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MUHAS/ KAROLINSKA INSTITUTET /UPPSALA UNIVERSITY

Clinical Research Protocol

"Aiming at prolonging the therapeutic life span of artemisinin-based combination therapies in an era of imminent Plasmodium falciparum resistance in Bagamoyo District, Tanzania - new strategies with old tools".

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"Aiming at prolonging the therapeutic life span of artemisinin-based combination therapies in an era of imminent Plasmodium falciparum resistance in Bagamoyo District, Tanzania - new strategies with old tools".

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Investigational Product:	Artemether-Lumefantrine and Primaquine
Development Phase:	Phase IV
Sponsors:	Muhimbili University of Health and Allied Sciences; Dept. of Parasitology and Medical Entomology P. O. Box 65001 Upanga, Dar es salaam Tanzania, Karolinska Institutet, Dept of Molecular, Tumor and Cell Biology, Nobelsväg 16 171 77 Stockholm, Sweden Uppsala University, Dept. of Women's and Children's Health, IMCH, Drottninggatan 4, 75310 Uppsala Sweden
Funding Organization:	Swedish International Development Agency (SIDA) & Swedish Research Council
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Approval:

Sponsor Signature (Name and Title) *Date*

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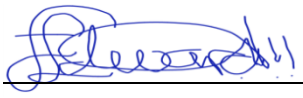
PROTOCOL AGREEMENT

I have read the protocol specified below. In my formal capacity as Investigator, my duties include ensuring the safety of the study subjects enrolled under my supervision and providing Muhimbili University of Health and Allied Sciences (MUHAS), Karolinska Institutet (KI) and Uppsala University, with complete and timely information, as outlined in the protocol. It is understood that all information pertaining to the study will be held strictly confidential and that this confidentiality requirement applies to all study staff at this site. Furthermore, on behalf of the study staff and myself, I agree to maintain the procedures required to carry out the study in accordance with accepted GCP principles and to abide by the terms of this protocol.

Protocol Number: 01.05.2017

Protocol Title: **Aiming at prolonging the therapeutic life span of artemisinin-based combination therapies in an era of imminent Plasmodium falciparum resistance in Bagamoyo District, Tanzania - new strategies with old tools.**

Protocol Date: 04th July 2017



July 4th 2017

Investigator Signature *Date*

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LIST OF ABBREVIATIONS

AE	adverse event
ACT	Artemisinin-Based Combination Therapy
AL	Artemether-Lumefantrine
ALT	Alanine aminotransferase
CRF	Case report form
DAPI	(4',6-diamidino-2-phenylindole)
DBS	Dried Blood Spot
DMC	Data Monitoring Committee
DSMB	Data Safety Monitoring Board
ECG	Electro- Cardiogram
FDA	Food and Drug Authority
GCP	Good Clinical Practice
GCT	Gametocyte Clearance Time
Hb	Hemoglobin
HIPAA	Health Insurance Portability and Accountability Act of 1996
ICF	informed consent form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IRB	Institutional Review Board
KI	Karolinska Institutet
LAMP	Loop-mediated isothermal Amplification
LLIN	Long Lasting Insecticide Treated Nets
MoMic	Mobile Microscopy
mRDT	Malaria Rapid Diagnostic Test
MUHAS	Muhimbili University of Health and Allied Sciences
mRNA	Messenger Ribonucleic Acid
NMCP	National Malaria Control Program
PCR	Polymerase Chain Reaction
PCR- RFLP	PCR-Restriction Fragment Length Polymorphism
PI	Principal Investigator
PK	Pharmacokinetics
PQ	Primaquine
QT-NASBA	Quantitative Nucleic Acid Sequence Based Assay
SAE	serious adverse experience
RNA	Ribonucleic Acid
SIDA	Swedish International Development Agency

SPSS	Statistical Package for Social Science
SNP	Single Nucleotide Polymorphism
WBC	White Blood Cells
WHO	World Health Organization

PROTOCOL SYNOPSIS

TITLE	Aiming at prolonging the therapeutic life span of artemisinin-based combination therapies in an era of imminent Plasmodium falciparum resistance in Bagamoyo District, Tanzania - new strategies with old tools.
SPONSOR	Muhimbili University of Health and Allied Sciences; Dept. of Parasitology and Medical Entomology P. O. Box 65001 Upanga, Dar es salaam Tanzania, Karolinska Institutet, Dept of Molecular, Tumor and Cell Biology, Nobelsväg 16 171 77 Stockholm, Sweden Uppsala University, Dept. of Women's and Children's Health, IMCH, Drottninggatan 4, 75310 Uppsala, Sweden
FUNDING ORGANIZATION	Swedish International Development Agency (SIDA) & Swedish Research Council
NUMBER OF SITES	ONE
RATIONALE	Despite documented high cure rates of ACT in Tanzania, and Africa elsewhere, clinical trials conducted in Tanzania with SIDA and Swedish Research Council support, provide evidence for in vivo selection of lumefantrine tolerant/resistant parasites among recurrent infections[1], [2]. Similarly, molecular epidemiology studies from Bagamoyo District, Tanzania, have shown temporal selection of lumefantrine associated genetic tolerance/resistance markers in the parasite population following wide scale use of artmether-lumefantrine, but without signs of compromised treatment efficacy [3]. During the last decade, and despite the documented rapid microscopy determined parasite clearance of artemether-lumefantrine in Bagamoyo District, interest has developed in understanding the observation of high residual PCR determined positivity rate on day 3 after supervised artemether-lumefantrine treatment in the magnitude of almost 30% in previous assessments from 2015 [4]. Using deep sequencing approaches studies have recently detected PCR determined delayed parasite clearance curves in *P. falciparum* sub-populations in Bagamoyo District, [5]. The clearance times by PCR of these sub-populations were similar to artemisinin resistant parasites in Myanmar as assessed by microscopy, but the former did, importantly, not harbor any of the described mutations in Kelch13 propeller associated with

	artemisinin resistance. However, these Tanzanian parasite sub-populations need to be further studied and characterized since they may provide important clues to the understanding of artemisinin survival strategies among the East African *P. falciparum* parasite population. Taken together, our longitudinal clinical and molecular data described above from a defined geographical area of Tanzania, East Africa, extending from pre-ACT implementation, i.e. before 2006, to a decade of wide scale artemether-lumefantrine use in Bagamoyo district, provide evidence for declining susceptibility to ACT, both to artemether and lumefantrine, among the *P. falciparum* population. These parasites ("last man standing") that survived 10 years of ACT exposure have indeed shown excellent survival instincts and may thus be particularly resistant prone. However, if we loose ACT to P. *falciparum* resistance in Africa, this will have devastating effects on malaria morbidity and mortality and may swiftly ruin the improvements the global malaria community achieved during the past decade with ACT as a key component for success. Based on the above we suggest prolonged treatment with ACT and addition of transmission blocking treatment using a single low dose of primaquine administered on the last day of ACT treatment.
STUDY DESIGN	A two arm randomized, single-blinded clinical trial. The intervention arm will receive a six days treatment course of artemether-lumefantrine together with a single low-dose of primaquine (0.25 mg/kg) administered at the sixth day of treatment. The control arm will receive standard 3-day course of artemether-lumefantrine followed by placebo. The blinded party shall be the patients enrolled. Enrolled patients will be receiving Directly Observed Therapy during the treatment phase. Follow-up will be 42 days.
PRIMARY OBJECTIVE	To assess the therapeutic efficacy of standard versus extended artemether-lumefantrine treatment from 3 to 6 days and the effect of a single low-dose of primaquine administered on day 6 on gametocyte clearance in an era of imminent *P. falciparum* resistance in Bagamoyo District, Tanzania.

SECONDARY OBJECTIVES	1. To compare the therapeutic efficacy of standard 3 day course versus an extended 6 day course of artemether-lumefantrine on PCR determined parasite clearance, PCR corrected cure rate on days 28 and 42, post treatment prophylaxis and safety in patients with uncomplicated *P. falciparum* during high transmission season. 2. To assess if the addition of single low-dose of primaquine (0.25 mg/kg) on the 6th day of ACT treatment would improve the therapeutic efficacy of primaquine in malaria transmission blocking by reducing PCR determined gametocyte carriage/clearance. 3. To characterize molecular markers of individual *P. falciparum* sub-populations that exhibit delayed PCR-determined parasite clearance in relation to known genetic markers associated with ACT resistance/tolerance. 4. To compare the diagnostic accuracy of MoMic, LAMP, and conventional microscopy with PCR as gold standard in determination of day 3 parasitemia.
NUMBER OF SUBJECTS	280
SUBJECT SELECTION CRITERIA	Inclusion Criteria: 1. Age more than 1 year and less than 65 years. 2. Weight 10 kg and above; 3. Body temperature ≥37.5°C or history of fever in the last 24 hours; 4. Microscopy determined asexual *P. falciparum* mono-infection regardless of parasitemia 5. Normal – QTc Interval in Baseline ECG of less than 440ms in male and 460ms in females Exclusion Criteria: 1. Symptoms/signs of severe malaria or danger signs; 2. Pregnancy, Breastfeeding or unwilling to practice birth control during participation in the study. 3. Known allergy to study medications; 4. Hb <8 g/dl; 5. Reported antimalarial intake within last 2 weeks; 6. On regular medication, which may interfere with antimalarial pharmacokinetics and 7. Blood transfusion within last 90 days.

CONTROL PRODUCT, DOSE AND ROUTE OF ADMINISTRATION	1. **Artemether-lumefantrine (AL)** Enrolled patients in the control arm will be treated with artemether-lumefantrine (Coartem®, Novartis or any other WHO prequalified ALU) according to body weight and Tanzanian national treatment guidelines for uncomplicated *P. falciparum* malaria, as follows: One tablet to those weighing 5-14 kg; two tablets to children with 15-24 kg or three tables to children with 25 – 34 kg. The full course of treatment for all study patients consists of 6-doses given twice daily, at 0, 8, 24, 36, 48, 60 hours, with the dose being given as directly observed by a health worker, and the second dose should strictly be given after 8 hours. A fatty snack (biscuits) will be administered together with all artemether-lumefantrine doses to optimise absorption. Participants will be observed for 30 minutes after each drug dose. **2. Placebo** This is a placebo controlled study where patients who will be in the control arm will receive placebo tablets and a placebo aqueous solution in place of the Primaquine that will be given with the 12th dose of ALU.
TEST PRODUCT, DOSE, AND ROUTE OF ADMINISTRATION	1. **Artemether-lumefantrine (AL)** In the intervention arm, extended from 3 to 6 days. In the control arm, patients will be receiving placebo after completion of the standard 3 days-six dose regimen. For practical purposes, a simpler dosage regimen is recommended in order to improve compliance; subsequent doses could be given twice daily (morning-evening) in the second and third days of treatment until completion of the doses. A fatty snack (biscuits) will be administered together with all artemether-lumefantrine doses to optimise absorption. Participants will be observed for 30 minutes after each drug dose. **2. Primaquine** For patients allocated to the prolonged treatment course, a single 0.25 mg/kg primaquine dose (Primaquine phosphate, Sanofi) will be administered concomitantly with the last (i.e. twelfth) artemether-lumefantrine dose. Primaquine will be prepared and administered in an aqueous solution [6]. To preserve the accuracy of lower weight-based doses, all primaquine doses will be administered in aqueous solution and measured using a sterile syringe. The primaquine dose will be given based on weight bands. A snack will also be made available to reduce the side effects like abdominal discomfort.

DURATION OF SUBJECT PARTICIPATION AND DURATION OF STUDY	Subjects will be in the Study for about 42 days ***Screening:*** *at Day 0* ***Active Treatment:*** *3-6 days depending on the treatment Arm* ***Follow-up:*** *42 days* *The total duration of the study is expected to be SIX Months. Four (4) months for subject recruitment and two (2) for final subject follow-up.*
CONCOMMITANT MEDICATIONS	**Allowed**: Paracetamol or acetaminophen according to national treatment guidelines. Patients given tetracycline as an eye ointment will not be excluded **Prohibited**: in the case of self-medication or if an antimalarial drug or an antibiotic with antimalarial activity is administered by a third party.
EFFICACY EVALUATIONS	1. PCR Determined Parasite clearance by day 5 and 7 2. Crude and PCR Corrected Cure Rate by day 28 and 42 3. Gametocyte clearance on Day 7 and 14
PRIMARY ENDPOINT	The primary outcome is proportion of PCR detectable parasitemia on days 5 and 7 in the respective arms.
SECONDARY ENDPOINTS	Secondary outcomes include: 1. Microscopy and PCR determined parasite clearance times, 2. selection of genetic drug resistance markers during the early treatment phase, 3. PCR determined gametocyte carriage/clearance times, 4. Hemoglobin recovery, 5. Fever clearance time 6. Crude and PCR corrected cure rates by day 28, 7. Safety and tolerability, and 8. Day 7 plasma lumefantrine concentrations in the respective arms.
OTHER EVALUATIONS	Pharmacokinetics of Artemisinin and its derivatives, Lumefantrine and its derivatives
SAFETY EVALUATIONS	Change in clinical safety labs from baseline in the following investigations: 1. Drop in Hb by more than 2 g/dl 2. Hematuria observed color change will be gauged against the Hillmen color chart 3. Prolongation QTc Interval in ECG above the upper limits of the normal range Incidence of adverse events: All adverse events, drug-related or not, will be recorded on the case report form. Serious adverse events must

	be reported to the sponsor. At the end of the trial, all relevant clinical and molecular results will be reported to the sponsor and the Ministry of Health. Signs and symptoms such as fatigue, weakness, dizziness, headache, palpitations or allergic drug reactions (rash), diarrhea, abdominal pain, dizziness, itching, fever and Hb prior, during and after treatment will be recorded and determined to whether they are related to the trial medicine.
PLANNED INTERIM ANALYSES	When approximately 50% of patients have completed the study through Visit 10, an interim analysis for safety will be conducted by an independent data monitoring committee. Serious adverse events will be monitored by the committee on an ongoing basis throughout the study.
STATISTICS **Primary Analysis Plan**	Data will be double entered into a password protected SPSS V. 20 database. Data will be cleaned by visual inspection for outliers. Preliminary univariate and bivariate analyses will be carried out to estimate the effects of lumefantrine level, age, and parasitemia and host polymorphisms. Descriptive statistics such as mean, standard deviation and percentages will be reported in the univariate analysis according to the type of the data and using ANOVA statistical output will be obtained. Comparison of fever to parasite clearance among treatment arms will be done using Kaplan-Meiyer's Curves and the Logistic Regression Model. Both adjusted and unadjusted analysis by confounding factors will be implemented. Interaction terms will be used to assess effect measure modification. $P< 0.05$ will be considered significant.
Rationale for Number of Subjects	The sample size was calculated based on an assumed clinically meaningful difference between the arms in PCR positivity rate of 15% on day 5 (20% after standard 3-day artemether-lumefantrine treatment and 5% in the interventional arm). To be able to show this difference with 80% power at 0.05 significance level, 116 patients are needed in each arm. To allow for 20% attrition, a total of 140 patients will be included in each arm.

1 BACKGROUND

General background

Wide scale use of artemisinin-based combination therapy (ACT) for treatment of uncomplicated *Plasmodium falciparum* in malaria endemic areas during the past decade has dramatically improved malaria case management and the possibility to ensure parasitological cure. This has in turn resulted in large number of deaths avarted, especially among African children below 5 years of age and pregnant women, i.e. the two most vulnerable groups for severe malaria disease and death. Thus, ACT has significantly contributed to the recent decline in global malaria burden [7]. Its importance for global health was highlighetd when Professor You You Tu received the Nobel Prize 2015 *"for her discoveries concerning a novel therapy against Malaria"*, i.e. artemisinin.

The rationale behind ACT is to improve treatment efficacy and delay development of resistance by the use of two or more drugs with different modes of action, including an artemisinin-derivative with rapid and effective reduction of the parasite bio-mass (the effect being particularly pronounced on asexual ring stages in the erythrocytic lifecycle) and gametocyte carriage (with effect on young gametocytes only), combined with a partner drug with longer duration of action. To improve rational use and delay development and spread of ACT resistance, WHO recommends ACT to be solely prescribed to patients with a parasite-based malaria diagnosis, either rapid diagnostic test (RDT) or microscopy [8].

In 2009 the first report of emerging artemisinin resistance in *P. falciparum* malaria from Southeast Asia was published. The resistance is phenotypically characterized by delayed parasite clearance times following ACT treatment [9]. Microscopy based *P. falciparum* positivity rate on day 3 after initiation of ACT treatment is considered an important determinant, and if the day-3 positivity rate exceeds 10% this is considered an alert for artemisinin resistance. The initial reports of artemisinin resistance originated from western Cambodia (Pailin), where also chloroquine and sulfadoxine-pyrimethamine resistance was first documented. Despite containment campaigns parasites with delayed clearance post-ACT treatment has spread geographically and are presently found in five countries in the Mekong region (Myanmar, Thailand, Cambodia, Laos and Vietnam) [7].

