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Assessment of Therapeutic Efficacy of Antimalarial Drugs

For Uncomplicated Falciparum Malaria in Areas with Intense Transmission

World Health Organization
Division of Control of Tropical Diseases

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1. INTRODUCTION

The first standardised test systems for the assessment of *in vivo* drug response in *Plasmodium falciparum* were developed shortly after the first reports of chloroquine resistance in this species (WHO, 1965). These test systems were subsequently revised (WHO, 1967) and remained basically unchanged since the WHO Scientific Group on the Chemotherapy of Malaria and Resistance to Antimalarials in 1972 put them in their present form (WHO, 1973). The standardised tests were originally developed for chloroquine but, with the appropriate modifications, they lend themselves also to the evaluation of the response to other blood schizontocidal drugs.

In their performance, these tests follow set criteria for the selection of patients, the administration of a standard treatment regimen of the appropriate drug, and daily parasitological blood examination for the stipulated period, e.g. 7 or 28 days for chloroquine, or longer periods for drugs with a long elimination half-life.

While the value of these tests in the context of clinical trials is undisputed, their performance in the field met with considerable constraints due to the need for daily blood examination, especially when follow-up needed to be extended beyond 7 days. In addition, these tests were primarily conceived for the assessment of the parasitological response of *P.falciparum* in non-immune persons and took practically no note of the clinical response to the drugs.

There is certainly a need for simplifying the conventional *in vivo* test procedure for field use in populations with little or no naturally acquired immunity to malaria, but the priority is the development of a test system for the determination of the therapeutic efficacy of antimalarials in patients to guide the national drug policy. The test system should provide the information required for guiding drug policies and for monitoring the efficacy of antimalarial drugs over time especially in the most vulnerable population group in areas with high endemicity of malaria, i.e. in infants and young children.

In order to assess the therapeutic efficacy of routine treatment regimens the test should be carried out only in persons suffering from clinically manifest, microscopically confirmed falciparum malaria. The clinical response of the patients should be the main criterion and the number of parasitological examinations be restricted to the minimum required for ensuring the patient's safety.

2. STATEMENT OF INTENT

The standard protocol described in this document has been developed specifically for the testing of the therapeutic efficacy of antimalarial drugs against clinically manifest infections with *Plasmodium falciparum* in infants and young children in areas of intense transmission. In the development of this protocol, due note has been taken of earlier work towards the same objective, as reflected in WHO document WHO/MAL/94.1070, *Antimalarial Drug Policies.* In addition it is based on the practical evaluation of a draft protocol, carried out in May 1996 by an international group of malaria workers in the District of Muheza, Tanzania. This group also considered the epidemiological heterogeneity of malaria in various parts of tropical Africa, and carefully scrutinised the inclusion criteria on the basis of test results obtained in Ethiopia (National Organisation for the Control of Malaria and Other Vector-borne Diseases) and of the WHO studies in Kenya, Rwanda, Tanzania, Uganda and Zambia.

An advanced version of the protocol was reviewed in August 1996, at the intercountry workshop on "Malaria treatment and resistance in Kenya, Zambia and Malawi" (Mangochi, Malawi). The meeting endorsed the WHO standard protocol for monitoring the therapeutic efficacy of antimalarial drugs, and recommended the inclusion of different follow-up periods, i.e. 7 days, 14 days or 28 days, with indication of their role and applications. The present document presents the basic 14 days test system and discusses its possible adaptations into a shorter 7 day test or an extended 28 day test. The basic protocol has been developed through the consensus of participants to these meetings and of several international malaria experts, and is presented as the current WHO standard method for monitoring the therapeutic efficacy of antimalarial drugs for the treatment of children suffering from uncomplicated malaria in areas of intense transmission.

The standard protocol takes into account clinical and parasitological response, the need for an efficient technique that provides accurate, reliable and representative results which lend themselves to inter-area comparison, and applicability under different epidemiological conditions. In the described form the test is simple and feasible, provides the essential information, and requires only modest resources in terms of staff and material.

The therapeutic efficacy protocol has the purpose of determining the practical efficacy of a particular drug regimen, with the ultimate objective of ascertaining its continued usefulness or the need for replacing it in the routine treatment of uncomplicated falciparum malaria. This application serves the monitoring of drug response and the determination of drug policies.

This protocol should be applied wherever a drug policy needs to be developed or revised with the intention of effective implementation and evaluation. This implies the availability of appropriate

antimalarial drugs at all levels of the health care system. It is envisaged that the protocol will provide data that will eventually become part of the routine health information system at district level as an instrument of updating drug policy at the appropriate levels.

It has been prepared with particular emphasis on areas with intensive malaria transmission. However, there are large areas in tropical Africa where malaria transmission is of low intensity or showing large cyclical variations with epidemics. In these areas the level of immunity is generally low. As these areas are also affected by drug-resistant *P. falciparum* and the clinical consequences of such resistance being even more marked than in areas with stable malaria, this document still requires adaptation for areas with moderate or low endemicity.

3. ETHICAL CONSIDERATIONS

The therapeutic efficacy test should be carried out under the responsibility of qualified medical personnel whose first responsibility is the welfare of the patients enrolled in the test. At all times, proper patient management takes priority over continuation of the test. The protocol should be carried out following the WHO Guidelines for Good Clinical Practice (WHO, 1995).

4. THE TEST SYSTEM

The protocol consists of recording essential patient information, clinical assessment, body temperature, parasitaemia, body weight on Day 0 (prior to treatment), supervised treatment with the stipulated drug, clinical assessment with examination of body temperature on Days 1, 2, 3, 7, and 14, and parasitological examination on Days 3, 7 and 14 (see test schedule in Annex 1).

The minimal data requirements are shown in the table below:

	Clinical Examination	Axillary temperature	Parasitaemia	Hematocrit/ Hemoglobin	Treatment
DAY 0	x	x	x	x	x
DAY 1	x	x			x
DAY 2	x	x			x
DAY 3	x	x	x		
DAY 7	x	x	x		
DAY 14	x	x	x	x §	
Any other day	x	x			

- On Day 1 the patient should be examined for parasitaemia if he/she has danger signs;
- On Day 2 or any other day the patient should also be examined for parasitaemia, if he/she has any danger sign or axillary temperature $\geq$ 37.5°C;

§ only children with Hb < 8 g/dl or Ht < 25% on Day 0.

Before the performance of the test the patient will undergo a pre-treatment examination (see Section 4.1). If the patient meets all inclusion criteria (see Section 4.2), shows no danger signs (see Box 1 below), and informed consent has been obtained from the parent/guardian, the patient qualifies for enrolment in the test.

