Total mg/kg Dose** |
| **Day 0** | **Day 1** | **Day 2** |  |
| 20.0 – 21.9 | 1 ¼ | 1 ¼ | 1 | 24.0-26.3 |
| 22.0 – 22.9 | 1 ½ | 1 ½ | ¾ | 24.6-25.6 |
| 23.0 – 24.9 | 1 ½ | 1 ½ | 1 | 24.1-26.1 |
| 25.0 – 25.9 | 1 ½ | 1 ½ | 1 ¼ | 24.6-25.5 |
| 26.0 – 28.9 | 1 ¾ | 1 ¾ | 1 | 23.4-26.0 |
| 29.0 – 32.9 | 2 | 2 | 1 | 22.8-25.9 |
| 33.0 – 37.9 | 2 ½ | 2 ¼ | 1 ¼ | 24.7-28.4 |
| 38.0 – 43.9 | 2 ¾ | 2 ¾ | 1 ½ | 23.9-27.6 |
| 44.0 – 48.9 | 3 | 3 | 1 ½ | 23.0-25.6 |
| 49.0 – 53.9 | 3 ½ | 3 ¼ | 1 ¾ | 24.4-26.8 |
| 54.0 – 58.9 | 3 ¾ | 3 ½ | 2 | 24.2-26.4 |
| 59 + | 4 | 4 | 2 | ≥25.4 |

**Chloroquine Dosing Table (Syrup containing Chloroquine base 50 mg/5 ml ) for patients <20kg**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Weight**  **(kg)** | **Syrup in ml** | | | **Total mg/kg Dose** |
| **Day 0** | **Day 1** | **Day 2** |  |
| 5.0 - 6.9 | 5 | 5 | 2.5 | 18.12-25.0 |
| 7.0 – 9.9 | 7.5 | 7.5 | 5 | 20.2 -28.57 |
| 10.0 - 12.9 | 10 | 10 | 5 | 19.38-25.0 |
| 13.0 – 15.9 | 12.5 | 12.5 | 7.5 | 20.44-25.0 |
| 16.0 – 18.9 | 15 | 15 | 10 | 21.16-25.0 |
| 19.0 – 19.9 | 20 | 20 | 10 | 25.13-26.32 |

# ANNEX VI

**Weight for Height Chart for children under 5 years old**



# ANNEX VII

**Procedures after Enrolment**

**DAY 0**

* Allocation of Code and treatment group according to Randomization procedure
* Baseline Data:
  + History
  + Examination / Vital Signs
  + Adverse Effects
  + Concomitant Medication
* Drug Administration: Repeat if vomiting within an hour
* Blood sampling:
  + Repeat Thick and Thin film
  + Hb
  + G6PD
  + Sample for molecular work
  + Sample for drug levels

**DAY 1-2**

* Questionnaire:
  + Adverse Effects
  + Concomitant Medication
* Examination: Temperature / Vital Signs
* Blood sampling:
  + Blood Smear
* Drug Administration: Repeat if vomiting within an hour.

**DAY 3**

* Questionnaire:
  + Adverse Effects
  + Concomitant Medication
* Examination: Temperature / Vital Signs
* Blood sampling:
  + Blood Smear
  + Hb

**DAY 7**

* Questionnaire:
  + Adverse Effects
  + Concomitant Medication
* Examination: Temperature/Vital Signs
* Blood sampling:
  + Blood Smear
  + Hb
  + Sample for drug concentration

**DAY 14, 21, 28, 35, 42**

* Questionnaire:
  + Adverse Effects
  + Concomitant medication
* Examination: Temperature/Vital Signs
* Blood sampling:
  + Blood Smear
  + Hb

**DAY of Parasite Recurrence**

* Questionnaire:
  + Adverse Effects
  + Concomitant Medication
* Examination: Temperature/Vital Signs
* Blood Sampling:
  + Blood smear
  + Hb
  + Sample for molecular work
* Administration of Rescue Therapy

# ANNEX VIII

**Information Sheet**

**Evaluating the efficacy of CQ compared to ACT for the treatment of *Plasmodium vivax* infections**

Malaria can be a serious disease if we don’t treat it quickly and effectively. Studies in other countries have shown that there are several new drugs are very effective even against the worse strains of malaria. They work very fast and have few known side effects. We are conducting a study in this clinic to investigate which new drugs work best against malaria, so that we can introduce better treatments for this community.