The molecular basis for artemisinin resistance in Southeast Asia has been linked to mutations in the *P. falciparum* Kelch13 propeller domain. This was first described by Ariey et al. 2014. Kelch13 encods a 726 amino acid protein containing a BTB/POZ domain and a C-terminal 6-blade propeller domain [10]. Mutations in the Kelch13 propeller domain, particullarly in position M4761, Y493H, R539T, I543T and C580Y, are associated with both in vivo and ex vivo artemisinin resistance [11]. Large-scale in vivo studies conducted in Africa and Asia have revealed around 20 non-synonymous Kelch13 mutations associated with delayed parasite clearance following ACT treatment [12], whereas molecular epidemiological studies have reported 60 non-synonymous mutations.

If these resistant parasites, in line with the historical experiences from chloroquine and sulfadoxine-pyrimethamine resistance, will spread westward across Asia and the Indian sub-continent and eventually reach Africa, or emerge independently on the African continent, this will

have devastating effects on malaria morbidity and mortality globally. However, in Africa there has to date been no clear evidence of artemisinin resistant *P. falciparum* [7].

1.1 Overview of Clinical Studies

Specific background

Few WHO prequalified ACT combinations are available. The most commonly used ACT in Africa is artmether-lumefantrine [8]. Tanzania, East Africa, where this project will be conducted, introduced artemether-lumefantrine as first-line treatment for uncomplicated malaria in 2006.

The development of tolerance/resistance against lumefantrine, and other long acting partner drugs in ACT, has been suggested to start through post-treatment selection among recurrent infections of less sensitive *P. falciparum* parasites, as re-infecting parasites need to be able to survive the exposure of sub-therapeutic blood levels of lumefantrine. This hypothesis is supported by our own data from Bagamoyo District, indicating that re-infecting parasites carrying the *pfmdr1* N86/184F/D1246 haplotype were able to withstand 15-fold higher lumefantrine blood concentrations than those with the alternative haplotype (86Y/Y184/1246Y) [13]. This may in turn lead to a gradually shortened post-treatment prophylactic period, long before clinical treatment failures are apparent, why temporal surveillance of genetic antimalarial drug resistance markers of *P. falciparum* have been proposed as an early warning system of evolution of ACT tolerance/resistance.

While awaiting development of alternative, but hopefully equally efficacious antimalarial drugs, it is critical to be proactive and identify and scientifically evaluate new strategies to protect/prolong the therapeutic lifespan of ACT. We propose two practical and feasible means in this regard, one is extending the ACT regimen by three days and the other is introducing a single low dose primaquine (0.25mg/kg) administered on the 6th day of artemether-lumefantrine treatment with the 12th dose.

The utility of the proposed new strategies with old tools are feasible interventions that can be programmatically rolled out without delay since the tools are well known and already in place. The assessment of these new strategies will provide an opportunity to further characterize the PCR determined day-3 and even day-5 positive parasite sub-population to improve the understanding of the genetic repertoire and thus artemisinin survival strategies among the East-African *P. falciparum* population and comparing them with the previously described Kelch13 mutations associated with artemisinin resistance.

2 STUDY RATIONALE

Despite documented high cure rates of ACT in Tanzania, and Africa elsewhere, clinical trials conducted in Tanzania with SIDA and Swedish Research Council support, provide evidence for in vivo selection of lumefantrine tolerant/resistant parasites among recurrent infections [1], [2]. Similarly, molecular epidemiology studies from Bagamoyo District, Tanzania, have shown temporal selection of lumefantrine associated genetic tolerance/resistance markers in the parasite population following wide scale use of artmether-lumefantrine, but without signs of compromised treatment efficacy [3].

During the last decade, and despite the documented rapid microscopy determined parasite clearance of artemether-lumefantrine in Bagamoyo District, interest has developed in understanding the observation of high residual PCR determined positivity rate on day 3 after supervised artemether-lumefantrine treatment in the magnitude of almost 30% in previous assessments from 2015 [11]. Using deep sequencing approaches studies have recently detected PCR determined delayed parasite clearance curves in P. falciparum sub-populations in Bagamoyo District, [12]. The clearance times by PCR of these sub-populations were similar to artemisinin resistant parasites in Myanmar as assessed by microscopy, but the former did, importantly, not harbor any of the described mutations in Kelch13 propeller associated with artemisinin resistance. However, these Tanzanian parasite sub-populations need to be further studied and characterized since they may provide important clues to the understanding of artemisinin survival strategies among the East African *P. falciparum* parasite population.

Taken together, our longitudinal clinical and molecular data described above from a defined geographical area of Tanzania, East Africa, extending from pre-ACT implementation, i.e. before 2006, to a decade of wide scale artemether-lumefantrine use in Bagamoyo district, provide evidence for declining susceptibility to ACT, both to artemether and lumefantrine, among the P. falciparum population. These parasites ("last man standing") that survived 10 years of ACT exposure have indeed shown excellent survival instincts and may thus be particularly resistant prone. However, if we loose ACT to P. falciparum resistance in Africa, this will have devastating effects on malaria morbidity and mortality and may swiftly ruin the improvements the global malaria community achieved during the past decade with ACT as a key component for success.

2.1 Risk / Benefit Assessment

Potential Risks

The primary risk associated with this study is the drawing of frequent blood samples. In the first 134 hours, there will be 8 sampling points, each requiring less than 2 milliliters of blood. The total volume collected over the course of the study (42 days) 6mls is significantly less than 5% of a participant's total blood volume. This amount is generally considered acceptable for research studies. It should also be acceptable to participants and their families. In order to ensure that harms are reduced, we have planned a hemoglobin check at enrollment (baseline) and at day 5 before receiving low dose primaquine (0.25 mg/kg). Then Hb level will be assessed at subsequent visits as well as at any ill visit to ensure that significant anemia does not occur in the children. Any children with a significant drop in hemoglobin will be admitted for further evaluation. In addition to anemia, blood draws can be associated with pain, bruising and bleeding. Symptomatic control of all of these complications will be provided.

A secondary risk associated with the study is breach of confidentiality. Measures will be in place to ensure confidentiality of participants and data generated. Malaria is a common childhood illness in both trial site locations and does not carry any significant stigma associated with it.

Potential Benefits

In the local context it is standard to provide some level of remuneration to participants/families at each site. For the first 6 days, patients who are living far from the site will be retained at the hospital after the first dose to allow for adequate sample collection, but also providing close clinical monitoring during initial follow-up and Directly Observed Therapy (DOT). They will receive payment such as food and transportation allowance reimbursement equivalent of the local

transportation cost for the participant and families during the observations period at the hospital, since they will need to come twice a day. In addition, participants will be receiving high quality care during a febrile illness. Patients will receive treatment for their malaria infection according to National Treatment Guidelines. They will then benefit from routine weekly follow-up to ensure resolution of infection during the 42 day follow up period.

3 STUDY OBJECTIVES

3.1 Broad Objective

To assess the therapeutic efficacy of extended artemether-lumefantrine treatment from 3 to 6 days and the effect of a single low dose of primaquine administered on day 6 on gametocyte clearance in an era of imminent *Plasmodium falciparum* resistance in Bagamoyo District, Tanzania

3.2 Specific Objectives

1. To compare the therapeutic efficacy of standard 3 day course versus extended 6 day course of artemether-lumefantrine on PCR determined parasite clearance, post treatment prophylaxis and safety in patients with uncomplicated *P. falciparum* during high transmission season.

2. To assess if the addition of single low-dose of primaquine (0.25 mg/kg) on the 6th day of ACT treatment would improve the therapeutic efficacy of Primaquine in malaria transmission blocking by reducing PCR determined gametocyte carriage/clearance.

3. To characterize molecular markers of individual *P. falciparum* sub-populations that exhibit delayed PCR-determined parasite clearance in relation to known genetic markers associated with ACT resistance/tolerance.

4. To compare the diagnostic accuracy of MoMic, LAMP, and conventional microscopy with PCR as gold standard in determination of day 3 parasitemia.

4 STUDY DESIGN

4.1 Study Area

Bagamoyo district, Coast region, Tanzania, has an estimated population of about 3 117,400 most of whom are peasants and fishermen [14]. Bagamoyo District is divided into 6 divisions, and 22 wards, comprising 97 villages and 67 health facilities, including 1 hospital, 5 health centers and 59 dispensaries, 44 of which belong to government institutions, 5 to voluntary agencies, and 10 are privately run [15]. The proposed study site, i.e. Yombo primary health care clinic serves a total population of more than 8000 people, within easy access to the referral hospital in Bagamoyo town.

Yombo dispensary has access to two clinical officers, two nurses and one laboratory technician, all trained in malaria case management, microscopy and good clinical practice. Malaria transmission is moderate, and perennial with peaks related to the rainy seasons. After the introduction of artemether-lumefantrine as first line treatment for uncomplicated malaria in 2006 together with insecticidal treated bed-net distribution campaigns the burden of malaria has declined significantly. *P. falciparum* is the predominant species responsible for >95% of diagnosed malaria cases.

4.2 Study Overview

A two arm randomized, single-blinded clinical trial. The intervention arm will receive a six days treatment course of artemether-lumefantrine together with a single low-dose of primaquine (0.25 mg/kg) administered at the sixth day of treatment. The control arm will receive standard 3-day course of artemether-lumefantrine followed by placebo for 3 days.

The blinded party shall be the patients enrolled. Enrolled patients will be have an option of remaining at the during the treatment phase to avoid coming twice a day for medication and blood sampling. Follow-up will be 42 days.

Screening data will be reviewed to determine subject eligibility. Subjects who meet all inclusion criteria and none of the exclusion criteria will be entered into the study. The study is planned to have 280 subjects. Total duration of subject participation will be six weeks.

5 CRITERIA FOR EVALUATION

5.1 Primary Efficacy Endpoint

The primary outcome is proportion of PCR detectable parasitemia on days 5 and 7 in the respective arms.

5.2 Secondary Efficacy Endpoints

Secondary outcomes include microscopy and PCR determined parasite clearance times, fever clearance time, selection of genetic drug resistance markers during the early treatment phase, gametocyte carriage/clearance times, hemoglobin recovery, crude and PCR corrected cure rates by day 28, safety and tolerability, and day 7 plasma lumefantrine concentrations in the respective arms. Analysis will be done using both intention-to-treat and per-protocol approaches.

5.3 Safety Evaluations

An adverse event is defined as any unfavourable, unintended sign, symptom, syndrome or disease that develops or worsens with the use of a medicinal product, regardless of whether it is related to the medicinal product. All adverse events will be recorded on the case report form.
A serious adverse event is defined as any untoward medical occurrence that at any dose: results in death, is life threatening; requires hospitalization or prolongation of hospitalization; results in a persistent or significant disability or incapacity; or is a congenital anomaly or birth defect. Safety will be assessed by direct questioning and recording the nature and incidence of adverse events and serious adverse events. Signs and symptoms such as fatigue, weakness, dizziness, headache, palpitations or allergic drug reactions (rash), diarrhea, abdominal pain, dizziness, itching, fever and Hb prior, during and after treatment will be recorded and determined to whether they are related to the trial medicine. patients will also be asked to observe the color of their urine, and whenever they observe a change they will be advised to collect it in a white container, and then the observed color change will be gauged against the Hillmen color chart. A color change of ≥5 scores represents hemolysis.

Moreover due to prolonged use of lumefantrine, prolonged QTc interval in ECG above the highest limit will be monitored at baseline and 4-5 hours after the last treatment dose. It is expected to be less than 440 milliseconds in men and less than 460 in women.

In addition, data safety monitoring board (DSMB) will be installed; clinically relevant hemolytic events, hospital admissions, blood transfusions and deaths will be reported within 72 hours to the DSMB.

6 SUBJECT SELECTION

6.1 Study Population

Study participants will be recruited from patients attending the study site (Yombo Dispensary) with suspected uncomplicated malaria infection and screened for eligibility.

6.2 Inclusion Criteria

1. Male or female ≥ 1 years of age and 65 years ≤ at Visit Yombo Dispensary.
2. Weight 10 kg and above.
3. Body temperature ≥37.5°C or history of fever in the last 24 hours;
4. Microscopy determined asexual *P. falciparum* mono-infection regardless of parasitemia.
5. Written informed consent (and assent when applicable) obtained from subject or subject's legal representative and ability for subject to comply with the requirements of the study.
6. Normal QTc Interval in an ECG, between 360 – 440 milliseconds in men and 370 - 460 in women.

6.3 Exclusion Criteria

1. Symptoms/signs of severe malaria or danger signs
2. Pregnant, breastfeeding, or unwilling to practice birth control during participation in the study.

3. Presence of a condition or abnormality that in the opinion of the Investigator would compromise the safety of the patient or the quality of the data.
4. Known allergy to study medications
5. Hb <8 g/dl
6. Reported antimalarial intake within last 2 weeks
7. On regular medication, which may interfere with antimalarial pharmacokinetics and blood transfusion within last 90 days. *(see Section 7.1 below)*

7 CONCURRENT MEDICATIONS

All subjects should be maintained on the same medications throughout the entire study period, as medically feasible, with no introduction of new chronic therapies.

7.1 Allowed Medications and Treatments

Standard therapy for Uncomplicated *P. falciparum* malaria is allowed except for treatments noted in the exclusion criteria described above.

Patients with fever ≥38.0°C will be treated with paracetamol or acetaminophen according to national treatment guidelines. Parents or guardians will be instructed in the use of tepid sponging for children under 5 years of age. Prior treatment with antimalarial drugs will not be considered an exclusion criterion; however, during follow-up, if infections other than malaria require the administration of medicines with antimalarial activity, the patient will be withdrawn from the study. Patients given tetracycline as an eye ointment will not be excluded. Patients will be withdrawn from the study in the case of self-medication or if an antimalarial drug or an antibiotic with antimalarial activity is administered by a third party.

Adverse events requiring treatment can be treated according to local practice in Tanzania. If there is a clinical indication for any additional medication during the course of the study, including medication given to treat an adverse event related to the study medicine, the name of the medicine, the dosage and the date and time of administration must be recorded on the case report form. The use of herbal remedies during the study should be avoided, and participants should be encouraged to return to the study site for treatment if they feel unwell. If any herbal remedies are taken during the study, this should be captured on the case report form, under 'study medication administration'.

Prohibited Medications and Treatments

The following medications are prohibited during the study and administration will be considered a protocol violation.

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

- pentamidine.

* Tetracycline eye ointments can be used.

8 STUDY TREATMENTS

8.1 Method of Assigning Subjects to Treatment Groups

Computer generated randomization using Microsoft Excel (Ms Excel). This will be done in blocks of 10, stratified by sex will be done and treatment allocation will be kept in sealed envelopes. Up to 280 eligible patients will be randomly assigned to 3 days or 6 days + PQ treatment groups in a 1:1 ratio using a Ms-Excel computer-generated randomization scheme developed by the study data management provider. The investigator will complete a randomization worksheet at Visit 1.

8.2 Blinding

Due to the objectives of the study, the identity of test and control treatments will be known only to investigators, research staff, but NOT patients. The following study procedures will be in place to ensure single-blind administration of study treatments.

1. Access to the randomization code will be strictly controlled.
2. A taste-matching agent for the placebo.
3. Packaging and labeling of test and control treatments will be identical to maintain the blind.

During the study, the blind may be broken **only** in emergencies when knowledge of the patient's treatment group is necessary for further patient management. When possible, the Investigator should discuss the emergency with the Medical Monitor prior to un-blinding.

8.3 Formulation of Test and Control Products

During the study, there will be two test drugs and two test instruments used as listed below;

1. Artemether-lumefantrine (20/120mg) (Coartem®, Novartis) or any other pre-qualified ALU by WHO according to Tanzanian national treatment guidelines for uncomplicated *P. falciparum* malaria
2. For patients allocated to the prolonged treatment course, a single 0.25 mg/kg primaquine dose (Primaquine phosphate, Sanofi). Primaquine will be prepared and administered in an aqueous solution [6]. To preserve the accuracy of lower weight-based doses, all primaquine doses will be administered in aqueous solution and measured using a sterile syringe.

8.3.1 Formulation of Test Product

Primaquine phosphate, a synthetic compound manufactured by Sanofi with potent antimalarial activity. Each tablet contains 26.3 mg of Primaquine phosphate (equivalent to 15 mg of primaquine base). The dosage is customarily expressed in terms of the base. See Table 1. for the formulation of primaquine phosphate.

Table 1: Formulation and Measured pH of primaquine phosphate

	Primaquine phosphate
Active Ingredient, mg/mL	8-[(4-Amino-1-methylbutyl) amino]-6-methoxyquinoline phosphate 15
Other ingredient, mg/mL	Carnauba Wax, Hydroxypropyl Methylcellulose, Lactose, Magnesium Stearate, Microcrystalline Cellulose, Polyethylene Glycol 400, Polysorbate 80, Pregelatinized Starch, Red Ferric Oxide , Talc, Titanium Dioxide

8.3.2 Formulation of Control Product

A placebo solution (0.9% saline).

8.3.3 Packaging and Labeling

Study drug is supplied in blister packs containing 14 single use tablets each pack. The blister packs will be packaged in boxes of 100 packs enclosed. Each box will have a total of 1400 tablets contained.

Each box of study drug will be labeled with the required TFDA warning statement, the protocol number, a treatment number, the name of the sponsors, and directions for patient use and storage.