All treatment doses will be given under supervision, and the patient will be observed for at least 30 minutes post administration to ascertain retention of the drug. If the patient vomits within the first 30 minutes post administration, the treatment should be repeated with the same dose. Children with persistent vomiting will be excluded from the study and referred urgently to the appropriate health facility after giving the first dose of parenteral quinine.

The patient data will be recorded in a log book and entered in the record form (see Annex 3) on the appropriate days. After completion of the test the patient data including the overall results will be entered in an appropriate computer programme for epidemiological analysis, e.g. Epi-Info.

At all visits the patient's condition and body temperature are assessed, and a parasitological examination performed, at any time, if the clinical condition warrants it. The parent/guardian should be instructed to bring the child to the clinic on any of the days 1-14 if he/she develops any of the danger signs (see Box 1 below), if the child is still sick or if there is any cause for worry. At any time, if the child shows clear clinical deterioration a blood film should be taken, in order to differentiate resistant malaria from other causes of treatment failure (see Overall Classification of Therapeutic Response, section 5., below).

On each visit if the parent/guardian reports that the child had fever within the last 48 hours, but the axillary temperature is below 37.5°C, the child should be seen on the next day for closer follow-up.

BOX I GENERAL DANGER SIGNS

- not able to drink or breastfeed
- vomiting everything
- recent history of convulsions
- lethargic or unconscious state
- unable to sit or stand up

4.1 INITIAL EXAMINATION

The patient should be checked for fever, parasitaemia and haematocrit/haemoglobin and given a full clinical examination. A rapid screening procedure is needed in an outpatient setting to identify children who may be enrolled in the study. This can be done by identifying all children < 5 years of age coming to the health facility and by measuring their axillary temperature. If the temperature is ≥ 37.5°C, the child should be examined by a physician or clinical officer.

Special care should be taken to detect the presence or early signs of possible other febrile diseases besides malaria, as these will lead to the exclusion of the patient from the test protocol. The most frequent confounding condition is the presence of lower respiratory tract infections such as bronchopneumonia or lobar pneumonia. Cough or difficult breathing together with fast breathing is an indicator for identifying and excluding patients suffering from such conditions. Fast breathing is defined by a respiratory frequency of > 50 per minute in infants below 12 months of age, and a frequency of > 40 in children of 12-59 months. Other relatively common febrile conditions are otitis media, tonsillitis, measles and abscesses. Although these patients should not be enrolled, they need to be treated both for malaria and the other infection if they have parasitaemia.

The recruitment of febrile patients can be increased by rechecking the temperature 2-3 hours later. A proportion of children with recent history of fever will have axillary temperature ≥ 37.5°C on re-examination.

The case record form (see Annex 3) can be used to record the general information and the clinical observations of each child under screening. Particular care should be given to record fully the patient's address in order to be able to follow-up each child at home, in case he will not be brought to the health facility at scheduled visits.

If the child meets the clinical criteria, he/she should be assigned a consecutive screening number and examined for parasitaemia and haemoglobin/haematocrit. Once the child meets ALL the enrolment criteria (see section 4.2, below), the parent/guardian should be asked for consent to participate in the trial.

4.2 INCLUSION CRITERIA

The inclusion criteria are listed below.

Age between 6 and 59 months, i.e. under 5 years (NB: in areas with low endemicity recruitment may be extended to all age groups, but there will be a specific test protocol for these areas);
Absence of severe malnutrition;
Mono-infection with *Plasmodium falciparum,* with a parasitaemia in the range of 2000 to 100,000 asexual parasites per µl;
Absence of general danger signs (see Box 1 above) or signs of severe and complicated falciparum malaria according to definition given by WHO (see Annex 4);
Presence of axillary temperature $\geq$ 37.5 and < 39.5°C at visit (*);
Absence of febrile conditions caused by diseases other than malaria;
Ability to come for the stipulated follow-up visits, and easy access to the health facility;
Informed consent of parent/guardian (see form Annex 9)

In addition, if sulfonamide/pyrimethamine combinations are being tested:

Absence of history of hypersensitivity reactions to sulfonamides or any other drugs.
Absence of skin conditions which could increase the risk of severe adverse reactions to the scheduled drug, e.g. eczema and pemphigoid exanthemas;

(*) - There is clinical and parasitological evidence that children with only a history of fever during the last 24 hours have a similar response to antimalarial treatment compared to children with temperature at the time of visit. However, history of fever with axillary temperature below 37.5°C will not be a sufficient inclusion criterion, since parent/guardian's perceptions of childhood illness might interfere with inter-area comparisons of the results.

4.3 METHODS OF MEASUREMENT & LABORATORY EXAMINATIONS

4.3.1 WEIGHING

Treatment doses are guided by the patient's body weight. The patient will be weighed on a reliably calibrated scale. The weight is recorded to the nearest kg. Due allowance should be made for the weight of clothing as in some areas and seasons acutely ill children tend to be heavily clad.

4.3.2 MEASURING BODY TEMPERATURE

The axillary temperature is recorded to one decimal point, preferably with electronic thermometers. The conventional mercury thermometers may be unreliable and easily subject to damage. If the axillary temperature is less than 36.0 °C, the measurement must be repeated.

4.3.3 MICROSCOPIC BLOOD EXAMINATION

Preparation and staining of the blood slides follows the procedures outlined in *Basic Malaria Microscopy*, Part 1 (WHO, 1991), using Giemsa staining at pH 7.2. Two slides should be always taken: one with a thick film (for rapid staining, 10-15 min. with 10% Giemsa stain, and screening while the patient is in attendance), the other with a thick and thin film on the same slide for subsequent standard staining (30-45 min. with 3% Giemsa stain). The use of slides with one frosted edge capable of being marked, or conventional slides marked with a 'permanent' glass writing pen is recommended.

The thick blood smear for initial screening should be examined for the presence of parasitaemia by counting the number of asexual parasites and the number of white blood cells in a limited number of microscopic fields. Adequate parasitaemia for enrolment requires at least 1 parasite for every 3-4 white blood cells, corresponding to approximately 2000 asexual parasites/mm^3.

A second blood smear will be used to calculate the parasite density. Parasitaemia is measured by counting the number of asexual parasites against a number of leucocytes in the thick blood film, based on a putative mean count of 8000 leucocytes per µl. The number of asexual parasites is counted against 200+ leucocytes using hand tally-counters (NB. once started, a field is always counted to the end. Therefore, it is usual that the final leucocyte count will be over 200). The parasitaemia per µl is calculated by using the formula:

Parasitaemia (per µl) = number of parasites x 8000 / number of leucocytes

If 500+ parasites have been counted without having reached 200 leucocytes, the count is stopped after completing the reading of the last field, and the parasitaemia is calculated according to the formula above.