In order to show that these new drugs are as good or even better than the present drugs we will give you/your child either Chloroquine or a new treatment (-*Give different Regimens*-). To find out which is the best treatment we will ask you questions about your symptoms and examine you. We will also see you every week for 6 weeks, to see whether your malaria returns.

If you agree to be in the study the following procedures will happen:

1. You will be asked a questionnaire about your symptoms and have an examination by a doctor.

2. You will then be given antimalarial tablets and asked to wait one hour to make sure you don’t vomit your medication.

3. You will then be asked to return to the clinic each day until you are feeling better. At each visit we will ask questions to see whether you are getting better, we will also prick your finger to see whether the malaria parasites in your blood are decreasing.

4. A nurse will give your medication each day to be taken in front of her/him. It is important that you/your child take all the tablets prescribed.

5. After the first week you will be asked to return to the clinic every week for 42 days to see whether your treatment has been successful.

6. If your symptoms or fever returns you should come as soon as possible to the clinic for a blood test. If your/your child’s malaria returns we will treat you/your child with another drug which is standard treatment at this clinic.

7. If you/your child agrees we would also like to take a blood sample from your arm now and then again in 7 days time. This will be used to test the sensitivity of the malaria parasite infecting you and look at the amount of drug in your body.

The potential benefit of being part of this study is to give you / your child a good treatment against malaria and help to introduce the best treatment for everybody in your community. You will not be charged any money for your malaria treatment or to be seen on the follow up visits. You will be reimbursed for costs of transportation back to the clinic.

***If you do not wish to participate in this study it will NOT affect your right to receive standard health care administered at this clinic.***

Any time you can withdraw you/your child from the study and still receive the treatment as you would normally.

**If you have any questions** about this study, you may contact Dr *XXXX* or the study doctors in this clinic.

**In case of an emergency** you should return to this clinic or if it is after hours present yourself to the –*Name Local Emergency Health Care Post*- and inform the doctor that you have been a participant in this study.

**If you have a complaint** about the study then these should be addressed to Dr *XXX*. Telephone Number: *XXXXX*

# ANNEX IX

**Consent Form for Adults**

**Evaluating the efficacy of CQ compared to ACT for the treatment of *Plasmodium vivax* infections**

I ………………………………………………………… agree to participate in the above study.

***If you do not wish to participate in this study it will NOT affect your right to receive standard health care administered at this clinic.***

I DO / DO NOT \* agree to having a venous blood sample taken at enrollment, day7 and if you have again malaria.

(\* Delete as applicable)

I am aware that I can withdraw consent at any time of my own choosing.

**Signature of Patient …………………………………………………**

**Date ……….…………………………………………**

**Witness Name …….……………………………………………**

**Signature ……….…………………………………………**

# ANNEX X

**Consent Form for Children**

**Evaluating the efficacy of CQ compared to ACT for the treatment of *Plasmodium vivax* infections**

I agree as the PARENT / LEGAL GUARDIAN of ……………..………………………………. that he / she can be enrolled in the above study.

***If you do not wish to participate in this study it will NOT affect your right to receive standard health care administered at this clinic.***

I DO / DO NOT \* agree to him / her having a venous blood sample taken at enrollment, day 7 and if he/she has again malaria (\* Delete as applicable).

I am aware that I can withdraw our consent at any time of my own choosing.

**Signature of Parent …………………………………………………**

**Date ……….…………………………………………**

**Witness Name …….……………………………………………**

**Signature ……….…………………………………………**

1. *for more details check: http://apmen.org/storage/apmen-iii/vxwg/APMEN%20VxWG%20Genotyping%20Workshop%20Minutes\_8%20May%202011\_FINAL.pdf* [↑](#footnote-ref-1)