8.4 Supply of Study Drug at the Site

The sponsor will ship study drug to the investigational site. The initial study drug shipment will be shipped after site activation (i.e., all required regulatory documentation has been received by the Sponsor and a contract has been executed). Subsequent study drug shipments will be made after site request for resupply.

8.4.1 Dosage/Dosage Regimen

Artemether-lumefantrine (AL)

Enrolled patients will be treated with oral tablets of artemether-lumefantrine (WHO pre-qualified formulation) according to body weight and Tanzanian national treatment guidelines for uncomplicated *P. falciparum* malaria, as follows: One tablet to those weighing 5-14kg; two tablets to children with 15-24 kg or three tables to children with 25 – 34kg and 4 tablets to those participants above 35 kg.

Adverse events are generally mild, most commonly gastrointestinal (vomiting and diarrhea) and hematologic (anemia and eosinophilia). The full course of treatment for all study patients consists of 6-doses given twice daily, at 0, 8, 24, 36, 48, 60 with the dose being given as directly observed by a health worker, and the second dose should strictly be given after 8 hours.

But in the intervention arm, extended from 3 to 6 days. In the control arm, patients will be receiving oral placebo after completion of the standard 3 days-six dose regimen. For practical purposes, and to comply with standard practice, a simpler dosage regimen is recommended in order to improve

compliance; subsequent doses could be given twice daily (morning-evening) in the second and third days of treatment until completion of the doses [16].

A fatty snack (biscuits) will be administered together with all artemether-lumefantrine doses to optimise absorption. Participants will be observed for 30 minutes after each drug dose. Treatment will be re-administered in cases of vomiting. If the patient vomited within the 30 minutes, full treatment dose of antimalarial will be repeated and observed for additional 30 minutes. If vomiting occurs again, patient will be excluded and rescue drug will be administered.

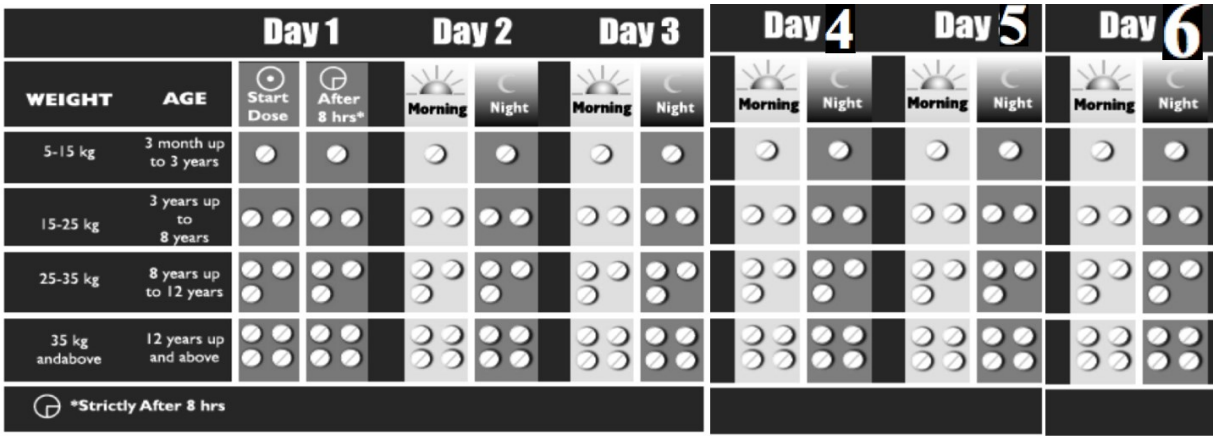


Figure 1: Dosage of AL per weight and age

Primaquine

For patients allocated to the prolonged treatment course, a single 0.25 mg/kg primaquine dose (Primaquine phosphate, Sanofi) will be administered concomitantly with the last (i.e. twelfth) artemether-lumefantrine dose. Primaquine will be prepared and administered in an aqueous solution as previously described [6].

To preserve the accuracy of lower weight-based doses, all primaquine doses will be administered in aqueous solution and measured using a sterile syringe. The primaquine dose will be given based on weight bands. All doses including placebo will be mixed with glucose-based syrup that masks the color and taste of primaquine. All treatments will be directly observed.

A snack with approximately 5g of fat will be administered prior to both AL and primaquine administration to optimize absorption of AL and minimize gastrointestinal side effects with primaquine. All treatment doses will be directly observed by a study nurse.

Primaquine is absorbed rapidly and peak concentrations are reached in approximately 2 hours. It has a half-life of 6 hours and is metabolized in the liver. The metabolically inert principle metabolite (carboxy-primaquine) reaches peak concentrations within 6 hours of administration. The active metabolite has not yet been identified. The kinetics of primaquine are affected by malaria (acute infection reduces oral clearance of primaquine), by food (increase primaquine bio-availability), or by other antimalarial (quinine induces a higher area under the curve (AUC) of the carboxy metabolite).

Table 2. Primaquine dose administration based on weight bands.

Weight (Kg)	Cc (15mg tab in 5mls) (Average)	mg/day	Tablets (15mg per tab)

10-14	0.83-1.16 (0.98)	2.50-3.50	
15-19	1.25-1.58 (1.42)	3.75-4.75	1/4
20-24	1.66-2.00 (1.83)	5.00-6.00	
25-29	2.08-2.42 (2.25)	6.25-7.25	
30-34	2.50-2.83 (2.67)	7.50-8.50	1/2
35-39	2.92-3.25 (3.09)	8.75-9.75	
40-44	3.33-3.66 (3.49)	10.00-11.00	
45-49	3.75-4.08 (3.92)	11.25-12.25	3/4
50-54	4.17-4.50 (4.34)	12.50-13.50	
55-59	4.58-4.92 (4.75)	13.75-14.75	
60-64	5.00-5.30 (5.15)	15.00-16.00	1
65-69	5.40-5.75 (5.58)	16.25-17.25	
70-74	5.83-6.17 (6.00)	17.50-18.50	
75-79	6.25-6.58 (6.42)	18.75-19.75	1 and 1/4
80-84	6.67-7.00 (6.82)	20.00-21.00	
≥85	7.08 (7.10)	21.25	

8.4.2 Dispensing

The Study clinician/nurse is the one responsible for dispensing all the study medications.

8.4.3 Storage

Study drug should be stored by the study site at controlled room temperature, 15 to 30ºC (59 to 86ºF). If the temperature of study drug storage in the clinic/pharmacy exceeds or falls below this range, this should be reported to the Sponsor or designee and captured as a deviation..

8.4.4 Study Drug Accountability

An accurate and current accounting of the dispensing and return of study drug for each subject will be maintained on an ongoing basis by a member of the study site staff. The number of study drug dispensed and returned by the subject will be recorded on the Investigational Drug Accountability Record. The study monitor will verify these documents throughout the course of the study.

8.5 Measures of Treatment Compliance

All the drug administration will be under Directly Observed Therapy by the study staff. Whom will document all the given medication in the CRF.

9 STUDY PROCEDURES AND GUIDELINES

A Schedule of events representing the required testing procedures to be performed for the duration of the study is diagrammed in Appendix 1.

Prior to conducting any study-related activities, written informed consent must be signed and dated by the subject or subject's legal representative. If appropriate, assent must also be obtained prior to conducting any study-related activities.

9.1 Clinical Assessments

9.1.1 Concomitant Medications

All concomitant medication and concurrent therapies will be documented at Baseline/Screening and at Study Days and at early termination when applicable. Dose, route, unit frequency of administration, and indication for administration and dates of medication will be captured.

9.1.2 Demographics

Demographic information (date of birth, gender, address) will be recorded at Screening.

9.1.3 Medical History

Relevant medical history, including history of current disease, other pertinent respiratory history, and information regarding underlying diseases will be recorded at Screening.

9.1.4 Physical Examination

A complete physical examination will be performed by either the investigator or a sub-investigator who is a physician at Visit 1. Qualified staff (MD, NP, RN, and PA) may complete the abbreviated physical exam at all other visits. New abnormal physical exam findings must be documented and will be followed by a physician or other qualified staff at the next scheduled visit.

9.1.5 Vital Signs

Body temperature, blood pressure, pulse and respirations will be performed after resting for 5 minutes on all Study Days.

9.1.6 ECG

Electrocardiography will be performed by a qualified physician. All study participants' cardiac profile will be examined by an ECG before enrolment and also will be taken 4-5 hours after the last dose. This is for the assessment of prolongation of QTc interval, should be less than 440ms form men and 460ms for women.

9.1.7 Pregnancy screening

This will be done to women of child bearing age (12-50 yrs) whom have reported to not seen their menstrual period bleeding more than one normal cycle.

9.1.8 Adverse Events

Information regarding occurrence of adverse events will be captured throughout the study. Duration (start and stop dates and times), severity/grade, outcome, treatment and relation to study drug will be recorded on the case report form (CRF).

9.2 Clinical Laboratory Measurements

9.2.1 Blood Collection Procedures:

Finger prick: The skin will be cleaned and sterilized using an alcohol wipe. A sterile disposable lancet will be used for the procedure. Blood will be collected into sample collection slides, tubes

and filter papers will be labelled with the subject's study ID, date and time of collection. Hemostasis will be achieved and a bandage placed on. Symptomatic control will be provided as needed.

Venipuncture: A tourniquet will be applied to the arm and the skin cleaned with alcohol. A sterile disposable venipuncture needle will be used and blood collected into appropriate vacutainers. After removal of the needle, hemostasis will be achieved and a bandage placed on the site. Symptomatic control will be provided as needed. Vacutainers will be labelled with the subject's study ID, date and time of collection. Blood will then be processed for the appropriate assays.

9.2.2 Microscopy

Conventional Microscopy

A malaria rapid diagnostic test (mRDT) will be collected for quick screening. Thick and thin blood films for parasite counts and species identification should also be obtained and examined at screening on day 0 to confirm adherence to the inclusion and exclusion criteria. Thick blood films will also be examined on day 1, 2, 3, 4, 5, 6, 7, 14, 21, 28, 35 and 42. Also on any other day if the patient returns spontaneously and parasitological reassessment is required.
During day 0, parasite clearance will be assessed at eight hours intervals to elucidate the mean parasite clearance time. Filter paper for molecular genotyping will be collected for each sample of blood that will be taken. Specimens will be labelled anonymously with a unique study ID, day of follow-up and date.

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

Two blood slides with thick and thin smears per patient will be obtained at screening. One slide will then be stained rapidly (10% Giemsa for 10–15 min) for initial screening, while the second slide will be retained. If the patient is subsequently enrolled, the second slide will be stained more carefully (e.g. 2.5–3% Giemsa for 45–60 min), and slower staining will also be used for all slides obtained at follow-up visits. The study number of the patient, the date and the day of follow-up will be recorded either on the frosted edge of the slide or on the glass with a permanent glass pen.

The thick blood smear for initial screening will be used to count the numbers of asexual parasites and white blood cells in a limited number of microscopic fields.
The second blood smear will be used to calculate the parasite density, by counting the number of asexual parasites per 200 White Blood Cells (WBCs) with a hand tally counter. Once a field has been started, it must be counted to completion; the final number of WBCs will therefore rarely be exactly 200. If more than 500 parasites have been counted before 200 WBCs have been reached, the count will be stopped after the reading of the last field has been completed. Parasite density, expressed as the number of asexual parasites per µl of blood, will be calculated by dividing the number of asexual parasites by the number of WBCs counted and then multiplying by assumed WBCs of 8000 per µl.

$$\text{Parasite density (per } \mu\text{l)} = \frac{\text{number of parasites counted} \times (8000)}{\text{Number of leukocytes counted}}$$

The same technique will be used to establish the parasite count on each subsequent blood film. When the number of asexual parasites is less than 10 per 200 WBCs in follow-up smears, counting will be done against at least 500 WBCs (i.e. to completion of the field in which the 500th WBC is counted). A blood slide will be considered negative when examination of 1000 white blood cells **or 100 fields containing at least 10 white blood cells per field reveals no asexual parasites.** The presence of gametocytes on an enrolment or follow-up slide will be noted, but this information will not contribute to basic evaluation.

In addition, 100 fields of the second-thick film will be examined to exclude mixed infections; in case of any doubt, the thin film will be examined for confirmation. If examination of the thin film is not conclusive, the patient will be excluded from the analysis after complete treatment and follow-up.
Two qualified microscopists will read all the slides independently, and parasite densities will be calculated by averaging the two counts. Blood smears with discordant results (differences between the two microscopists in species diagnosis, in parasite density of > 50% or in the presence of parasites) will be re-examined by a third, independent microscopist, and parasite density will be calculated by averaging the two closest counts.

All the microscopy slides will be stored at MUHAS for long term storage.

Mobile Microscopy MOMIC

The aim of this study is to assess the clinical feasibility of a mobile mini-microscope for providing remote, image-based aid to diagnostics in fever patients in Tanzania. In this pilot study, we will evaluate the prototype for a miniaturized, high-resolution microscope developed by our research group. We will combine the mini microscope with remote image analysis of malaria parasites and blood cells, into a diagnostic method for the fever patient.

We have developed technology for computer vision analysis of *P. falciparum*, and quantification of white and red blood cells in blood smear images, captured with the mini microscope and uploaded to our webmicroscopy platform (http://www.webmicroscope.net) [17], [18]. The webmicroscope platform is adapted to perform image analysis remotely, to run several computer vision analyses simultaneously and rapidly return results over mobile wireless networks to the health professional at the point-of-care (POC)

Specific aims

The specific aims and objectives of the proof-of-concept field study are to test the feasibility of the mini microscope and to assess the diagnostic accuracy of the method. The study will be performed in patients presenting with fever during screening and conventional blood smear microscopy (above) will serve as a gold standard.

1. Primary objectives: Diagnostic accuracy (sensitivity, specificity, positive and negative predictive value) for malaria in fever patients.

2. Secondary objectives:

a. Determining percentage parasitemia from the blood smears of those patients who were considered to have a malaria infection.

b. Sample evaluation time and ease-of-use

Two hundred and eighty (280) consecutive patients eligible for a malaria rapid test screening will be included into the study. The malaria rapid test will be assessed according to a standard protocol from a finger-prick capillary blood sample. From the same finger prick two additional blood drops for two thin smears will be taken on separate glass slides, two for DAPI staining.

The thin blood smear samples will be analyzed with conventional microscopy at the point-of-care (Primary Health Care Center, Yombo, Bagamoyo District, Tanzania).

The blood films will be stored after fixing on site by an experienced microscopist (recruited for the study). The slides will be analyzed at a later date. With the aid of the mini microscope, the analysis of the collected blood slides will be performed. The result i.e. the diagnosis, and if malaria is detected also the parasite count, will be compared to the corresponding results of the routinely analyzed sample.

Before analysis with the mini microscope, any personal identification information will be replaced with internal bar codes and the label area of the slides covered. Body temperature, symptoms, and prescription of drugs will be recorded in the case record form (CRF). On the CRF, the corresponding unique study ID number, which appears on the blood smear slides, will be documented.

9.2.3 Loop Mediated Isothermal Amplification (LAMP)

In order to check for malaria clearance on day 3 LAMP procedure will be used. LAMP is a highly efficient and less costly method that amplifies P. falciparum DNA allowing researchers to detect malaria [19]. The mechanism that LAMP works includes DNA amplification using primers designed to bind the parasite's DNA, amplifying the DNA in a circular fashion under isothermal conditions, forming a cauliflower-like DNA sequence in a globe, which can easily be detected due to its cloudiness or fluorescence. This technique fits well to be used in a clinical setting where there is no access to expensive instruments such as PCR machines. Additionally, the design of the procedure (with the amplification taking in a tube) reduces the chance of contamination, and can be done at the time blood samples have been taken, ensuring accuracy and less contamination of the samples collected [20]. This tool has been used for detections of asymptomatic malaria patients in low transmission setting, and its specificity and sensitivity has shown to be comparable to PCR as gold standard [21].

The parasites DNA will be extracted from blood using (400 mM NaCl, 40 mM Tris pH 6.5, 0.4% SDS), heating at 95 degrees for 5mins. The clear supernant will be transferred into dilution tube

with 150microL of sterile water ready for lamp amplification using Loopamp TM MALARIA Pan/Pf detection kit . 30 µl of Positive Control, negative control and samples will be added into a reaction tube and mixed thoroughly. Thereafter the parasites DNA will be amplified by setting the temperature at 65°C for 40 minutes. To terminate amplification process, samples in the reaction tubes will be heated at 85°C for 5 minutes. To detect for parasite presence, UV light will be illuminated under each reaction tube, whereby green light will be observed for positive controls and samples; and no light will be illuminated for the negative controls and samples.

9.2.4 Haemoglobin

As baseline investigation during screening, approximately 20µl of blood in Hemocue cuvettes will be collected for the haematological measurements. This will provide haemoglobin measures in addition to other haematological parameters, some of which will be used for patient management. This will be also taken at Day 7.

9.2.5 Urinalysis

Urine sample will be obtained at two points, screening and day 7. Patients will also be asked to observe the color of their urine, and whenever they observe a change they will be advised to collect it in a white container, and then the observed color change will be gauged against the Hillmen color chart. A color change of ≥5 scores represents hemolysis.