In addition, 100 fields of the second thick film should be examined for the exclusion of mixed infections, which should be confirmed on the thin film in case of any doubt. If the examination of the thin film is not conclusive, the patient should be excluded from the study after complete treatment.

The same technique should be employed for establishing parasite counts on each of the subsequent blood film examinations. Parasitaemia is measured by counting the number of asexual parasites against a number of leucocytes in the thick blood film. When the number of asexual parasites has dropped below 10 parasites per 200 leucocytes, counting should be done against 500+ leucocytes (i.e. to the completion of the field in which the 500th leucocyte has been counted).

A blood slide should be pronounced negative when the examination of 100 thick film fields does not show the presence of asexual forms of *P. falciparum*. The presence of *P. falciparum* gametocytes should be noted irrespective of asexual forms, but will not figure in the evaluation of the test.

4.3.4 HAEMATOLOGICAL ASSESSMENT

Haematological assessment should be done by measuring haematocrit or haemoglobin, when possible. Haematocrit can be measured by means of the microhaematocrit method described by Lévy and Lambert (1974). In healthy persons, the haematocrit (expressed in %) is roughly 3 times the haemoglobin concentration when the latter is expressed in grams per decilitre. This ratio is maintained in normocytic anaemia, but in most of the tropical forms of chronic anaemia the ratio is 3.3, denoting an hypochromic type of anaemia.

For valid comparisons between the Day 0 and Day 14 either haematocrit readings or the quantitative determination of haemoglobin levels are required. Semi-quantitative methods, such as the "Haemocue" technique (John & Lewis, 1989) or colour scales using a card test (Stott & Lewis, 1995), are more suitable for the quick detection of anaemia and can be used to identify children with severe anaemia, which should be immediately referred to the hospital and excluded from the protocol. Enrolment requires an haemoglobin value above 5.0 g/dl or an haematocrit above 15%.

4.3.5 PREVIOUS ANTIMALARIAL DRUG USE

A history of previous antimalarial drug use or the presence of antimalarial drugs in the urine or blood is not an exclusion criterion. As prior antimalarial treatment is the rule rather than the exception in many situations, the restriction of the test to previously untreated patients would not yield a representative sample of the target population. However, the information on previous drug use should be carefully collected and recorded for each patient. Screening of the urine for detection of antimalarial drugs is desirable since it may give an indication of current drug use in the population, and this information can be used to stratify the results.

In addition it may be desirable to do a 'consumer survey' of the availability of different antimalarial drugs (Government health services and private sector) in the study area. This is part of the preliminary activities of the test team in the study area, especially if the study area has been selected as a permanent sentinel site for monitoring the drug resistance.

A history of adverse reactions to antimalarials or other drugs is vital medical information that should be marked with a red pen or a highlighter on the patient record form. While such reactions are rather rare and relatively mild with chloroquine, quinine and mefloquine, they may be life-threatening with drugs containing sulfonamides. In the case of a history of allergic reactions to drugs, the precise nature of which can not be elucidated, it is advisable to exclude the patient from tests involving sulfonamides. In this case he should be treated with the recommended alternative malaria treatment in the study area, i.e. amodiaquine, quinine or mefloquine.

4.4 TREATMENT

Due to the need for supervising treatment on an outpatient basis, the therapeutic efficacy test system is suitable for all drugs requiring a single dose administration or daily dosing for up to three days. As the therapeutic efficacy test relates to the treatment of non-complicated, non-severe falciparum malaria, it involves only the oral administration of drugs. Detailed information on the various drugs to be used may be found in WHO document WHO/MAL/96.1075, *Management of uncomplicated malaria and the use of antimalarial drugs for the protection of travellers.*

4.4.1 DRUGS AND FORMULATIONS

The drugs employed for therapeutic efficacy testing should be of a reliable, quality controlled batch. WHO can provide assistance for procurement of the drugs if needed. The drugs should not be used beyond the expiry date mentioned on the package. For eventual identification at a later stage, the manufacturer and batch number of the administered drug should be recorded on the patient record form. In Africa, the following drugs and formulations will be most often used for the therapeutic efficacy test:

DRUG	FORMULATION	REMARKS
Chloroquine	Tablets 150 mg base	as phosphate or sulphate
	Tablets 100 mg base	as phosphate or sulphate
	Syrup 50 mg/ 5ml	as phosphate or sulphate
Amodiaquine[1]	Tablets 153 mg base	as chlorohydrate
Sulfadoxine / Pyrimethamine	Tablets 500 mg S + 25 mg P	
Sulfalene / Pyrimethamine	Tablets 500 mg S + 25 mg P	

4.4.2 TREATMENT WITH CHLOROQUINE

The treatment with chloroquine consists of a three-day course with the following doses:

Day-0	10 mg / kg body weight
Day-1	10 mg / kg body weight
Day-2	5 mg / kg body weight.

In practice it will be often quite difficult to divide the tablets into fractions containing the stipulated dose. For this reason Annex 4 provides a list of dose regimens for use in the various weight groups, adjusted to the nearest manageable fractions of the tablets.

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[1] Amodiaquine is also available in tablets of 200 and 600 mg amodiaquine base, as hydrochloride, but these are difficult to divide.

In case syrup formulations of chloroquine are not available, the bitter taste of chloroquine may render difficult the administration to infants and young children. This constraint can be overcome by crushing the tablets and mixing them with a little water and sugar on a spoon. For children with a marked tendency of vomiting the crushed tablets can be mixed with banana or other locally available foods.

4.4.3 TREATMENT WITH AMODIAQUINE

This follows the same dose regimen as that given for chloroquine above.

4.4.4 TREATMENT WITH SULFONAMIDE / PYRIMETHAMINE COMBINATIONS

Sulfadoxine/pyrimethamine or sulfalene/pyrimethamine are given as a single dose equivalent to 1.25 mg pyrimethamine/kg body weight (up to a maximum adult dose of 3 tablets). For the doses appropriate to the various weight groups see Annex 4. If the temperature exceeds 38.5°C, the child should receive one dose of paracetamol (<3 years of age = 1/4 tablet; 3-5 years = 1/2 tablet) to be taken immediately, and one for later use at home, if the fever persists. Parents/guardians should be instructed to use tepid sponging during the initial 24 to 48 hours. Failure to discuss this issue may lead to perception that treatment is not effective, and parents/guardians may seek alternative medication which may interfere with the study protocol.