9.2.6 Blood Chemistry Profile

Blood will be obtained on day 0 and sent to each site's clinical chemistry lab for determination of serum sodium, potassium, chloride, bicarbonate, random glucose, BUN, creatinine, aspartate aminotransferase (AST/SGOT), alanine aminotransferase (ALT/SGPT), alkaline phosphatase, total bilirubin, direct bilirubin, gamma-glutamyl transferase (GGT), albumin and LD. A total of about 2ml of venous blood will be required.

9.3 Research Laboratory Measurements

9.3.1 Molecular Genotyping

Four Dried Blood Spots (DBS), each containing approximately 60 microliter of blood, will be prepared. Blood samples will be collected on PerkinElmer 226 filter paper, and DNA extraction done by either Chelex-100 or QIAamp DNA minikit. *P. falciparum* will be detected using a highly sensitive real time based quantitative PCR targeting the cytochrome b gene [22]. Pfs25 female specific and P230p male specific transcripts will be used to detect and quantify male and female gametocytes using previously described protocols [23], [24]. Genotyping of SNPs in *pfmdr1* and *pfcrt* will be done by PCR-RLFP based methods [25], [26], and sequencing of especially *pfcrt* positions 70-77. Analysis of *pfmdr1* gene copy numbers will be done by a comparative $\Delta\Delta C_q$ method after Tag Man RT multiple qPCR [27]. Sequencing of Kelch13 (858 bp portion covering almost all of the six propeller domains),will be done as previously described, and 3D7 used as reference in numbering of nucleotide and amino acid positions Haplotype diversity (h) calculated as $h = \{n/n-1\}\ \{1-\Sigma\ p_i^2\}$where n=nr infections sampled and p_i =frequency of i^{th} haplotype in a group [27]

A special emphasis will be put on characterization of parasite sub-populations that remain PCR detectable on day 5 and 7. These parasites will be subjected to multi targeted deep sequencing in

a collaborative project with Prof Juliano, University of North Carolina, using recently described methods [5]. PCR analysis of *msp2, msp1* and *glurp* will be done in order to distinguish between recrudescence and reinfections.

The backup DBS will be stored at Karolinska Institutet in Sweden for long-term storage from 10 years

9.3.2 Pharmacokinetic Measurements

Procedures during sample collection: A standard history will be taken and clinical examination performed. A Dried Blood Spots (DBS) of about 200 µL will be taken before treatment for plasma drug assay using the Whatman 903 Protein Saver Card filter papers then two hours after the first dose and two hours after the last dose. Each child will be given artemether-lumefantrine (Coartem, Novartis Pharma, Switzerland) at the standard dose according to the Standard Treatment Guideline in Tanzania. This dose will be repeated at 8, 24, 36, 48, 60, for control arm, and at 8, 24, 36, 48, 60, 72, 84, 96, 108, 120, and 132 hours. All doses will be given under direct observation with a fatty snack (equivalent if 2gm of fat). Further six DBS samples will be taken from randomly selected time-points in the following schedule: 4hrs/12hrs (before second dose), 16hrs/ 24hrs (before third dose), 36hrs (before fourth dose), 40hrs/ 48hrs (before fifth dose), 52hrs/ 60hrs (before sixth dose), 64hrs and 72hrs (before seventh dose), and then before first doses on Days 4 (ninth dose at 96hrs), 5hrs (eleventh dose at 120hrs), and 5hrs (twelfth and last dose at 123hrs).

An additional 3 mL venous sample will be taken at one randomly selected time-point in parallel with a DBS for assay validation. For collection of DBS, the fingertip/heel/earlobe will be cleaned with alcohol. A spring-loaded lancet will be used to express a blood droplet which will be applied to the filter paper. At each time-point, 2-5 blood spots will be collected from the single sampling site. The DBS will be air dried (for >1 h), placed into a gas impermeable plastic bag with desiccant and stored in a laboratory freezer at -80oC until analysis. Blood for determination of serum concentrations of Lumefantrine will be done at Prof. Tim Davis laboratory in Australia using established method.

10 ADVERSE EXPERIENCE REPORTING AND DOCUMENTATION

10.1 Adverse Events

An adverse event (AE) is any untoward medical occurrence in a clinical investigation of a patient administered a pharmaceutical product and that does not necessarily have a causal relationship with the treatment. An AE is therefore any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the administration of an investigational product, whether or not related to that investigational product. An unexpected AE is one of a type not identified in nature, severity, or frequency in the current Investigator's Brochure or of greater severity or frequency than expected based on the information in the Investigator's Brochure.

The Investigator will probe, via discussion with the subject, for the occurrence of AEs during each subject visit and record the information in the site's source documents. Adverse events will be recorded in the patient CRF. Adverse events will be described by duration (start and stop dates and times), severity, outcome, treatment and relation to study drug, or if unrelated, the cause.

AE Severity

Table below should be used to grade severity. It should be pointed out that the term "severe" is a measure of intensity and that a severe AE is not necessarily serious.

Table 3. AE Severity Grading

Severity (Toxicity Grade)	Description
Mild (1)	Transient or mild discomfort; no limitation in activity; no medical intervention or therapy required. The subject may be aware of the sign or symptom but tolerates it reasonably well.
Moderate (2)	Mild to moderate limitation in activity, no or minimal medical intervention/therapy required.
Severe (3)	Marked limitation in activity, medical intervention/therapy required, hospitalizations possible.
Life-threatening (4)	The subject is at risk of death due to the adverse experience as it occurred. This does not refer to an experience that hypothetically might have caused death if it were more severe.

AE Relationship to Study Drug

The relationship of an AE to the study drug should be assessed using the following the guidelines in Table 4.

Table 4. AE Relationship to Study Drug

Relationship to Drug	Comment
Definitely	Previously known toxicity of agent; or an event that follows a reasonable temporal sequence from administration of the drug; that follows a known or expected response pattern to the suspected drug; that is confirmed by stopping or reducing the dosage of the drug; and that is not explained by any other reasonable hypothesis.
Probably	An event that follows a reasonable temporal sequence from administration of the drug; that follows a known or expected response pattern to the suspected drug; that is confirmed by stopping or reducing the dosage of the drug; and that is unlikely to be explained by the known characteristics of the subject's clinical state or by other interventions.
Possibly	An event that follows a reasonable temporal sequence from administration of the drug; that follows a known or expected response pattern to that suspected drug; but that could readily have been produced by a number of other factors.
Unrelated	An event that can be determined with certainty to have no relationship to the study drug.

10.2 Serious Adverse Experiences (SAE)

An SAE is defined as any AE occurring at any dose that results in any of the following outcomes:

- death
- a life-threatening adverse experience
- inpatient hospitalization or prolongation of existing hospitalization
- a persistent or significant disability/incapacity
- a congenital anomaly/birth defect

Other important medical events may also be considered an SAE when, based on appropriate medical judgment, they jeopardize the subject or require intervention to prevent one of the outcomes listed.

10.2.1 Serious Adverse Experience Reporting

Study sites will document all SAEs that occur (whether or not related to study drug). The collection period for all SAEs will begin after informed consent is obtained and end after procedures for the final study visit have been completed.

In accordance with the standard operating procedures and policies of the MUHAS Institutional Review Board (IRB)/Independent Ethics Committee (IEC), the site investigator will report SAEs to the IRB/IEC.

10.3 Medical Monitoring

Dr. Nahya Salim should be contacted directly at these numbers to report medical concerns or questions regarding safety.

Phone: 0713 250074
Email: nahyasalim@hotmail.com

11 DISCONTINUATION AND REPLACEMENT OF SUBJECTS

11.1 Early Discontinuation of Study Drug

A subject may be discontinued from study treatment at any time if the subject, the investigator, or the Sponsor feels that it is not in the subject's best interest to continue. The following is a list of possible reasons for study treatment discontinuation:

1. Subject is not compliant with study procedures
2. Adverse event that in the opinion of the investigator would be in the best interest of the subject to discontinue study treatment
3. Subject withdrawal of consent (or assent)
4. Protocol violation requiring discontinuation of study treatment
5. Lost to follow-up
6. Sponsor request for early termination of study
7. Positive pregnancy test (females)

If a subject is withdrawn from treatment due to an adverse event, the subject will be followed and treated by the Investigator until the abnormal parameter or symptom has resolved or stabilized.

All subjects who discontinue study treatment should come in for an early discontinuation visit as soon as possible and then should be encouraged to complete all remaining scheduled visits and procedures.

All subjects are free to withdraw from participation at any time, for any reason, specified or unspecified, and without prejudice.

Reasonable attempts will be made by the investigator to provide a reason for subject withdrawals. The reason for the subject's withdrawal from the study will be specified in the subject's source documents.

11.2 Withdrawal of Subjects from the Study

A subject may be withdrawn from the study at any time if the subject, the investigator, or the Sponsor feels that it is not in the subject's best interest to continue.

All subjects are free to withdraw from participation at any time, for any reason, specified or unspecified, and without prejudice.

Reasonable attempts will be made by the investigator to provide a reason for subject withdrawals. The reason for the subject's withdrawal from the study will be specified in the subject's source documents. As noted above, subjects who discontinue study treatment early (i.e., they withdraw prior to Visit 12) should have an early discontinuation visit. Subjects who withdraw after Visit 12 but prior to Visit 18 should be encouraged to come in for a final visit (and the procedures to be followed would include those for their next scheduled visit).

11.3 Replacement of Subjects

Subjects who withdraw from the study treatment will be replaced.

Subjects who withdraw from the study will not be replaced.

12 PROTOCOL VIOLATIONS

A protocol violation occurs when the subject, investigator, or Sponsor fails to adhere to significant protocol requirements affecting the inclusion, exclusion, subject safety and primary endpoint criteria. Protocol violations for this study include, but are not limited to, the following:

1. Failure to meet inclusion/exclusion criteria
2. Use of a prohibited concomitant medication
3. Non-compliance with study drug regimen

Failure to comply with Good Clinical Practice (GCP) guidelines will also result in a protocol violation. The Sponsor will determine if a protocol violation will result in withdrawal of a subject.

When a protocol violation occurs, it will be discussed with the investigator and a Protocol Violation Form detailing the violation will be generated. This form will be signed by a Sponsor representative and the Investigator. A copy of the form will be filed in the site's regulatory binder and in the Sponsor's files.

13 DATA SAFETY MONITORING

The Muhimbili University of Health and Allied Sciences (MUHAS) Data Safety Monitoring Board (DSMB) will establish a Data Monitoring Committee (DMC) to review data relating to safety and efficacy, to conduct and review interim analyses, and to ensure the continued scientific validity and merit of the study, according to the MUHAS Data Safety Monitoring Board Operations Manual and a DMC Charter to be established for this protocol. There will be three interim review(s) conducted by the DMC for the purpose of monitoring study conduct and assessing patient safety. Further details regarding the timing and content of the interim reviews is included in the statistical section below.

14 STATISTICAL METHODS AND CONSIDERATIONS

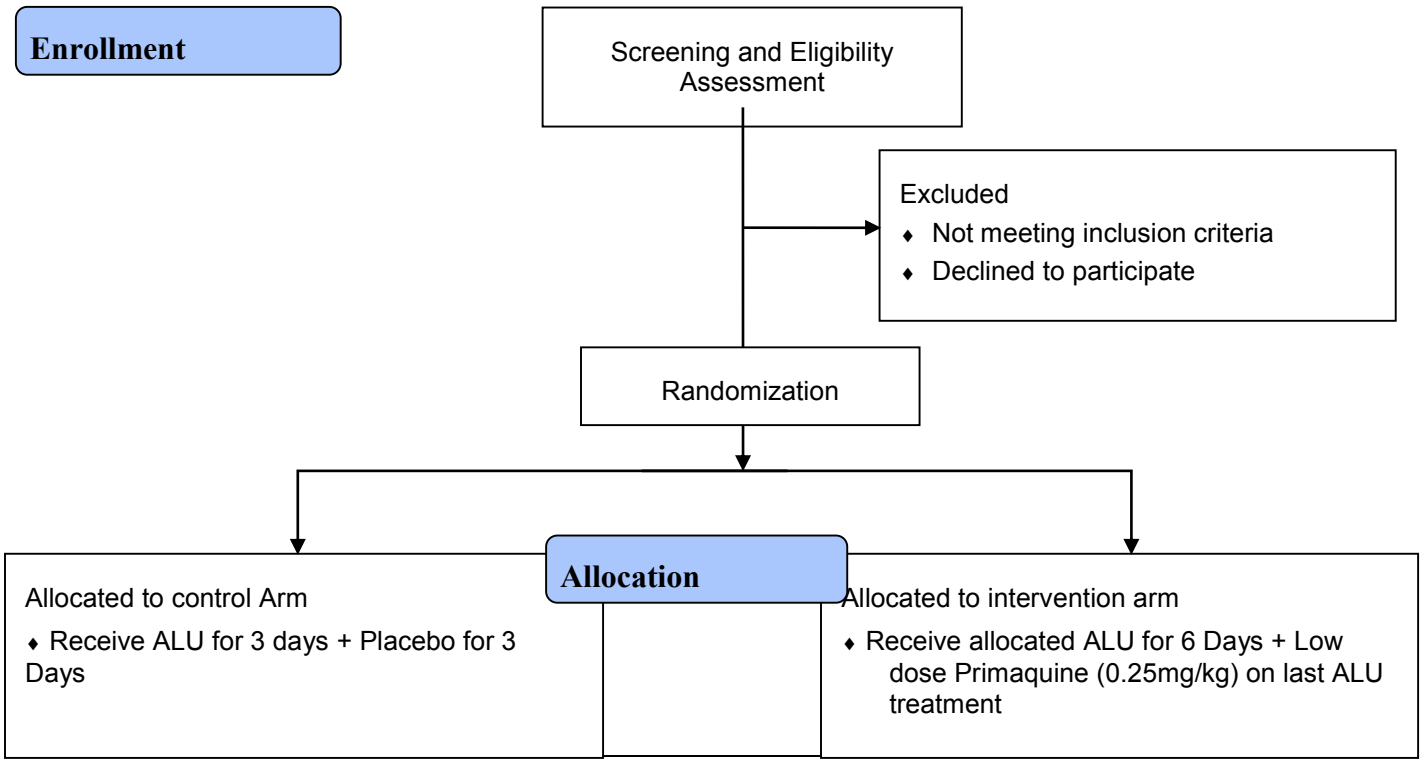
Prior to the analysis of the final study data, a detailed Statistical Analysis Plan (SAP) will be written describing all analyses that will be performed. The SAP will contain any modifications to the analysis plan described below.

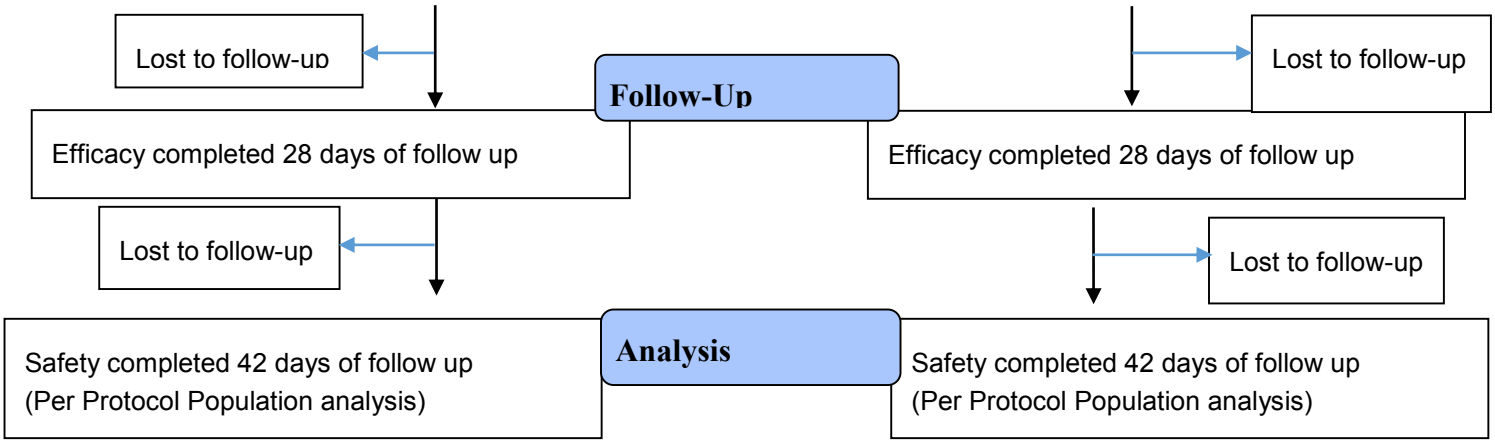
14.1 Data Sets Analyzed

All eligible patients who are randomized into the study and receive at least one dose of the study drug (the Intention to Treat -ITT Population) will be included in the Intention to Treat analysis.

All eligible patients who have completed the study with all the follow up and received treatment medication will be the Per Protocol Population and included in the Per Protocol Analysis.