4.4.5 OTHER MEDICATION

The administration of paracetamol on Day 0, Day 1 and Day 2 is permissible if the patient's condition warrants such medication. If during the follow-up, infections other than malaria require the administration of medicaments with antimalarial activity, e.g. cotrimoxazole, the patient should be excluded from the study. Patients given tetracycline as eye ointment should not be excluded.

4.5 FOLLOW-UP PROCEDURES

Rarely, if ever, will all patients enrolled for therapeutic efficacy tests complete the post-treatment follow-up. The representativeness of the study diminishes with an increasing number of drop-outs, especially when the reasons of failing post-treatment follow-up are related to an unsatisfactory outcome of the treatment. There is thus a need for the precise registration of the addresses of the patients at enrolment, and for the rigorous tracing of patients who fail to show up on the scheduled

days. This should limit the number of losses to < 10 %, the maximum permitted drop-out rate. The reason for dropping out should be ascertained in every individual case to exclude an association with the outcome of the test.

A drop-out is defined as a patient lost to follow-up despite fulfilling all inclusion criteria, without developing exclusion criteria during the follow-up period. The following conditions should not be considered as drop-outs but classified as exclusions:

(1) Occurrence, during follow-up, of concomitant disease that would interfere with the clear classification of treatment outcome;
(2) Movement of a patient from the study site to a place outside the reach of active follow-up (this movement must be unrelated to the response to treatment);
(3) Failure to complete the treatment due to withdrawal of consent;
(4) Antimalarial treatment administered by a third party during the follow-up period; and,
(5) Detection, during follow-up, of a mixed malaria infection.

5. OVERALL CLASSIFICATION OF THERAPEUTIC RESPONSE

There are three categories of therapeutic response, namely early treatment failure (ETF), late treatment failure (LTF) and adequate clinical response (ACR). These are defined as follows:

The therapeutic response will be classified as early treatment failure (ETF) if the patients develops one of the following conditions during the first three days of follow-up:

ETF
- Development of danger signs or severe malaria on Day 1, Day 2 or Day 3, in the presence of parasitaemia;
- Axillary temperature $\geq$ 37.5°C on Day 2 with parasitaemia > of Day 0 count;
- Axillary temperature $\geq$ 37.5°C on Day 3 in the presence of parasitaemia;
- Parasitaemia on Day 3 $\geq$ 25 % of count on Day 0.

The therapeutic response will be classified as late treatment failure (LTF) if the patients develops one of the following conditions during the follow-up period from Day 4 to Day 14:

LTF
- Development of danger signs or severe malaria in the presence of parasitaemia on any day from Day 4 to Day 14, without previously meeting any of the criteria of early treatment failure;

- Axillary temperature $\geq$ 37.5°C in the presence of parasitaemia on any day from Day 4 to Day 14, without previously meeting any of the criteria of early treatment failure.

The response to treatment will be classified as adequate clinical response (ACR) if the patients shows one of the following conditions during the follow-up period (up to Day 14):

ACR
- Absence of parasitaemia on Day 14 irrespective of axillary temperature, without previously meeting any of the criteria of early or late treatment failure;
- Axillary temperature < 37.5°C irrespective of the presence of parasitaemia, without previously meeting any of the criteria of early or late treatment failure.

5.1 ALTERNATIVE TREATMENT OF DRUG FAILURES

The indication for alternative treatment at any time between Day 0 and Day 14 should be based on clinical and parasitological criteria, with the aim of avoiding an aggravation of the clinical condition and risk to the patient. In this context the evaluation of the patient's clinical condition should not be limited to fever, since danger signs may develop also in afebrile patients, e.g. with shock and in algid malaria. On the other hand, the clinical judgement should always be supported by parasitological evidence (see Classification of Therapeutic Response, Section 5.1, above).

The recommended alternative antimalarial treatment will be sulfa-pyrimethamine compounds when the drug under test is chloroquine or amodiaquine, and quinine or mefloquine in the case of poor response to sulfa - pyrimethamine. Although the therapeutic efficacy test ends when the patient has been classified as early treatment failure (ETF) or late treatment failure (LTF) and given alternative medication, the team has to ascertain that the alternative medication resolves the risk to the patient.

If the patient develops any signs of severe or complicated malaria or any of the general danger signs during the follow-up period, he should be given the first dose of parenteral quinine and taken urgently to the appropriate health facility (WHO, 1991). All children with parasitaemia on Day 14, irrespective of symptoms, should be treated for ethical reasons with the alternative antimalarial drug at the end of the follow-up period.

5.2 INTERPRETATION OF TEST RESULTS

The test system aims at the assessment of the proportion of all treatment failures (early plus late treatment failures) in the sample of patients included in the study. The statistical procedure adapted for the interpretation of the results allows to test the hypothesis that the proportion of treatment failures is above a certain level in the study area, and, therefore, a decision to change is deemed necessary.

A high proportion of early treatment failures to the first-line antimalarial drug is *per se* a strong indicator of the need for changing the first line treatment. In practice, in most situations the proportion of early treatment failures will not be unacceptably high, and a full investigation with 14 days' follow-up period is needed to determine the extent of the problem (see section 5.4, below).

The haematological response should be evaluated on a sample basis, not on an individual basis. Analysis of haemoglobin in individuals is important clinically, but does not indicate drug resistance. The group of children with anaemia, i.e. with an initial haemoglobin of less than 8 g/dl (or haematocrit of less 25%), should be re-evaluated on day 14. Experience has shown that in African children with anaemia, the average haemoglobin levels on day 14 will have improved by 1.5-2 g/dl (or Ht by 5-6.5%) within 14 days of effective treatment. Haematological response can be analysed only if at least 30-40% of children have malaria-associated anaemia on Day 0.

5.3 ADAPTATION OF THE PROTOCOL TO A 7 DAYS TEST OR A 28 DAYS TEST

There is clearly a need for a test of shorter duration since follow-up for 14 days will not always be feasible (WHO/MAL/94.1070). A short 7 days' test, will not fully document the occurrence of late treatment failures, which may occur during the second week of follow-up and consequently these will be grossly underestimated by such a test.

Unfortunately, there is still no recognised early predictor of the frequency of clinical relapses which occur after day 7, and the standard test should last 14 days. The current test, however, does provide a basis for further research to determine if early predictions of treatment efficacy can be identified.