14.2 Patients Flow Diagram





14.3 Primary Analysis plan

Data will be double entered into a password protected SPSS V. 20 database. Data will be cleaned by visual inspection for outliers. Preliminary univariate and bivariate analyses will be carried out to estimate the effects of lumefantrine level, age, and parasitemia and host polymorphisms. Descriptive statistics such as mean, standard deviation and percentages will be reported in the univariate analysis according to the type of the data and using ANOVA statistical output will be obtained. Comparison of fever to parasite clearance among treatment arms will be done using Kaplan-Meiyer's Curves and the Logistic Regression Model. Both adjusted and unadjusted analysis by confounding factors will be implemented. Interaction terms will be used to assess effect measure modification. $P< 0.05$ will be considered significant.

14.4 Analysis of Secondary Endpoints

Safety and tolerability data will be summarized by treatment group. Adverse event rates will be coded by body system and MedDra classification term. Adverse events will be tabulated by treatment group and will include the number of patients for whom the event occurred, the rate of occurrence, and the severity and relationship to study drug.

14.5 Interim Analysis

When approximately 50% of patients have completed the study through Visit 10, an interim analysis for safety will be conducted by an independent data monitoring committee. Serious adverse events will be monitored by the committee on an ongoing basis throughout the study.

14.6 Sample Size and Randomization

The sample size was calculated based on an assumed clinically meaningful difference between the arms in PCR positivity rate of 15% on day 6 (20% after standard 3-day artemether-lumefantrine treatment and 5% in the interventional arm). To be able to show this difference with 80% power at 0.05 significance level, 116 patients are needed in each arm. To allow for 20% attrition, a total of 140 patients will be included in each arm.

For clinical superiority design, the formula is:

$$N = 2 \times \left(\frac{z_{1-\alpha} + z_{1-\beta}}{\mathrm{d} - \delta_0} \right)^2 \times p \times (1-p)$$

N = size of group
p = response rate of standard treatment group

d = difference between the two treatment groups

δ= the clinically acceptable margin **β= probability of Type II error**
α= probability of Type I error **z = test statistic of assuming normal population**

15 DATA COLLECTION, RETENTION AND MONITORING

15.1 Data Collection Instruments

The Investigator will prepare and maintain adequate and accurate source documents designed to record all observations and other pertinent data for each subject treated with the study drug.

Study personnel at the site will enter data from source documents corresponding to a subject's visit into the protocol-specific paper CRF when the information corresponding to that visit is available. Subjects will not be identified by name in the study database or on any study documents to be collected by the Sponsor (or designee), but will be identified by a site number, subject number and initials or a barcode.

If a correction is made on a CRF, the study staff member will line through the incorrect data, write in the correct data and initial and date the change.

The Investigator is responsible for all information collected on subjects enrolled in this study. All data collected during the course of this study must be reviewed and verified for completeness and accuracy by the Investigator. A copy of the CRF will remain at the Investigator's site at the completion of the study.

15.2 Data Management Procedures

The data will be entered into a validated SPSS database. The Data Management group will be responsible for data processing, in accordance with procedural documentation. Database lock will occur once quality assurance procedures have been completed.

All procedures for the handling and analysis of data will be conducted using good computing practices meeting NIMR and TFDA guidelines for the handling and analysis of data for clinical trials.

15.3 Data Quality Control and Reporting

After data have been entered into the study database, a system of computerized data validation checks will be implemented and applied to the database on a regular basis. The study database will

be updated in accordance with the resolved queries. All changes to the study database will be documented.

15.4 Archival of Data

The database is safeguarded against unauthorized access by established security procedures; appropriate backup copies of the database and related software files will be maintained. Databases are backed up by the database administrator in conjunction with any updates or changes to the database. At critical junctures of the protocol (e.g., production of interim reports and final reports), data for analysis is locked and cleaned per established procedures.

15.5 Availability and Retention of Investigational Records

The Investigator will make study data accessible to the monitor, other authorized representatives of the Sponsor (or designee), IRB/IEC, and Regulatory Agency (e.g., NIMR and TFDA) inspectors upon request. A file for each subject must be maintained that includes the signed Informed Consent, Assent Form and copies of all source documentation related to that subject. The Investigator will ensure the reliability and availability of source documents from which the information on the CRF was derived.

All study documents (patient files, signed informed consent forms, copies of CRFs, Study File Notebook, etc.) must be kept secured for a period of 10 years following completion of the study. The study documents will be stored at MUHAS. There may be other circumstances for which the Sponsor is required to maintain study records and, therefore, the Sponsor should be contacted prior to removing study records for any reason.

15.6 Monitoring

Monitoring visits will be conducted by representatives of the Sponsor. By signing this protocol, the Investigator grants permission to the Sponsor (or designee), and appropriate regulatory authorities to conduct on-site monitoring and/or auditing of all appropriate study documentation.

15.7 Subject Confidentiality

In order to maintain subject confidentiality, only a site number, subject number and subject initials will identify all study subjects on CRFs and other documentation submitted to the Sponsor.

16 ADMINISTRATIVE, ETHICAL, REGULATORY CONSIDERATIONS

The study will be conducted according to the Declaration of Helsinki, Protection of Human Volunteers, Institutional Review Boards, and Obligations of Clinical Investigators.

To maintain confidentiality, all laboratory specimens, evaluation forms, reports and other records will be identified by a coded number and initials only. All study records will be kept in a locked file cabinet and code sheets linking a patient's name to a patient identification number will be stored separately in another locked file cabinet. Clinical information will not be released without written permission of the subject, except as necessary for monitoring by the NIMR and TFDA. The Investigator must also comply with all applicable privacy regulations.

16.1 Protocol Amendments

Any amendment to the protocol will be written by the Investigator. Protocol amendments cannot be implemented without prior written IRB/IEC approval except as necessary to eliminate immediate safety hazards to patients. A protocol amendment intended to eliminate an apparent immediate hazard to patients may be implemented immediately, provided the IRBs are notified within five working days.

16.2 Institutional Review Boards and Independent Ethics Committees

The protocol and consent form will be reviewed and approved by the IRB/IEC of each participating center prior to study initiation, including NIMR and TFDA. Ethical clearance from MUHAS has been sought and granted. The procedures for ethical review stipulated by the Swedish law on ethical review in medical research have been followed, and approval from the Regional Ethics Review Board, Stockholm, has been granted (Dnr: 2016/2286-32). Serious adverse experiences regardless of causality will be reported to the IRB/IEC in accordance with the standard operating procedures and policies of the IRB/IEC, and the Investigator will keep the IRB/IEC informed as to the progress of the study. The Investigator will obtain assurance of IRB/IEC compliance with regulations.

Any documents that the IRB/IEC may need to fulfill its responsibilities (such as protocol, protocol amendments, Investigator's Brochure, consent forms, information concerning patient recruitment, payment or compensation procedures, or other pertinent information) will be submitted to the IRB/IEC. The IRB/IECs written unconditional approval of the study protocol and the informed consent form will be in the possession of the Investigator before the study is initiated. The IRB/IECs unconditional approval statement will be transmitted by the Investigator to the Sponsor prior to the shipment of study supplies to the site. This approval must refer to the study by exact protocol title and number and should identify the documents reviewed and the date of review.

Protocol and/or informed consent modifications or changes may not be initiated without prior written IRB/IEC approval except when necessary to eliminate immediate hazards to the patients or when the change(s) involves only logistical or administrative aspects of the study. Such modifications will be submitted to the IRB/IEC and written verification that the modification was submitted and subsequently approved should be obtained.

The IRB/IEC must be informed of revisions to other documents originally submitted for review; serious and/or unexpected adverse experiences occurring during the study in accordance with the standard operating procedures and policies of the IRB; new information that may affect adversely the safety of the patients of the conduct of the study; an annual update and/or request for re-approval; and when the study has been completed.

16.3 Informed Consent Form

Informed consent will be obtained in accordance with the Declaration of Helsinki, ICH GCP.The Investigator will prepare the informed consent and assent form, and provide the documents to the Sponsor or designee for approval prior to submission to the IRB/IEC. The consent form generated by the Investigator must be acceptable to the Sponsor and be approved by the IRB/IEC. The written consent document will embody the elements of informed consent as described in the International Conference on Harmonisation and will also comply with local regulations. The

Investigator will send an IRB/IEC-approved copy of the Informed Consent Form to the Sponsor for the study file.

A properly executed, written, informed consent will be obtained from each subject prior to entering the subject into the trial. Information should be given in both oral and written form and subjects (or their legal representatives) must be given ample opportunity to inquire about details of the study. If appropriate and required by the local IRB/IEC, assent from the subject will also be obtained. If a subject is unable to sign the informed consent form (ICF), a legal representative may sign for the subject. A copy of the signed consent form (and assent) will be given to the subject or legal representative of the subject and the original will be maintained with the subject's records.

16.4 Publications

This is a PhD Study. The preparation and submittal for publication of manuscripts containing the study results shall be in accordance with a process determined by mutual written agreement among the study Sponsor and participating institutions. The publication or presentation of any study results shall comply with all applicable privacy laws.

17 BUDGET

No	Category	Item	Specification	Quantity	Unit Cost	Total Cost
1	Chemicals/ consumables	AL tablets	p/12	120	2,000	240,000
			p/24	120	2,000	240,000
		Primaquine tablets		100	2550	255,000
		Paracetamol tablets	p/1000	1	12,000	12,000
		Amoxy caps/tabs	Doses	50	2,500	125,000
		Quinine Tablets	Doses	50	4000	200,000
		Giemsa stain	Liter	1	10,000	10,000
		Immersion oil	Tubes	5	5000	25,000
		Methanol	Liter	1	10,000	10,000

		Blood slides	p/72 pks	50	4000	200,000
		Filter papers	Pcs	10	20,000	200,000
		Slide boxes	Pcs	30	6,000	180,000
		Plastic bags	p/100	30	12,000	360,000
		Descicants		3,000	33	99,000
		Blood lancet	p/100	40	6,000	240,000
		Cotton wool	Pcs	4	11,000	44,000
		Cotton gauze	Pcs	2	15,000	30,000
		Cuvettes	p/50	44	5,000	220,000
		Syringes	p/1000	1	20,000	20,000
		Gloves	p/50 pcs	100	11,500	1,150,000
		Stopwatch		2	25,000	50,000
		Digital thermometre	Pcs	4	7,000	28,000
		Bed nets	pcs	10	8,000	80,000
		Bed sheets	pcs	20	5,000	100,000
		Flat files		280	1,000	240,000
		Screening books	pcs	2	4000	8,000
		Envelopes		280	100	24,000
		Fuel	liters	200	2200	440,000
	Sub total					4,830,000
No.	Category	Item	Specification	Quantity	Unit cost(Tsh)	
2	Field work and allowances	Per diem for PhD student	1	180	60,000	10,800,000

		Per diem for the supervisor	1	20	80,000	1,600,000
		Per diem for the driver	1	90	60,000	5,400,000
		Research assistants	2 Nurses	4	100,000	5,360,000
			2 Clinical officer		150,000	
			2 Technicians		400,000	
		Meal for the participants and their parents/ guardians	Maximum 280 subjects and 120 relatives	3	8,000	6,720,000
		Transport per visit	Maximam 280 participants	16	5,000	22,400,000
		Training	6 Research assistances+ 1 Trainer	2	20,000	280,000
	Sub-total					46,725,000
	Grand Total					57,135,000

17.1 Budget Justification

The project work is under the bilateral (Tanzania-Sweden) Malaria sub-project supported by the Swedish Development Agency (Sida). An estimated Tshs 57,135,000 /= will be required to carry out this study. The reagents will be used for fixing and staining of blood slides and analysis of lumefantrine plasma concentration. Primaquine is a drugs under investigation, and artemether-lumefantrine will be used as a control whereas, Quinine as rescue drug and Amoxicillin and Paracetamol will be used to treat other accompanying morbidities. Blood slides and filter papers will be used to collect blood samples whereas slide boxes and plastic bags will be used to store slides and filter paper respectively after the sample is taken. The patients may be admitted/ retained for up to 12 hours after initial dose; therefore, they will need bed nets and sheets, and food. In addition, patients will be refunded for their transport costs for every visit.

The PhD student will be staying at the study site for the whole time of patient's enrolment and treatment to ensure that the protocol and standard operating procedures are followed. The per diems required are Tshs. 60,000 per day whereas a total of 180 days will be spent at the site. To ensure adherence to protocol and provide guidance on the conduct of the research the Supervisor will have to visit the study sites at least twice a month, and will need Tshs 80,000 per day and he will go to the field for a total of 20 days in a period of 5 months. A project car will be used throughout this study to ease transportation of samples and the visits at the study site. The project driver will be required at all times during the visits at the sites, therefore the driver will require the allowance for 90 days.

Since continuous collection of blood samples will be required, the study will recruit six research assistants (2 Nurses, 2 Clinical Officers and 2 Laboratory technicians). The clinical officers will be screening the patients with fever or history of fever, the technicians will be taking blood samples, staining and reading of blood slides and other tests as required. The nurses will be administering the medications and taking care of the wards and issues related to food for patients. The researcher (PhD student) will be the overseer of all activities in site. The study will be conducted during the high malaria transmission season in the area from June to October, thus it will be preferable to pay the research assistances per month. The clinical officers will be paid Tshs. 150, 000 per month each and nurses will be paid Tshs 100, 000 per month each, whereas the technicians will be paid Tshs. 400,000 per month each.

17.2 Work plan

	Item/Task	Duration of Task 1 mo. = 30 days .75 mo=22.5 .5 mo=15 days .235 mo=7 days .2 mo=6 days .05 mo=2 days (can be changed)	Days (=C*30)	Start Date	Finish Date	Predecessor Task FS=task indicated in this column must finish prior to start of current task line SS=tasks can both start on the same day and run in parallel (can be changed)
	Award Notification to First Subject Enrolled Totals:		260	15-May-16	29-Jan-17	
1	Notification of SIDA-Award Approval Received		0	15-May-16	15-May-16	NA
2	Protocol Development to Final Draft (Includes protocol development and vetting through SIDA and MUHAS. Time presented is an average based on experience. Can be longer or shorter based on status of protocol at award.)	2	60	15-May-16	14-Jul-16	1 FS
3	Submit final draft protocol and consent document to MUHAS Reviewers for review and comment; incorporate revisions	0.05	2	14-Jul-16	15-Jul-16	2 FS
4	MUHAS reviewers Review of Final Draft	0.5	15	15-Jul-16	30-Jul-16	3 FS

5	Oversight Senate Committee Review of Protocol	0.5	15	30-Jul-16	14-Aug-16	4 FS
6	Protocol & Consent Document Finalization (Includes review, comment and recommendations by IRB/NIMR.)	2	60	14-Aug-16	13-Oct-16	5 FS
7	Submission & Approval of Protocol & Consent Documents to necessary to Uppsala University for admission (Assumes single site with one IRB.)	1.5	45	13-Oct-16	27-Nov-16	6 FS
8	Preparation and submission of IND (if applicable) (Minimum of 30 days must elapse between submission of IND and beginning of enrollment. IRB may request documentation of IND approval prior to issuing final IRB approval.)	2	60	14-Aug-16	13-Oct-16	6 SS
9	Data Management & Safety Management Tasks for Site Activation (This time includes creation of source documents, CRFs, designing and implementing a database, (EDC or a paper study) training on the data system, setting up safety reporting (SAEs), and all associated Plans.)	2.25	68	27-Oct-16	3-Jan-17	7 SS +14 days
10	Site Staff Preparation (Time includes writing a Manual of Procedures, assessing SOPs, training staff on protocol, specimen collection, processing, storage and shipping, study time and events tables, full protocol training identification of site staff for study roles.)	3	90	13-Oct-16	11-Jan-17	7 SS
11	Site Facility Preparedness (Includes collection of necessary supplies, assuring physical facilities meet privacy and security standards as well as any labs meeting requirements per protocol, for example: appropriate specimen processing equipment, freezers, centrifuges etc.)	1.5	45	13-Oct-16	27-Nov-16	7 SS

12	Study Product Ready on Site (Time includes identification of study product supplier, calculating amount of study product needed, ordering study product, shipment prior to Site Initiation Visit, QC of received product, development of process for study product distribution to patients.)	3	90	13-Oct-16	11-Jan-17	6 FS
13	Site Initiation Visit	0.05	2	11-Jan-17	13-Jan-17	6FS, 7FS, 8FS, 9FS, 10FS, 12FS
14	Site Activation Checklist Completed (Includes time for completion of checklist, approval, and signature by NIDCR.)	0.5	15	13-Jan-17	28-Jan-17	9 FS
15	Site is Activated	0.05	2	28-Jan-17	29-Jan-17	10 FS
16	Data Collection (Patients enrollment, filling CRF, Follow up, Specimen collection and storage)	5	150	29-Jan-17	28-Jun-17	11 FS
17	Data Processing (Data entry and Data cleaning and analysis of preliminary data to get initial finding and preparing samples for shipment to Karolinska)	4	120	28-Jun-17	26-Oct-17	12 FS
18	Lab works (Processing the blood samples and running analysis as per protocol, Attending short courses and seminars)	3	90	26-Oct-17	24-Jan-18	13 FS
19	Preparing Manuscripts for publication, and contacting Journals for publishing requirements	3	90	24-Jan-18	24-Apr-18	14 SS
20	Publishing the Papers, Attending Short courses, More lab/field works	9	270	24-Apr-18	19-Jan-19	15 SS