A 28 days' test may offer the best approach in areas where malaria associated anaemia is a significant problem in children to assess the haematological response to drug treatment. In this case the haematological response should be evaluated as in the 14 days' test (see above). In the analysis and presentation of the results, observations up to day 14 should be separated from those

carried out over the third and fourth weeks to ensure comparability of the results between areas where tests of different duration are carried out.

6. STATISTICAL CONSIDERATIONS

In trying to estimate the proportion of treatment failures in the overall population from a limited number of patients, bias in the study design is a source of major concern. The results of the study will be biased if its design systematically favours certain outcomes.

Selection bias is likely to occur, where the study subjects are systematically not representative of the patient population at large. It may be, for instance, that the presence of the medical team attracts those patients who have already suffered a treatment failure with drugs they got from elsewhere. On the other hand, the presence of the investigators and the availability of diagnostic and treatment facilities during the study, will attract to the clinic patients who would not have come for treatment otherwise, especially in highly endemic areas.

Under most circumstances, the investigator will be able to detect major bias in the sample of patients recruited for the study. Close interaction with the local staff in the clinic will be very fruitful to detect these conditions, and the major concerns in this respect should be noted in the activity report. The sample of patients enrolled in the study should be representative of the patients with uncomplicated falciparum malaria seeking treatment in the health services in that locality.

In this respect, a study conducted in an outpatient department (OPD) of a district hospital may provide different results from a study in a rural clinic or dispensary, since patients may refer to the hospital only when the clinical condition is severe and serious complications occur. Often patients may have already tried different treatments without success and symptoms were present for a longer period. In some areas the patients visiting the OPD may be highly representative of the resident population in the town itself, and results obtained cannot be extrapolated to the population living in the near rural areas.

In addition, a study carried out in the OPD of a district hospital may present additional difficulties in the enrolment of the patients, since a significant proportion of sick children may need to be excluded because of concomitant febrile diseases or severe signs and symptoms. Moreover, the follow-up of these patients after treatment is more difficult, for both patients living in the town as well as for those coming from distant rural areas. This may have, of course, adverse effects on the resources needed and the quality of the investigation.

To a certain extent, it is possible to reduce bias in the survey and to improve the representativeness of the results by following some practical rules. The study should be carried out in a rural health centre (clinic or dispensary) very close to a well-defined community, preferably in two or more health centres at relatively short distance. The study team should avoid awareness campaign in the community and the registration book of the clinic can be used to determine the normal load of patients. Information on drug utilisation in the area should be obtained from the clinic staff. In order to reduce the recruitment time, the survey should be carried at the peak malaria season, selecting those clinics which receive at least 15-20 febrile children per day.

6.1 SAMPLE SIZE DETERMINATION

The aim of monitoring the therapeutic efficacy of antimalarial drugs is to determine if the current policy is still valid and to guide the decision to change the recommended treatment of uncomplicated malaria, if a systematic study of sample of patients shows an unacceptably high proportion of treatment failures. The proportion of clinical failures which is unacceptable can only be considered from within a national programme. This will vary with the options and the financial, institutional and personnel resources available to each programme (for more discussion, see WHO/MAL/94.1070).

Sample size can be determined using the Lot Quality Assurance Sampling or LQAS method (Lemeshow & Taber, 1991). This allows identification of communities in which the prevalence of drug resistance is above the critical level, with smaller sample sizes than would be required using more traditional procedures. Sample sizes may be reduced further while maintaining statistical precision by using the double sampling procedure of LQAS.

For calculating the minimal sample size according to this method, the investigators must first define two threshold levels: a level at which the proportion of treatment failures is considered acceptable, and a level of treatment failures which is unacceptable, i.e. above which a change in the first-line drug is necessary.

According to the Double Lot Quality Assurance (DLQAS) method the sample size is calculated in two stages, according to the example given below. In the first stage, a relatively small sample is selected and monitored. If the results from the first sample are "extreme" , i.e. very low or very high levels of treatment failures are found, then sampling stops and conclusions can be drawn from the smaller sample. On the other hand, if the results of the preliminary sample are

equivocal, then a second sample is chosen and conclusions should be based on the results of both combined samples.

If the study shows that the critical proportion of treatment failures is unacceptable according to the threshold defined at the start of the study, then the decision of changing the first-line treatment can be supported. If the proportion of treatment failures is below the threshold level considered as acceptable, then the area can be maintained under routine monitoring.

The size of the sample needed depends on the following parameters, specified by the health planner.

N The study population size, presumed to be large;

Po Upper threshold level of clinical failures beyond which replacement of the drug under study is deemed necessary;

Pa Lower threshold level of clinical failures below which it would be more acceptable to continue the utilisation of present drug;

α Probability of concluding that a community has a low prevalence of clinical failures when, in fact, it has a high level (type I error);

β Probability of concluding that a community has a high prevalence of clinical failures when, in fact, it has a low level (type II error).

Example:

A prevalence of 25% treatment failures may be considered as an indication for the replacement of the first-line drug. Suppose the health authorities are interested in detecting communities with Po>0.25 and want to be 80% sure (power of the test) that communities with Pa $\leq$ 0.10 will not be wrongly classified as having high prevalence of drug resistance.

It is assumed that the community has a large value of N, and that α = 0.05. Locate in Annex 6, the table that correspond to Po = 0.25 and move down the row that correspond to Pa = 0.10. At the first stage of the study, the follow-up of the first 16 (= n1) patients should be evaluated.

a) If the observed number of treatment failures is 0 (= d1) it can be concluded that the actual proportion of treatment failures in the population of patients consulting with uncomplicated falciparum malaria is significantly less than 25% (Po);

b) If the observed number of treatment failures is greater than 5 (= d2), it can be concluded that the actual proportion of clinical failures in the population is not significantly less than 25 % (Po);

c) If the observed number of treatment failures in the first stage is > 0 and ≤ 5, a second stage of monitoring should be initiated in which more patients are evaluated until either 6 (= d2 + 1) treatment failures have been observed, indicating a high failure rate, or until the total number of patients with complete follow-up has reached 42 (= n1+n2) presenting no more than 5 (= d2) treatment failures, indicating a low prevalence of drug resistance.

Rarely, if ever, will all patients enrolled for therapeutic efficacy tests complete the post-treatment follow-up (see also Section 5.5). For this reason, the sample size should be adjusted multiplying the original sample size by the rate of loss to follow-up and exclusion from the study. In practice a minimum of 20% should be added to the minimal sample size, to allow for drop-outs of patients and for those which will be excluded from the protocol during the follow-up period.

In the example given above the practical approach will be to plan the survey and to recruit patients until 42 children (= n1 + n2) are enrolled. The conclusions of the test can already be made if during the follow-up of the first 16 (= n1) patients the number of treatment failures is 0 (= d1) or is greater than 5 (= d2). Once the proper clinical management of the remaining patients has been assured, the resources should be more efficiently used by repeating the survey in a different area.

6.2 PRESENTATION OF THE RESULTS

A standardised format for presenting study results will facilitate comparisons between studies. It will also make the presentation of the conclusions in an accessible format to health planners and policy makers.

All studies should report general information on the study area, a description of the health facility in which the survey was carried out, the characteristics of the sample population, including information on drug utilisation in the area. The frequency of the factors recorded on the case recording (see Annex 3) form should be presented, and possible bias in the study should be discussed, especially selection bias at the enrolment of the patients

Finally, the results should be summarized in a Table indicating the total number of patients enrolled in the study, the number of patients with adequate clinical response, the number of patients with early and late treatment failures, the number of those lost to follow-up, and of those excluded from the study. A detailed account of the reasons for patients lost to follow-up and those excluded from the study should be given. The conclusion of the study should clearly report if the

proportion of failures exceeds the 'unacceptable upper limit'. If the proportion of failures is below the critical level, the area may need to be maintained under surveillance.

7. STANDARD MATERIAL REQUIRED FOR THE TEST

The standard list of equipment for the therapeutic test is given in Annex 5a, that for the supplies (per 100 patients) in Annex 5b. All equipment and supplies should be of good quality and, while not in use, stored in a way that prevents deterioration. In many countries the equipment will be available from within the country health services. However, where it is not readily available, budgetary provision must be made. It is preferable to obtain supplies (except flammable liquids and locally available routine material) from one international source, such as through WHO, as this would ensure the comparability of technique and results.

8. QUALITY CONTROL

A centralised supply of drugs and laboratory equipment and supplies is preferable to ensure standardisation and good quality of the material. Specific quality control relates to the drugs used in the tests, to the reliability of laboratory work, and to the overall performance of the tests.

Drugs employed in the tests need to be of a reliable brand, i.e. produced under the principles of Good Manufacturing Practice (GMP) which ensures continuous quality control and the availability of the appropriate batch transcripts. If the drugs do not originate from such a source, part of the drugs from the same batch should be conserved for later use. In case the test shows equivocal results, they need to undergo quality control procedures at a reliable, officially appointed laboratory, according to International Pharmacopoeia, or other internationally recognised pharmacopoeias. The analysis should include drug content, inter-tablet variability, and dissolution tests.

For the quality control of microscopy work it will be appropriate to forward, at regular intervals, all slides and copies of the related records to the regional or central laboratory or an official reference laboratory where a random sample can be drawn for re-examination. (NB: in order to ensure that any of the individual slides of the series may be selected for rechecking, all slides need to be preserved and forwarded, in totality, to the checking laboratory). The procedure of Double Lot Quality Assurance (DLQA) may be utilised to assess whether a random sample of slides has an unacceptable high level of false results, i.e. >10% (see Annex 6). The re-examination should be blinded to the results of the original examination, and focus on negativity, asexual *P.falciparum* counts, and *Plasmodium* species.

Quality control of the overall performance of therapeutic efficacy testing is part of the supervisory activities of the responsible central/regional service which is also responsible for the organisation of therapeutic efficacy testing and for the analysis of the results. Site visits are indispensable for detecting shortcomings, solving local problems, ensuring the flow of material and information, and for the calibration of equipment such as scales, microscopes, haematocrit readers.

9. ORGANISATION OF WORK, THE TEAM

The team for therapeutic efficacy testing should include, as a minimum, one medically-qualified person (clinician), one well-qualified laboratory technician, one driver, and one multi-purpose worker, preferably a secretary or clerk.

In some circumstances it may be possible to conduct enrolment simultaneously in several localities, provided these localities are not too distant from each other, the necessary number of clinicians is available, and the laboratory logistics (flow of samples and feed-back) can be reliably arranged. If the resources allow, this can improve the representativeness of the study.

Before proceeding with the protocol in an envisaged site the team should scrutinise available records as to the suitability of the site for conducting the study. This should ensure that the study is being conducted during the most suitable season in a large enough community, and with the prospect of being completed within 4-5 weeks (at a minimum average of 5 enrolments per day). An adequate budget for the study (transport, material, local cost, allowances, including 10% contingency fund) is essential and has to be secured well before the implementation of the study. If necessary, incentives can be useful for the parents/guardians to come for follow up visits. For the selection of appropriate laboratory equipment and supplies, it will be essential to know whether electricity and clean water will be available at the study site.

All members of the team need to be familiar with the protocol, and appropriate training sessions should be arranged by the team leader before proceeding to the study site. The envisaged study and its schedule should be announced, well in advance, to the regional/district/local health authorities with whom personal contact should be established before moving to the study site itself. This will also help in obtaining the co-operation of the health personnel at the site, an indispensable prerequisite for success.

Immediately upon arrival at the study site, contact should be made with the community leaders and the local health personnel, explaining purpose and performance of the study so as to ensure their acceptance and active co-operation.

As far as possible local health staff should be involved in the study in order to obtain a maximum of local support and confidence. Any such staff should be adequately briefed about all aspects of the protocol by appropriate training sessions. Where language may be a problem a translation of the protocol should be available.

The team needs the confidence of the study population. This is best achieved and maintained by taking adequate care of immediate health needs also in persons who are not eligible for recruitment into the study, e.g. emergency treatment of patients with severe or complicated falciparum malaria, and their transport to hospital, or patients with malaria and concomitant infections. The team needs to be adequately prepared for such contingencies by carrying not only the test drugs, but also a supply of other medicaments, especially if they are not locally available.

No member of the team (including the team leader) is authorised to make changes to the protocol. It is the team leader's responsibility to ensure that the test protocol will be strictly followed by all members of the team.