17.3 Investigator Responsibilities

By signing the Agreement of Investigator form, the Investigator agrees to:

1. Conduct the study in accordance with the protocol and only make changes after notifying the Sponsor (or designee), except when to protect the safety, rights or welfare of subjects.
2. Personally conduct or supervise the study (or investigation).
3. Ensure that the requirements relating to obtaining informed consent and IRB review and approval meet standard guidelines.
4. Report to the Sponsor or designee any AEs that occur in the course of the study.
5. Ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations in meeting the above commitments.
6. Maintain adequate and accurate records and to make those records available for inspection with the Sponsor (or designee).
7. Ensure that an IRB that complies with the requirements of §21 CFR part 56 will be responsible for initial and continuing review and approval of the clinical study.
8. Promptly report to the IRB and the Sponsor (or designee) all changes in the research activity and all unanticipated problems involving risks to subjects or others (to include amendments and IND safety reports)
9. Seek IRB approval before any changes are made in the research study, except when necessary to eliminate hazards to the patients/subjects.
10. Comply with all other requirements regarding the obligations of clinical investigators and all other pertinent requirements

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19 APPENDIX I. SCHEDULE OF EVENTS DURING STUDY VISITS

SAMPLING AND ACTIVITIES SCHEDULE AND BLOOD VOLUMES - ALU PQ STUDY 2017

S/N	Day of Visit	Events	Time for Activity - Hours after 1st Dose	Type of Activities	No. of Activiti	Activities to be done	Equipment needed	Volume of Blood	Mandatory / Randomised
1	Day 0	Screening	1 hour before	Blood Tests	2	mRDT	mRDT Kits	8µl	Mandatory for all
						Conventional Microscopy - Thick and Thin Smear	2 Blood Slides	15µl	
		Enrollment	0 hour	Blood Tests	5	DBS for Molecular Genotyping	PerkinElmer 226 filter paper	100µl	
						DBS for Pharmacokinetics	Whatman 903 Protein Saver	200µl	
						Random Venous Sample for PK	Sodium Heparin Tube	3ml	
						Blood for Biochemisty	Serology Tube (RED - top)	2ml	For Randomised Patients
						MoMic Screening - Thin Smear	2 Blood Slides	15µl	Mandatory for all
						Haematology - (HB)	HB Machine&Cuvette	20µl	
				Other Enrollment Criterion Parameters	5	Weight	Weighing scale	NA	
						Body Temp	Thermometer	NA	
						Urinalysis	Urinary Dip Sticks	NA	
						Pregnancy test if applicable	Urinary Pregnacy Tests	NA	As per clinician indicatio
						Electrocardiography (ECG)	ECG Machine	NA	For Randomised Patients
				Logistical activities realted to study	3	Randomization	Randomization List	NA	Mandatory for all
						Medication (ALU)/kg	Artemether-Lumefantrine	NA	
						Transportation allowance reimbursement	Money	NA	
			2 hours	Blood Tests	1	DBS for Pharmacokinetics	Whatman 903 Protein Saver	200µl	
			4 hours	Blood Tests	1	DBS for Pharmacokinetics	Whatman 903 Protein Saver	200µl	For Randomised Patients
			8 hours	Blood Tests	1	DBS for Pharmacokinetics	Whatman 903 Protein Saver	200µl	
						Random Venous Sample for PK	Sodium Heparin Tube	3ml	
				Logistical activities realted to study	2	Medication (ALU) /kg	Artemether-Lumefantrine	NA	Mandatory for all
						Transportation allowance reimbursement	Money	NA	
2	Day 1	Follow up	24 hours	Blood Tests	4	Conventional Microscopy - Thick and Thin Smear	2 Blood Slides	15µl	Mandatory for all
						DBS for Molecular Genotyping	PerkinElmer 226 filter paper	100µl	
						Random Venous Sample for PK	Sodium Heparin Tube	3ml	For Randomised Patients
						DBS for Pharmacokinetics	Whatman 903 Protein Saver	200µl	
				logistical activities realted to study	2	Medication (ALU) /kg	Artemether-Lumefantrine	NA	Mandatory for all
						Transportation allowance reimbursement	Money	NA	
			36 hours	Blood Tests	2	Medication (ALU) /kg	Artemether-Lumefantrine	NA	
						DBS for Pharmacokinetics	Whatman 903 Protein Saver	200µl	
			40 hours	Blood Tests	1	DBS for Pharmacokinetics	Whatman 903 Protein Saver	200µl	For Randomised Patients
				Logistical activities realted to study	2	Random Venous Sample for PK	Sodium Heparin Tube	3ml	
						Transportation allowance reimbursement	Money	NA	
3	Day 2	Follow up	48 hours	Blood Tests	4	Conventional Microscopy - Thick and Thin Smear	2 Blood Slides	60µl	Mandatory for all
						DBS for Molecular Genotyping	PerkinElmer 226 filter paper	60µl	
						Random Venous Sample for PK	Sodium Heparin Tube	3ml	For Randomised Patients
						DBS for Pharmacokinetics	Whatman 903 Protein Saver	200µl	
				logistical activities realted to study	2	Medication (ALU) /kg	Artemether-Lumefantrine	NA	Mandatory for all
						Transportation allowance reimbursement	Money	NA	
			52 hours	Blood Tests	2	DBS for Pharmacokinetics	Whatman 903 Protein Saver	200µl	
						Random Venous Sample for PK	Sodium Heparin Tube	3ml	For Randomised Patients
			60 hours	Blood Tests	1	DBS for Pharmacokinetics	Whatman 903 Protein Saver	200µl	
				Logistical activities realted	2	Medication (ALU)/kg	Artemether-Lumefantrine	NA	

				to study	2	Transportation allowance reimbursement	Money	NA	Mandatory for all
4	Day 3	Follow up	72 hours	Blood Tests	4	Conventional Microscopy - Thick and Thin Smear	2 Blood Slides	15µl	
						LAMP Study Sample	Microcuveates	40µl	
						MoMic Screening - Thin Smear	2 Blood Slides	15µl	
						DBS for Molecular Genotyping	PerkinElmer 226 filter paper	100µl	For Randomised Patients
				logistical activities realted to study	2	DBS for Pharmacokinetics	Whatman 903 Protein Saver	200µl	
						Medication (ALU) /kg	Artemether-Lumefantrine	NA	
			84 hours	Blood Tests	2	Transportation allowance reimbursement	Money	NA	
						DBS for Pharmacokinetics	Whatman 903 Protein Saver	200µl	
			88 hours	Blood Tests	1	Medication (ALU)/kg	Artemether-Lumefantrine	NA	
				Logistical activities realted to study	2	DBS for Pharmacokinetics	Whatman 903 Protein Saver	200µl	
						Transportation allowance reimbursement	Money	NA	Mandatory for all
						Random Venous Sample for PK	Sodium Heparin Tube	3ml	
5	Day 4	Follow up	96 hours	Blood Tests	3	Conventional Microscopy - Thick and Thin Smear	2 Blood Slides	15µl	
						DBS for Molecular Genotyping	PerkinElmer 226 filter paper	100µl	
						Random Venous Sample for PK	Sodium Heparin Tube	3ml	For Randomised Patients
				logistical activities realted to study	2	Medication (ALU) /kg	Artemether-Lumefantrine	NA	
						Transportation allowance reimbursement	Money	NA	
			100 hours	Blood Tests	2	DBS for Pharmacokinetics	Whatman 903 Protein Saver	200µl	
						Random Venous Sample for PK	Sodium Heparin Tube	3ml	
				Logistical activities realted to study	2	Medication (ALU)/kg	Artemether-Lumefantrine	NA	
						Transportation allowance reimbursement	Money	NA	Mandatory for all
6	Day 5	Follow up	120 hours	Blood Tests	4	Conventional Microscopy - Thick and Thin Smear	2 Blood Slides	15µl	
						DBS for Molecular Genotyping	PerkinElmer 226 filter paper	100µl	
						Random Venous Sample for PK	Sodium Heparin Tube	3ml	For Randomised Patients
						DBS for Pharmacokinetics	Whatman 903 Protein Saver	200µl	
				logistical activities realted to study	2	Medication (ALU) /kg	Artemether-Lumefantrine	NA	
						Transportation allowance reimbursement	Money	NA	Mandatory for all
			132 hours	Blood Tests	2	Blood for Biochemisty	Serology Tube (RED - top)	2ml	
						DBS for Pharmacokinetics	Whatman 903 Protein Saver	200µl	
						Random Venous Sample for PK	Sodium Heparin Tube	3ml	
				Medication	2	Primaquine 0.25mg/kg	Primaquine Aqueous Soln	NA	
						Medication (ALU)/kg	Artemether-Lumefantrine	NA	For Randomised Patients
			134 hours	Blood Tests	1	DBS for Pharmacokinetics	Whatman 903 Protein Saver	200µl	
			136 hours	Logistical activities realted to study	4	DBS for Pharmacokinetics	Whatman 903 Protein Saver	200µl	
						Electrocardiography (ECG)	ECG Machine	NA	
						Transportation allowance reimbursement	Money	NA	Mandatory for all
7	Day 6	Follow up	144 hours	Blood Tests	4	Conventional Microscopy - Thick and Thin Smear	2 Blood Slides	15µl	
						DBS for Molecular Genotyping	PerkinElmer 226 filter paper	100µl	
						Random Venous Sample for PK	Sodium Heparin Tube	3ml	For Randomised Patients
						DBS for Pharmacokinetics	Whatman 903 Protein Saver	200µl	
				logistical activities realted to study	2	Urinalysis	Urinary Dip Sticks	NA	
						Transportation allowance reimbursement	Money	NA	Mandatory for all
8	Day 7	Follow up	168 hours	Blood Tests	4	Conventional Microscopy - Thick and Thin Smear	2 Blood Slides	15µl	
						Haematology - (HB)	HB Machine&Cuvette	20µl	
						DBS for Molecular Genotyping	PerkinElmer 226 filter paper	100µl	
						Random Venous Sample for PK	Sodium Heparin Tube	3ml	For Randomised Patients
						DBS for Pharmacokinetics	1 Filter paper 5x5	200µl	
				logistical activities realted to	2	Urinalysis	Urinary Dip Sticks	NA	

				study	2	Transportation allowance reimbursement	Money	NA	Mandatory for all
9	Day 14	Follow up	336 hours	Blood Tests	4	Conventional Microscopy - Thick and Thin Smear	2 Blood Slides	15µl	
						DBS for Molecular Genotyping	PerkinElmer 226 filter paper	100µl	
						Random Venous Sample for PK	Sodium Heparin Tube	3ml	For Randomised Patients
						DBS for Pharmacokinetics	Whatman 903 Protein Saver	200µl	
						Transportation allowance reimbursement	Money	NA	Mandatory for all
10	Day 21	Follow up	504 hours	Blood Tests	4	Conventional Microscopy - Thick and Thin Smear	2 Blood Slides	15µl	
						DBS for Molecular Genotyping	PerkinElmer 226 filter paper	100µl	
						Random Venous Sample for PK	Sodium Heparin Tube	3ml	For Randomised Patients
						DBS for Pharmacokinetics	Whatman 903 Protein Saver		
						Transportation allowance reimbursement	Money	NA	Mandatory for all
11	Day 28	Follow up	672 hours	Blood Tests	4	Conventional Microscopy - Thick and Thin Smear	2 Blood Slides	60µl	
						DBS for Molecular Genotyping	PerkinElmer 226 filter paper	100µl	
						Random Venous Sample for PK	Sodium Heparin Tube	3ml	For Randomised Patients
						DBS for Pharmacokinetics	Whatman 903 Protein Saver	200µl	
				Logistical activities realted to study		Transportation allowance reimbursement	Money	NA	Mandatory for all
12	Day 35	Follow up	840 hours	Blood Tests	4	Conventional Microscopy - Thick and Thin Smear	2 Blood Slides	15µl	
						DBS for Molecular Genotyping	PerkinElmer 226 filter paper	100µl	
						Random Venous Sample for PK	Serology Tube (RED - top)	3ml	For Randomised Patients
						DBS for Pharmacokinetics	1 Filter paper 5x5	200µl	
				logistical activities realted to study		Transportation allowance reimbursement	Money	NA	Mandatory for all
13	Day 42	Follow up	1008 hours	Blood Tests	4	Conventional Microscopy - Thick and Thin Smear	2 Blood Slides	15µl	
						DBS for Molecular Genotyping		100µl	
						Random Venous Sample for PK		3ml	For Randomised Patients
						DBS for Pharmacokinetics	1 Filter paper 5x5	200µl	
						Transportation allowance reimbursement	Money	NA	Mandatory for all

20 APPENDIX II: INFORMED CONSENT

20.1 English Version

Muhimbili University of Health and Allied Sciences (MUHAS)

Karolinska Institute (KI)

Uppsala University

Consent to Participate in a Research Study

Adult and Parental/guardian permission for a Minor Child to Participate in a Research Study

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Protocol No. 01.05.2017/04

Consent Form Version Date: Version 4.0 dated 4th July 2017

Title of Study: Aiming at prolonging the therapeutic life span of artemisinin-based combination therapies in an era of imminent *Plasmodium falciparum* resistance in Bagamoyo District, Tanzania - new strategies with old tools.

Protocol Version 4.0, dated 4th July 2017

Principal Investigator: Dr. Lwidiko Edward Mhamilawa (Tanzania)

Principal Investigator Phone number: +255 712 865 206

Principal Investigator Email Address: lwidikoedward@gmail.com

Co-Investigators: Dr. Billy Ngasala, MUHAS; Prof. Anders Bjorkman (KI) Prof. Andreas Martenson (Uppsala)

Study Sponsors: Swedish International Development Cooperation Agency(SIDA) and Swedish Research Council.

Study Contact telephone number: +255 712 865 206

This informed consent form has two parts:

I. Information sheet (to share information about the study with you)
II. Certificate of consent (for signatures if you agree your child to take part in the study).

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

Part I: Information sheet

My name ……, and I work for..... We are doing a study on the treatment of malaria. Malaria is a dangerous disease; however, it can be treated. The purpose of this study is to determine the effects of prolonging the therapeutic life span of artemisinin-based combination therapies when is combined with a single lower-dose primaquine, another antimalarial drug which is capable of killing mature *P. falciparum* gametocytes; the combination can stop transmission of the disease. We have screened your blood/ blood of your child and we have determined that you have been infected with malaria parasites. Thus, we are inviting all patients with uncomplicated malaria aged 1 year and above living in this area to take part in this study.

a. Introduction to the Study

I am going to give you information and invite you to consent for yourself or your child to participate in this study. There will be other 280 participants in total of this research study. Before you decide whether you want yourself or your child to participate, you can talk to anyone you feel comfortable with. There may be some words that you do not understand. Please ask me to stop as we go through the information, and I will take time to explain. If you have questions later, you can ask me, the study doctor or the staff. Your decision to have yourself/your child participate in this study is entirely voluntary. If you choose not to consent, all the services you/your child receives at this clinic will continue as usual. Even if you agree now but decide to change your mind and withdraw later, the services you/your child receives at the clinic will continue.

Your participation or that of your child can be terminated without the need for consent from you when you violate the study protocol agreements or when the study staff determine it is for your own good not to continue participating in the study.

b. Inclusion and Exclusion criterion

In order to participate in the study, you can be male or female with more than 1 years of age but below 65 years at Visit Yombo Dispensary. Minimum weight is 10 kg. You or your child must present with a body temperature of more than 37.5°C or history of fever in the last 24 hours; Microscopy determined asexual *P. falciparum* mono-infection regardless of parasitemia. We will also asses the condition of your heart if there are no conditions that may prevent you from using study drugs.

If you/ your child has any of the following, or develop them during the study, we will have to withdraw you from the study. Symptoms/signs of severe malaria or danger signs as deemed by study staff. If you are Pregnant or breastfeeding, or have allergy to study medications. You/ your child is not expected to take any medication without prior consultation with study clinician, if you/your child have taken anti-malarial within last two weeks you will not be eligible to the study. Moreover, if you have hemoglobin level of less than 8 g/dl you cannot continue with the study. You are not expected to be on regular medication, which may interfere with antimalarial pharmacokinetics and blood transfusion within last 90 days.

c. About the Study Medication and Dosage

We will use two types of medication in our research study, Artemether Lumefantrine (AL) and Primaquine. AL is the first-line treatment for uncomplicated malaria in Tanzania. It is registered and licensed for use in Tanzania. There are reports of AL resistance from South-East Asia which could spread to Africa. Additionally, there are areas of low malaria transmission in the country where malaria elimination programs by using primaquine can be implemented. Furthermore, WHO emphasizes on assessing the safety and efficacy of lower doses of primaquine and where it is accepted to be used for the above mentioned purposes in combination with artemether-lumefantrine.

Primaquine however is not registered for routine use in Tanzania, hence clearance for use in human has been sought from TFDA, and Insurance cover from the National insurance corporation of Tanzania (NIC) in case of study related injuries. Many countries including Tanzania are fighting hard to control and eventually eliminate malaria. Primaquine given as a single dose in addition to ACTs such as AL is said to be potent in killing the transmissible malaria parasites, the gametocytes, thus aid in elimination efforts. Nonetheless, this medicine has side effects including hemolysis which can be fatal to those with G6PD deficiency. Otherwise, its side effects includes: nausea, vomiting, epigastric distress and abdominal pain. It is advised to take food before medication to avoid most of the side effects. Similarly, acute hemolytic anemia due to Primaquine is a dose dependent phenomenon, thus to avoid this a lower dose of 0.25 mg/kg which is recommended by WHO will be used. Conversely, AL is known to be very effective, but you should know that may have some minor side-effects: weakness, headache, nausea, vomiting, abdominal pain, diarrhea and itching. These symptoms are usually transient and of mild or moderate intensity.

Artemether-lumefantrine is usually given at six doses spread twice a day over three days. For the purpose of this study, there will be two treatment arms, one will receive standard 3 days regimen, and the other one will receive extended treatment for 6 days. You/your child will receive artemether-lumefantrine twice a day for three days or six days depending on which arm of the study you will be randomly assigned to. In addition to that, for those of you who will be in the primaquine arm will receive a single low-dose (0.25mg/kg) of primaquine together with the last dose of AL on the sixth day of AL. Food will be taken prior to all medications to alleviate primaquine gastrointestinal side effects and to improve absorption of AL.

If we find that the medicine you have received is not able to cure the malaria infection that you are infected with, we will instead give you what is called 'rescue medicine'. The rescue medicine is called quinine and is given orally at a dose of 10mg/kg body weight thrice daily to complete a total of 21 doses in 7 days. You should also know that this medicine has some minor side-effects: such as tinnitus, muffled hearing, sometimes vertigo or dizziness. In case you/your child develop signs of severe malaria infection we will provide in-patient care and treat you/your child with quinine given directly into your blood using a drip.

d. Follow up days and blood sample collection

During the follow-up, a small amount of blood of about 6mls total (teaspoon full) will be taken from your finger, 8 hourly on day 0, followed by 12 hourly on days 1, 2, 3, 4 and 5, and thereafter once daily on days 6, 7, 14, 21, 28, 35, 42 and on any day of recurrent illness. You/your child may experience a bit of pain or fear when the finger is pricked or during the venous phlebotomy. The pain should disappear within 1 day. The blood will be dropped onto a slide or a small piece of paper. The blood samples will be used to study malaria parasites in your blood, the level of drug concentration and to determine the level of your blood (Hb), nothing else will be done with the blood.

The study period for each patient in this study is 42 days. During that time, you/your child will have to come to the health facility for 1 hour, which in total will be 19 visits including today's visit. At each visit, you will be asked a few questions about your health condition, including if you/your child have/has developed any new symptoms since last visit and if you were taking any other medicines than the study medication. In addition, you will also undergo a brief physical examination by study clinician at every visit.

e. More information about the Study administration

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

The blood samples on the filter papers will be transported to Sweden because the labs in Tanzania do not have the capacity to process the analysis needed. They will be stored for about 10 years as it is a policy for studies like this. By signing this consent, you authorize the transportation and storage of the blood samples taken for use and purpose of this study.

Today, we will take few drops of blood for testing. We will also take your picture/of your child which will aid us during follow-up. If you decide that you/your child will participate in this study, any illnesses related to malaria or to the malaria treatment will be treated at no charge to you. Your participation will help us to know whether the medicine is working as envisaged, and this will benefit the society and future generations. Accommodation and food will be provided to you, should you decide to stay here after first visit and as you are waiting for the next 8 hourly dose and in case of children then to the child and one parent/guardian**.** In addition, travel expenses will be reimbursed for every visit according to local transport rates.

f. Confidentiality Section

We will not share the identity of participants in the study with anyone. The information that we collect from this study will be kept confidential. There is a possibility that we will share the information

with the study monitors, sponsors, ethics committees from TFDA and NIMR**.** Any information collected will have a number on it instead of names. Only the study team members will know what the number is it about.

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

This proposal has been reviewed and approved by the institutional ethical committee of the Muhimbili University of Health and Allied Sciences, Tanzania Food and Drug Authority and Tanzania National Institute for Medical Research. The committees have carefully assessed the study in advance to make sure that study participants are protected from any harm. If you wish to find more about the study approval, you may contact the Director of research and publication +255 22 2152489, Muhimbili University, National Institute for medical research +255 22 2121400 or Tanzania Food and Drug Authority +255 22 2452108. Or you can contact the Principle Investigator at Lwidiko Edward Mhamilawa, 0712865206.

Part II: Certificate of consent

I have been invited to participate/have my child participate in a study of a medicine used to treat malaria. I have read the above information/or it has been read to me. I have had the opportunity to

ask questions, and any questions that I have asked have been answered to my satisfaction. I consent voluntarily to participate/my child's participation in this study.

Name of participant: _____

Name of parent or guardian: _____

Signature of parent or guardian: _____

Date: __ ___ _____ (dd/mm/yy)

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

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

Name of witness: _____: Signature of witness: _____

Thumbprint of parent/guardian_____Date:_____

Investigator's signature:

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

Name of investigator: _____

Signature of investigator: _____Date: _____

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

20.2 Swahili version

Muhimbili University of Health and Allied Sciences (MUHAS)

Karolinska Institute (KI)

Uppsala University

Fomu ya Ridhaa ya kushiriki kwenye Mradi wa Utafiti

Kwa ajili ya Watu wazima na Wazazi/ Walezi ili kutoa ridhaa ya Mtoto/ mwenyewe kushiriki kwenye mradi wa utafiti

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Protocol No. 01.05.2017/04

Toleo na Tarehe ya Fomu ya Ridhaa: Namba ya Toleo 4.0 Tarehe 4 Julai 2017

Jina la Mradi wa utafiti: Kulenga katika kuongeza muda wa tiba ya dawa mseto ya artemisia katika kipindi cha usugu wa vimelea malaria *Plasmodium falciparum* kwa dawa, wilaya ya Bagamoyo, Tanzania – mikakati mipya kwa kutumia zana zilizopo

Toleo la Andiko 4.0, Tarehe 4 Julai 2017

Mtafiti Mkuu: Dr. Lwidiko Edward Mhamilawa (Tanzania)

Namba ya simu: +255 712 865 206

Barua Pepe: lwidikoedward@gmail.com

Watafiti washiriki: Dr. Billy Ngasala, MUHAS; Prof. Anders Bjorkman (KI) Prof. Andreas Martenson (Uppsala)

Wafadhili: Swedish International Development Cooperation Agency(SIDA) and Swedish Research Council.

Mawasiliano ya Mradi: +255 712 865 206

Fomu ya maelezo ya ridhaa kwa Watu wazima na wazazi/walezi waliokuja na watoto wao kituoni.

Fomu hii ya maombi ya ridhaa ina sehemu mbili:

I. Fomu ya maelezo (itakupasha taarifa za utafiti)

II. Uthibirisho wa kukubali (utaweka saini yako iwapo utakubali ushiriki wa mwanao) na utapewa nakala ya taarifa hii kwa ajili ya kumbukumbu.

Sehemu ya I. Fomu ya maelezo

Mimi naitwa....., na ninafanya kazi ……..... Tunafanya utafiti kuhusu matibabu ya malaria. Malaria ni ugonjwa hatari; hata hivyo, ni ugonjwa unaotibika

kwa dawa. Lengo la utafiti huu ni kuchunguza faida za kuongeza muda wa tiba ya dawa mseto ya Artemisia pamoja na dozi ndogo ya Primaquine kwa kuangamiza vimelea vya malaria katika kipindi cha usugu wa vimelea wa malaria kwa dawa na kuzuia maambukizi ya ugonjwa huo. Tumechunguza damu ya mtoto wako na tumegundua ameambukizwa vimelea vya ugonjwa wa malaria. Huwa tunawaalika wagonjwa wote wenye malaria isiyo kali, wenye umri zaidi ya mwaka mmoja wanaoishi maeneo haya, kushiriki kwenye mradi huu.

a. Utangulizi kuhusu mradi huu wa utafiti

Kwa hivyo, nitakupa taarifa zinazohusu utafiti wetu huu unaofanyika hapa na kukuomba wewe / mwanao ashiriki. Kabla hujaamua ushiriki wako/ wa mwanao ama la, unapewa uhuru wa kupata ushauri kutoka kwa mshauri yeyote ili utoe mashaka kuhusu utafiti huu. Pengine kutatokea baadhi ya maneno hujayaelewa, tafadhali usisite kunirudisha kwenye taarifa hiyo ili nikufafanulie kwa kina. Kama utakuwa na swali lolote usisite kumuuliza mganga au mhudumu wa afya kituoni hapa.

Ushiriki wako / wa mwanao kwenye utafiti huu ni wa hiyari. Kutakuwa na washiriki wengine 280 kwenye mradi huu wa utafiti wanaoishi maeneo haya. Iwapo utaamua asishiriki, hakuna huduma yeyote atakayonyimwa kituoni hapa. Hata ukiamua kushiriki kwa sasa basi unaweza kubadili maamuzi yako baadae, huduma na msaada wa matibabu anayopewa itaendelea kama kawaida. Ushiriki wako/ mwanao unaweza kusitishwa wakati wowote bila kuhitaji ridhaa yako kama utakiuka makubaliano ya ushiriki ama wafanyakazi wa mradi wataona ni salama kwako/ kwa mwanao kusimamishwa ushiriki kwenye mradi.

b. Vigezo vya ushiriki au kutolewa kwenye mradi.

Ili ushiriki kwenye mradi unaweza kuwa wa kiume au wa kike, mwenye umri zaidi ya mwaka mmoja lakini chini ya miaka 65, wanaokuja kuhudumiwa zahanati ya Yombo. Uzito wa chini kushiriki ni Kg 10. Wewe/ mwanao lazima awe na Homa (joto mwili la digrii 37.5) ama historia ya kuwa na homa ndani ya masaa 24 yaliyopita. Vipimo vya darubini lazima viwe vimeonesha vimelea vya malaria aina ya *P. falciparum.* Pia tutakufanyia vipimo moyo wako kujua kama hakuna shida itakayojitokeza ukishiriki kwenye mradi.

Kama wewe/mwanao mna hali zifuatazo ama zikijitokeza wakati wa mradi, itatulazimu kusimamisha ushiriki. 1. Kupata dalili za malaria kali ama dalili za hatari, kama wafanyakazi wa mradi watakavyotambua. 2. Kama una ujauzito ama 3. Unanyonyesha au 4. Dawa za mradi zinakudhuru. Wewe/mwanao hategemewi kutumia matibabu mengine yoyote kipindi cha mradi bila kuwasiliana na dakitari wa mradi, na kama wewe au mwanao mmetumia dawa za malaria ndani ya wiki mbili, hautakidhi vigezo vya ushiriki. Zaidi ya hapo , wingi wa damu ni lazima uwe zaidi ya gramu 8 kwa desilita. Na kusiwe na matumizi ya dawa za muda mrefu ambazo zinaweza ingiliana na dawa za mradi kwenye ufanyaji kazi mwilini. Ndani ya siku 90 zilizopita inatakiwa kusiwe kumefanyika zoezi la kuongezewa damu.

c. Taarifa kuhusu dawa zinazotumika katika mradi huu na unywaji wa dozi

Tutatumia dawa aina mbili kwenye utafiti wetu, Dawa mseto ya Artemisia na dawa ya Primaquine. Dawa mseto ya Artemisia ni dawa ya awali ya matibabu ya malaria isiyo kali na imesajiliwa kwa matumizi ya tiba Tanzania. Kuna ripoti za Usugu wa Dawa mseto ya

Artemisia kutoka Kusini-Mashariki mwa Asia ambayo inaweza kuenea hadi Afrika. Pia kuna maeneo yenye kiwango kidogo cha maambukizi ya malaria ambapo miradi ya kutokomeza malaria kwa tutumia primaquine inaweza kufanyika. Shirika la afya duniani (WHO) linasisitiza upimaji wa usalama na uwezo tiba wa dozi ndogo ya dawa ya primaquine na kule iliko kubalika itumike kwa kazi tajwa hapo juu kwa kuunganishwa na dawa ya mseto ya Artemisia. Nchi nyingi ikiwemo Tanzania, zina pambana vikali ku mudu na hatimaye ku tokomeza malaria. Primaquine ikitolewa kama dozi moja ndogo pamoja na dawa mseto ya Artemisia kama vile AL, inasemekana kuwa na uwezo wa kuua vimelea ambukizi vya malaria, hivyo kusaidia kwenye jitihada za kutokomeza malaria.

Primaquine hata hivyo haijasajiliwa kwa matumizi ya tiba ya malaria Tanzania, hivyo kibali kimeombwa kutoka Mamlaka ya chakula na dawa (TFDA) na bima imekatwa kutoka Shirika la bima la Taifa (NIC). Hata hivyo dawa hii ina madhara ambata ikiwemo kuvunjika kwa chembe nyekundu hai za damu ambayo huweza kuua kwa watu wenye upungufu wa kimengenya cha G6PD. Madhara ambata mengine ni kichefuchefu, kutapika, na maumivu ya tumbo. Inashauriwa kula chakula kabla ya dawa ili kuepuka madhara haya ambata. Vivyo hivyo, upungufu wa damu unaotokana na primaquine ni hali inayotegemea kiwango cha dawa utakachopata, hivyo ku kwepa hilo, kiwango kidogo zaidi cha mg 0.25 kwa kg ambayo inapendekezwa na shirika la afya duniani (WHO) itatumika. Kwa upande mwingine AL inafahamika kuwa na ubora sana kwenye tiba, ila ni muhimu ujue kuwa ina madhara ambata kidogo: uchovu, maumivu ya kichwa, kichefuchefu kutapika, kuwashwa , maumivu ya tumbo na kuhara. Dalili hizi ni za mpito na za uzito mdogo ama hafifu.

Dawa mseto ya artemisia hutolewa kwa dozi sita zilizotawanywa marambili kwa siku kwa siku tatu. Katika tafiti hii, kutakuwa na makundi mawili yatakayopokea dawa kwa idadi tofauti za siku, kundi moja siku tatu mfululizo, kundi la pili siku sita mfululizo kutegemeana na kundi utakalopangiwa/atakalo pangiwa mtoto wako kwa bahati nasibu. Zaidi ya hayo, kama atakuwa kundi la siku sita za kunywa dawa ya mseto, atapewa dozi moja ya Primaquine ambayo itaambatana na dozi ya mwisho ya mseto. Kitu cha kula kitapatikana kabla ya dawa zote kupunguza madhara ambata ya tumboni ya primaquine na pia kuboresha unyonywaji wa dawa mseto mwilini.

Iwapo tutagundua dawa hizi zimeshindwa kuua vimelea vya malaria vilivyo kwenye damu yake, tutampa dawa nyingine tunayoiita ‘dawa ya kunusuru’ ambayo ni quinine na inatolewa kwa kunywa 10mg/kg moja ya mwili na zinanywewa mara tatu kwa siku hadi utimize dozi 21 kwa muda wa siku 7. Iwapo utapata dalili za malaria kali tutamlaza na kumtibu kwa dawa ya quinine ambayo tutaitia moja kwa moja kwenye damu kupitia mrija (drip).

d. Siku za kuja kituoni na kutoa vipimo vya damu

Wagonjwa wote tutakaowashirikisha kwenye utafiti huu wataombwa kurudi tena kituoni siku ya 1, 2, 3, 4, 5, 6, 7, 14, 21,28, 35 na 42 tangu siku waliposajiliwa, lakini unashauriwa kurudi/ kumleta mwanao wakati wowote ukihisi ana homa ambayo haijapoa. Kila siku mtakayokuja, kutatolewa damu kidogo isiyozidi mls 6 kwa ujumla (kijiko kidogo cha chai) itakayochukuliwa kutoka kwenye kidole chake/chako au mshipa wa damu. Kwa ujumla

mwanao atatolewa damu ya kidole kila mara atakapokuja hapa kituoni, ikiwepo leo pia. Kwa wastani tano siku ya kwanza na mara tatu kwa siku tano za mwanzo yaani siku ya 1,2,3,4, na 5. Baada ya hapo atatolewa mara moja kwa siku siku ya 6,7,14,21.28,35,42. Kutolewa damu kidoleni au kwenye mshipa wa damu kunaweza kusababisha maumivu kidogo. Maumivu haya ni ya muda mfupi tu na huweza kupotea ndani ya siku moja. Damu itakayotolewa itawekwa kwenye kigae na kwenye kipande cha karatasi ndogo tu. Damu itakayowekwa kwenye kigae itachunguzwa kuangalia ubora wa dawa ya kuua vimelea vya malaria na hivyo kuondoa uwezekano wa vimelea hivyo kurudi tena kwenye damu yake. Utafiti huu utafanywa kituoni kwa kila siku mgonjwa atakayopaswa kuja. Damu itakayochukuliwa kwenye kipande cha karatasi itatumika kuchunguza maumbile ya vimelea vya malaria. Kwa vile usomwaji huo utafanyika baada ya utafiti kumalizika majibu ya damu hizi hayatotumika kutoa mbadala wa matibabu wala hayatachunguza matibabu anayofanyiwa mwanao. Ukitoa uchunguzi ulioelezwa hapo juu pamoja na kuhifadhiwa chembe za damu kwenye kipande cha karatasi kwa ajili ya uchunguzi wa dawa kwa majaribio ya baadaye, damu yake haitotumika kuchunguza jambo jingine.