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ANNEX 1

BASIC TEST SCHEDULE

Day-0 Clinical assessment - referral in case of severe malaria/danger signs
Measuring axillary temperature
Parasitological assessment
Measuring haemoglobin/haematocrit
Informed consent - Enrolment
Weighing - Treatment, first dose

Day-1 Clinical assessment - referral in case of severe malaria/danger signs
Measuring axillary temperature
Parasitological assessment, in case of severe malaria/dangers signs
Treatment, second dose or alternative treatment in case of early treatment failure

Day-2 Clinical assessment - referral in case of severe malaria/danger signs
Measuring axillary temperature
Parasitological assessment, in case of severe malaria/danger signs or temp. ≥ 37.5°C
Treatment, third dose or alternative treatment in case of early treatment failure

Day-3 Clinical assessment - referral in case of severe malaria/danger signs
Measuring axillary temperature - Parasitological assessment
Alternative treatment in case of early treatment failure

Day-7 Clinical assessment - referral in case of severe malaria/danger signs
Measuring axillary temperature - Parasitological assessment
Alternative treatment in case of late treatment failure

Day-14 Clinical assessment - referral in case of severe malaria/danger signs
Measuring axillary temperature - Parasitological assessment
Measuring haemoglobin/haematocrit if anaemic on Day-0
Alternative treatment in case of late treatment failure

Any other day: Clinical assessment - referral in case of severe malaria/danger signs
Measuring axillary temperature
Parasitological assessment, in case of severe malaria/danger signs or temp. ≥ 37.5°C
Alternative treatment in case of Late Treatment Failure (LTF)

ANNEX 2

DEFINITION OF SEVERE MALARIA AND COMPLICATIONS (WHO, 1990)

One or more of the following criteria in the presence of asexual parasitaemia define severe falciparum malaria:

Defining criteria of severe disease

1	Cerebral malaria (unrousable coma) §
2	Severe normocytic anaemia (Hb < 5 g/dl)
3	Renal failure (serum creatinine > 3.0 mg/dl)
4	Pulmonary oedema
5	Hypoglycaemia (< 40 mg/dl)
6	Circulatory collapse/shock (systolic BP <70 mm Hg in adults; or <50 mm Hg in children < 5 years)
7	Spontaneous bleeding/disseminated intravascular coagulopathy
8	Repeated generalised convulsion(s)
9	Acidaemia/acidosis
10	Macroscopic haemoglobinuria

Other manifestations

1	Impaired consciousness but rousable
2	Prostration, extreme weakness (inability to stand or sit)
3	Hyperparasitaemia (> 5% RBC infected)
4	Jaundice (total serum bilirubin > 3 mg/dl)
5	Hyperpyrexia (axillary temp > 39.5°C)

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§ After generalised convulsion, coma should persist for at least 30 minutes to make the distinction from transient post-ictal coma

ANNEX 3

CASE RECORD FORM						Contact (home) address
Record Number	Study site	Full Name				Guardian's Name
Age (months)	Weight (kg)	Hb/Ht Day 0	Hb/Ht Day 14	Drug name		Total drug dose (mg base)
Previous antimalarials (Y/N/Unknown)	Drug	Dosage		Urine Test (drug)	(concentration)	

	DAY0	DAY1	DAY2	DAY3	DAY4	DAY5	DAY6	DAY7	DAY8	DAY9	DAY10	DAY11	DAY12	DAY13	DAY14
Date															
Danger signs															
History of fever (last 24 hrs)															
Previous medication															
Axillary temperature															
Parasite count															
Treatment (no. tabs)															
Concomitant treatment															
Reasons for exclusion or loss to f/up															
Observations															

Overall assessment ETF LTF ACR Exclude Loss to f/up

ANNEX 4

INFANT AND CHILDREN DOSES OF ANTIMALARIAL ACCORDING TO BODY WEIGHT, EXPRESSED AS FRACTIONS OF TABLETS

WEIGHT (kg)	CHLOROQUINE Tablets 100 mg *			CHLOROQUINE or AMODIAQUINE Tablets 150 mg *			SULFONAMIDE/ PYRIMETHAMINE Tablet 500 mg S + 25 mg P
	Day 0	Day 1	Day 2	Day 0	Day 1	Day 2	Day 0
5	1/2	1/2	1/4	1/2	1/4	1/4	1/4
6	1/2	1/2	1/2	1/2	1/4	1/4	1/4
7	3/4	1/2	1/2	1/2	1/2	1/4	1/2
8	3/4	3/4	1/2	1/2	/12	1/2	1/2
9	1	3/4	1/2	1/2	1/2	1/2	1/2
10	1	1	1/2	3/4	1/2	1/2	1/2
11	1	1	3/4	3/4	3/4	1/2	1/2
12	1	1	1	3/4	3/4	1/2	3/4
13	1 1/4	1	1	1	3/4	1/2	3/4
14	1 1/4	1 1/4	1	1	1	1/2	3/4
15	1 1/2	1 1/4	1	1	1	1/2	3/4
16	1 1/2	1 1/2	1	1	1	3/4	3/4
17	1 3/4	1 1/2	1	1	1	1	3/4
18	1 3/4	1 3/4	1	1	1	1	1
19	2	1 3/4	1	1 1/4	1	1	1
20	2	2	1	1 1/4	1 1/4	1	1
21	2	2	1 1/4	1 1/4	1 1/4	1	1
22	2 1/4	2 1/4	1	1 1/2	1 1/2	3/4	1
23	2 1/2	2	1 1/4	1 1/2	1 1/2	1	1 1/4
24	2 1/2	2 1/2	1	1 1/2	1 1/2	1	1 1/4
25	2 1/2	2 1/2	1 1/4	1 1/2	1 1/2	1 1/4	1 1/4

* expressed as base

ANNEX 5a

LIST OF EQUIPMENT REQUIRED BY ONE STUDY TEAM

	ITEM	No REQUIRED
(1) Clinical	Stethoscope	1 (per clinician)
	Balance	1 (per clinician)
	Fever thermometer, electronic	3 (per clinician)
	Tea spoons	2 (per clinician)
(2) Lab.	Microscope, binocular, w. illumination	1
	Microscope, monocular *	1
	Microhaematocrit centrifuge, electric	1
	Microhaematocrit centrifuge, hand-operated *	1
	Tally counter	2
	Hair dryer (for humid areas and seasons)	1
	Laboratory timer	2
	Slide box, for vertical storage	10
	Slide box, for horizontal storage, WHO type	2
	Slide tray, cardboard	2
	Drying rack, wood for slides	1
	Staining jar, Coplin or horizontal	3
	Bottle, screw-cap, plastic, 500 ml	2
	Bottle or jerrican, screw-cap, plastic, 5 l	2
	Measuring cylinder, plastic, 500 ml	2
	Measuring cylinder, plastic, 10 ml	2
	Dropping bottle, plastic or glass, 50 ml	2
	Glass rod, 50 cm, for quick staining	4
(3) General	Clipboard	1 (per clinician)
	File jacket, stiff carton	10
	Transport box, norm size 0.2 m'	3

* If no electricity available at the study site

ANNEX 5b

LIST OF SUPPLIES REQUIRED PER 100 PATIENTS

	ITEM	NO REQUIRED
(1) Clinical	Test drug	150 courses/doses
	Next line alternative drug	100 courses/doses
	Third line drug, if applicable	50 courses/doses
	Quinine for i.m. injection	20 ampoules
	Cotrimoxazole	200 tablets
	Paracetamol	200 tablets
	Amoxicillin	200 doses
	Injection syringes, sterile, disposable, 2 ml	20
	Injection syringes, sterile, disposable, 5 ml	20
	Injection needles for above, disposable, no.12 or 14	40
	Spare battery, for electronic thermometer	3
	Sweets (bon-bons), pkg of 100	10
	Biscuits, pkgs of ~ 50	10
	Sugar	1 kg
	Plastic cups	3
(2) Lab.	Microscope slides, frosted edge, pkg of 100	15
	Lens tissue, pkg of 100	2
	Haemolancets, pkg of 100	8
	Swabs, alcohol (70 %), pkg of 100	8
	Haematocrit tubes, pkg of 100	3
	Haemoglobinometer or measuring chart	1
	Sealant for haematocrit tubes, pad	2
	Paper strips for haemoglobin testing, pkg of 100	3
	Rubber gloves, disposable, medium size	50 pairs
	Rubber gloves, disposable, large size	50 pairs
	Pipettes, transfer, disposable, 5 ml, pkg of 100	1
	Pipettes, transfer, disposable, 1 ml, pkg of 100	1
	Glass writing pen, permanent, xylene-proof	5
	Plasticine	200 g
	Buffer tablets, pH 7.2	20
	Immersion oil, bottle of 50 ml	1
	Xylene, Bottle of 500 ml	1
	Methanol, bottle of 500 ml	1

(Lab)	Giemsa stain stock solution, Merck, bottle of 500 ml	1
	Distilled water	20 l
	Cotton wool, pkg 500 g	2
	Syringe, plastic, 10 ml	2
(3) General	Log book, DIN A4, 100 pp	1 (per clinician)
	Note pad, DIN A4	4
	Ball pen, black/blue	10
	Ball pen, red	10
	Cellotape, roll - 30 m	2
	Toilet paper, roll	10
	Patient forms	150
	Patient cards	150
	Laboratory form (microscopy and haematology)	700

ANNEX 6

TABLE FOR CALCULATING THE MINIMAL SAMPLE SIZE ACCORDING TO THE TWO STAGE LOT QUALITY ASSURANCE METHOD WITH CONFIDENCE LEVEL OF 95% AND POWER 80%

Po = 0.10

Pa=	n1+n2	d2	n1	d1
0.020	5	2	49	0
0.030	83	3	49	0
0.040	121	6	49	0
0.050	184	11	49	0
0.060	301	21	75	1
0.070	558	44	140	6
0.080	1303	112	326	20
0.090	5395	503	1349	109

Po = 0.15

Pa =	n1+n2	d2	n1	d1
0.030	38	2	31	0
0.045	53	3	31	0
0.060	77	6	31	0
0.075	117	11	31	0
0.090	191	20	48	1
0.105	354	42	89	5
0.120	824	106	206	19
0.135	3404	476	851	103

Po = 0.20

Pa =	n1+n2	d2	n1	d1
0.040	27	1	22	0
0.060	38	3	22	0
0.080	55	6	22	0
0.100	83	10	22	0
0.120	136	19	34	1
0.140	251	39	63	5
0.160	585	101	146	18
0.180	2409	449	602	98

Po = 0.25

Pa =	n1+n2	d2	n1	d1
0.050	21	1	16	0
0.075	29	3	16	0
0.100	42	5	16	0
0.125	63	10	16	0
0.150	103	18	26	1
0.175	190	37	48	5
0.200	441	95	110	17
0.225	1812	422	453	92

$P_0 = 0.3$

P_a =	n1+n2	d2	n1	d1
0.060	16	1	13	0
0.090	23	3	13	0
0.120	33	5	13	0
0.150	50	9	13	0
0.180	81	17	20	1
0.210	149	35	37	5
0.240	345	89	86	16
0.270	1413	395	353	86

$P_0 = 0.35$

P_a =	n1+n2	d2	n1	d1
0.070	13	1	10	0
0.105	19	3	10	0
0.140	27	5	10	0
0.175	40	9	10	0
0.210	65	16	16	1
0.245	120	33	30	4
0.280	276	83	69	15
0.315	1129	368	282	80

$P_0 = 0.4$

P_a =	n1+n2	d2	n1	d1
0.080	11	1	8	0
0.120	15	2	8	0
0.160	22	5	8	0
0.200	33	8	8	0
0.240	54	15	14	1
0.280	98	31	25	4
0.320	225	77	56	14
0.360	916	342	229	74

$P_0 = 0.45$

P_a =	n1+n2	d2	n1	d1
0.090	9	1	7	0
0.135	13	2	7	0
0.180	18	4	7	0
0.225	28	8	7	0
0.270	44	14	11	1
0.315	81	29	20	4
0.360	185	72	46	13
0.405	750	315	188	69

ANNEX 7

INFORMED CONSENT

The Ministry of Health is interested in knowing how well the current treatment for malaria is working in our country. To do this, we are carrying out a study in which we are treating a group of children for malaria and then following them for 14 days to see if their infection is cured. This is not a new treatment formulation as the test drug is .....

If you agree to participate in this study, we would like you to bring your child to the clinic 5 more times over the next 2 weeks, so that we can monitor the progress of the treatment. It is very important that we see your child on these days, so if you feel you will not be able to return on these days, please let us know now. At each visit your child will receive a full medical examination and on 3 of these visits we will take a small amount of blood by fingerprick to make blood smears to see if your child still has malaria parasites.

Your participation is completely voluntary. If you do not want your child to participate in this study, he will receive treatment as usual at this clinic. Participation in this study will not cost you or your family anything. You may also withdraw your child from the study at any time and for any reason.

Your child will benefit from participating in this study because he will be closely followed over the next 14 days. If your child continues to suffer from malaria, he will receive an alternative treatment which will cure the illness. There will be someone here at the clinic every day so that, even on days between scheduled visits and on week-ends you may bring your child in for a check-up if you feel that he is ill.

Do you have any questions about the study?

(Adapted from the " Standard protocol for assessing and monitoring malaria therapy efficacy in Zambia, EHP-USAID, Washington, 1995)