Muda wa kushiriki utafiti huu ni siku 42. Katika muda huu, tutakuomba uwe unakuja na mwanao hapa kituoni kwa zile siku tutakazokupangia, ambapo pamoja na siku ya mwanzo utakuja nae kwa jumla ni safari 19. Kila safari atakayokuja hapa mtatumia takribani muda wa saa 1 kwanzia kesho, ila kwa siku ya leo mtakaa kwa takribani masaa 12. Kila safari atakayokuja, ataulizwa maswali kidogo kuhusu afya yake, tutataka kufahamu maendeleo yake iwapo amepata dalili nyengine za homa tangu safari iliyopita na pia tutakuwa tunakuuliza iwapo umempa dawa nyingine yeyote zaidi ya ile tuliyompa. Atachunguzwa afya yake na mganga hapa kituoni kwa kila safari utakayokuja naye.

e. Taarifa za ziada kuhusu uongozi wa Mradi

Kama nilivyokueleza awali dawa tutakayotumia imekuwa inasababisha baadhi ya matokeo yasiyohitajika au yanaweza yakatokea mengine ambayo hatuyafahamu; hata hivyo, tutakuwa karibu nawe kufahamu na kulipatia ufumbuzi tokeo lolote litakalotokea, iwapo litatokea, pamoja na tatizo jengine la kiafya. Tutakupa nambari ya simu ambayo utaweza kupiga kama umegundua wewe/ mtoto ana tatizo lolote au kama una swali lolote, angalia simu zilizopo hapo chini. Unaweza pia kuja kituoni hapa wakati wowote kuuliza au kuonana na..... (jina la Mtabibu au muuguzi). Iwapo umetokewa na tatizo lolote lisilo la kawaida baada ya kutumia dawa hii tutakupa matibabu ya ziada, bila ya malipo, dawa ambazo zitasaidia kuondoa tatizo ulilonalo, au tunaweza kukushauri asiendelee na kutumia dawa hizi. Iwapo kuna umuhimu sana tutajadiliana pamoja nawe. Siku zote utashauriwa kuhusu hatua inayofuata.

Sampuli za damu kwenye vi karatasi zitapelekwa nje ya nchi, Sweden kwa ajili ya kufanyiwa uchunguzi zaidi kwasababu maabara za Tanzania hazina uwezo wa kufanya vipimo vinavyohitajika kwenye mradi huu. Sampuli hizo zitatunzwa kwa muda wa miaka kumi kama ilivo katika sera za utafiti. Kwa kusaini ridhaa hii unatoa pia ruhusa ya usafirishwaji wa sampuli zako/ za mwanao za damu kwenda nje ya nchi na pia kuhifadhiwa kwa matumizi ya mradi huu.

Faida za ushiriki wako/ wa mwanao

Ushiriki wako/ mwanao kwenye utafiti huu utasaidia kufahamu ufanisi wa dawa hizi katika kupambana na ugonjwa, na hii ni kwa faida ya jamii yetu pamoja na kizazi kijacho. Malazi na chakula vitatolewa hapa kituoni kwa mtoto na mzazi/mlezi mmoja kama utabaki kituoni kusubiri dozi na kipimo cha baada ya masaa nane ya awali kama unatoka mbali. Gharama za usafiri zitatolewa kwa kuja/ kumleta mtoto kituoni siku alizopangiwa kuendana na nauli halali za hapa.

f. Usiri wa taarifa zako/ za mwanao

Tunakuhakikishia hatutampa utambulisho wa mwanao mtu yeyote asiye husika na utafiti huu. Taarifa zote tunazochukua kwa wagonjwa wetu hapa tutaziweka kuwa ni siri kubwa. Kuna uwezekano tukawapa tarifa zako/za mwanao wakaguzi wa mradi, wafadhili ama kamati za maadili za TFDA na NIMR. Taarifa yeyote tutayochukua kutoka kwa mwanao tutaitambua kwa nambari atakayopewa badala ya jina lake. Ni baadhi ya wataalamu wanoshiriki utafiti huu ndio watakaofahamu taarifa zake.

Tutakupatieni matokeo ya utafiti huu pamoja na elimu tuliyoipata kabla hatujazitangaza hadharani. Tutaitisha mikutano kwenye jamii ili kuwapa wananchi matokeo ya utafiti wetu, na mikutano hiyo itatolewa taarifa mapema. Baada ya hapo, tutachapisha matokeo ya utafiti huu kwenye majarida ya kisayansi ili watu wasome na waelimike kutokana na utafiti wetu.

Rasimu ya utafiti huu imepitiwa na kuhakikiwa na Baraza la maadili ya utafiti la Chuo Kikuu cha Afya na sayansi shirikishi Muhimbili. Baraza limechunguza kwa kina rasimu ya utafiti huu ili kuhakikisha kuwa wagonjwa watakaoshiriki wanalindwa na hawataathiriwa. Iwapo unataka kuhakikisha unaweza Kupiga simu kwa Kurugenzi ya Utafiti na Uchapishaji, Muhimbili +255 22 2152489, Muhimbili University, National Institute for medical research +255 22 2121400 au Tanzania Food and Drug Authority +255 22 2452108. Ama kumpigia simu Mtafiti kiongozi Lwidiko Edward Mhamilawa, kwenye simu nambari 0712865206.

Iwapo una swali lolote kuhusu utafiti huu au kwa njia yeyote unataka kuwasiliana na wahusika wa utafiti huu unakaribishwa kufanya hivyo na unaweza kutumia namba hizi zifuatazo:

Bw/Bi_____Namba_____

Sehemu ya II. Ithibati ya ridhaa

Mimi _____nimeshauriwa ushiriki wa mtoto wangu kwenye utafiti wa kupima ufanisi wa dawa ya mseto ya malaria ikichanganywa na dozi ndogo ya Primaquine.

Nimesoma/nimesomewa taarifa hizo hapo juu. Nilipewa nafasi ya kuuliza swali lolote, na yale maswali niliyouliza nimejibiwa na nimeridhika na majibu niliyopewa. Kwa hiari yangu nakubali mimi/ mwanangu ashiriki utafiti huu.

Jina mtoto (mgonjwa): _____

Jina la mzazi/mlezi:_____

Sahihi ya mzazi/mlezi_____Tarehe_____

Sahihi ya shahidi: (Shahidi wa mshiriki na alama ya dole gumba la mshiriki itahitajika tu iwapo mzazi/mlezi wa mshiriki hafahamu kusoma na kuandika. Iwapo itatokea hivyo, shahidi wa mshiriki lazima aweke saini yake. Iwapo itawezekana, shahidi wa mshiriki ateuliwe na mshiriki mwenyewe na asiwe miongoni mwa watafiti).

Nimemsomea taarifa hizi mzazi/mlezi wa mshiriki mtarajiwa kikamilifu, na alipata nafasi ya kuuliza maswali. Nakubali kwamba mzazi/mlezi wa mtoto ametoa ridhaa yake kushiriki na hakulazimishwa.

Jina la shahidi_____

Sahihi ya shahidi_____

Alama ya dole gumba la mzazi/mlezi_____ Tarehe _____

Saini ya mtafiti: _____

Nimemsomea taarifa hizi mzazi/mlezi wa mshiriki mtarajiwa kikamilifu, na alipata nafasi ya kuuliza maswali. Nakubali mzazi/mlezi ametowa ridhaa ya mwanawe kushiriki katika utafiti huu, na hakulazimishwa.

Andika jina la mtafiti:_____

Saini ya mtafiti:_____Tarehe_____

Nakala ya fomu hii ya ombi la ridhaa amepewa mzazi/mlezi wa mshiriki _____ (weka herufi za majina ya Mtafiti mkuu au msaidizi wa mtafiti mkuu).

‘

21 APPENDIX III: INFORMED ASSENT FORM

21.1 English Version

Muhimbili University of Health and Allied Sciences (MUHAS)
Karolinska Institute (KI)
Uppsala University
Assent to Participate in a Research Study
Minor subjects (7-12 yrs)

Protocol No. 01.05.2017/04
Assent Form Version Date: Version 4.0 dated 4th July 2017

Title of Study: Aiming at prolonging the therapeutic life span of artemisinin-based combination therapies in an era of imminent *Plasmodium falciparum* resistance in Bagamoyo District, Tanzania - new strategies with old tools.

Protocol Version 4.0, dated 4th July 2017

Principal Investigator: Dr. Lwidiko Edward Mhamilawa (Tanzania)
Principal Investigator Phone number: +255 712 865 206
Principal Investigator Email Address: lwidikoedward@gmail.com
Co-Investigators: Dr. Billy Ngasala, MUHAS; Prof. Anders Bjorkman (KI) Prof. Andreas Martenson (Uppsala)

Study Sponsors: Swedish International Development Cooperation Agency(SIDA) and Swedish Research Council.

Study Contact telephone number: +255 712 865 206

The people named above are doing a research study.

These are some things we want you to know about research studies:

Your parent needs to give permission for you to be in this study. You do not have to be in this study if you don't want to, even if your parent has already given permission.

You may stop being in the study at any time. If you decide to stop, no one will be angry or upset with you. Your doctors will still continue to take good care of you.

Sometimes good things happen to people who take part in studies, and sometimes things happen that they may not like. We will tell you more about these things below.

Why are they doing this research study?

The reason for doing this research is to learn more about malaria disease where you live. Malaria can cause bad illnesses, mainly in babies and young children.

The information in this study will help us understand why some medicines are not working very well to help malaria. Also we are trying to find out if someone takes malaria medicine longer than it is normal, will it help to kill the malaria causing organisms better.

Why are you being asked to be in this research study?

You are being asked to be in the study because you have malaria.

How many people will take part in this study?

If you decide to be in this study, you will be one of about 280 other people, children and adults in this research study. The study is being done here in Yombo, Tanzania.

What will happen during this study?

If you wish to be in this study, this is what will happen:

- You may have to stay in the hospital for the day today, so the doctors can treat the malaria. While you are in the hospital, you will be given the regular treatment for malaria. For this study, you will have blood taken from a vein in your arm, and some other days on you finger. This will be done today, and then twice each day you are in the hospital for about seven days. The blood will be tested to check the amount of malaria in your blood, and if you are unwell because of anemia (low blood level).

-Your parent or guardian (the person who takes care of you) will also be asked questions about your health and your household.

-Today you will also be given medicine to treat your malaria, and a person on the study team will stay with you for 30 minutes after you get the medicine to see how you feel. You will also come tomorrow and day after tomorrow for six days to take some malaria medication.

-After coming to the hospital for 7 days taking medication and blood test, you will stay home for seven days, and then you will come to the clinic with your parent for another visit. At this visit we will ask your parent or guardian some questions about your health. You will also have several drops of blood taken by pricking your finger with a needle. The blood will be tested to see if the medicine is working to make your malaria better.

-There will be 5 other visits to the clinic like the one above. You will be in the study for 42 days.

Who will be told the things we learn about you in this study?

Information learned from this study will be kept private. The study doctor will talk about the study with your parent/guardian, but will not talk about it with anyone else except the people working on the study. If the study doctor needs to talk to anyone else about you, he will ask you and your parent or guardian if it is OK.

What are the good things that might happen?

The information from the study will help us to better understand malaria disease in your country. This will give us important information on how best to protect people at risk against malaria.

What are the bad things that might happen?

Sometimes things happen to people in research studies that may make them feel bad. These are called "risks." When having your blood taken, you might feel slight pain where the needle goes into the skin. There is a small chance of getting sick from drawing blood.

Not all of these things may happen to you. None of them may happen or things may happen that the researchers don't know about. You should report any problems to the researcher.

What if you or your parents don't want you to be in this study?

You may decide not to take part in the study at any time, without giving a reason.
Nobody will force you to take part in the study.

Will you get any money or gifts for being in this research study?

You will receive food for the time when you will stay at the hospital for the day if you take part in this study.

Who should you ask if you have any questions?

If you have questions you should ask the people listed on the first page of this form. If you have other questions, complaints or concerns about your rights while you are in this research study you may contact the Muhimbili University of Health and allied sciences Institutional Review Board at+255 22 2121400 or Tanzania Food and Drug Authority +255 22 2452108. Or you can contact the Principle Investigator at Lwidiko Edward 0712865206.

If you sign your name below, it means that you agree to take part in this research study.

_____ _____

Sign your name here if you want to be in the study Date

_____

Print your name here if you want to be in the study

_____ _____

Signature of Research Team Member Obtaining Assent Date

_____

Printed Name of Research Team Member Obtaining Assent

21.2 Swahili

Muhimbili University of Health and Allied Sciences (MUHAS)
Karolinska Institute (KI)
Uppsala University
Fomu ya Ridhaa ya Kushiriki kwenye mradi wa utafiti
Vijana wadogo (Miaka 7-12)

Protocol No. 01.05.2017/04
Toleo na Tarehe ya fomu ya ridhaa: Toleo 4.0 Tarehe 4 Julai 2017

Jina la Mradi wa utafiti: Kulenga katika kuongeza muda wa tiba ya dawa mseto ya artemisia katika kipindi cha usugu wa vimelea malaria *Plasmodium falciparum* kwa dawa, wilaya ya Bagamoyo, Tanzania – mikakati mipya kwa kutumia zana zilizopo

Toleo la Andiko 4.0, Tarehe 4 Julai 2017
Mtafiti Mkuu: Dr. Lwidiko Edward Mhamilawa (Tanzania)
Namba ya simu: +255 712 865 206
Barua Pepe: lwidikoedward@gmail.com

Watafiti washiriki: Dr. Billy Ngasala, MUHAS; Prof. Anders Bjorkman (KI) Prof. Andreas Martenson (Uppsala)

Wafadhili: Swedish International Development Cooperation Agency(SIDA) and Swedish Research Council.
Mawasiliano ya Mradi: +255 712 865 206

Watu waliotajwa hapo juu wanafanya huu mradi wa utafiti kuhusu malaria

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Kuna vitu tunataka wewe ujue kuhusu mardi huu wa utafiti:

Wazazi wako wanahitaji kutoa ruhusa ya wewe kushiriki kwenye mradi huu. Sio lazima wewe ushiriki kwenye mradi, kama hutaki, hata kama wazazi wako wametoa ridhaa, hautalazimishwa.

Unaweza kuacha kushiriki mradi huu muda wowote. Kama ukiamua kuacha kushiriki hakuna mtu ambaye atakasirika ama kukusikitikia. Dakitari wako ataendelea kukuhudumia kama kawaida.

Wakati mwengine mambo mazuri hutokea kwa watu wanaoshiriki mradi, na wakati mwingine vinaweza kutokea vitu usivyo vipenda. Tutakuambia kuhusu vitu hivi haoa chini.

Kwanini wanafanya mradi huu wa utafiti?

Sababu ya kufanya utafiti huu nu kujifunza kuhusu ugonjwa wa malaria kwenye maeneo unayo ishi. Malaria inaweza kusababisha kuumwa sana , hasa kwa vichanga na watoto wadogo.

Taarifa katika utafiti huu utatusaidia kuelewa kwanini baadhi ya dawa hazifanyi kazi sawasawa kusaidia kutibu malaria. Tunataka kujua pia kama mgonjwa akinywa dawa mseto ya malaria kwa siku nyingi zaidi ya kawaida kama itasaidia kuuwa wadudu wa malaria vizuri zaidi.

Kwanini wewe unaombwa kushiriki kwenye mradi huu wa utafiti?

Unaombwa kushiriki kwasababu umepimwa na kukutwa na wadudu wa malaria.

Watu wangapi watashiriki kwenye mradi huu wa utafiti?

Kama ukikubali kushiriki kwenye mradi huu, utakuwa mmoja kati ya watu 280 wengine, watoto na wakubwa. Mradi huu utafanyika hapa Yombo, Tanzania.

Nini kitatokea kwenye mradi huu?

Ukukubali kushiriki kwenye mradi, hivi vitatokea,

-Unaweza kuhitajika kukaa hospitalini siku nzima leo, ili dakitari wako akutibu malaria. Wakati upo hospitali utapewa vidonge vya malaria. Kwa mradi huu, itabidi utoe damu kidogo kwaajili ya vipimo kutoka kwenye mshipaya damu ama kidole chako, mara mbili kwa siku kwa siku saba za mwanzo. Damu hio itafanyiwa vipimo vya wadudu wa malaria, pia itapimwa wingi wa damu ambayo ikipungua unaumwa.

-Wazazi wako au walezi wataulizwa maswali kuhusu wewe na afya yako na nyumbani.

-Leo pia utapewa dawa za malaria, na mhudumu wa mradi atakuwa nawe kwa dakika 30 baada ya dawa kuangalia unaendeleaje na kama hauta tapika. Pia utakuja kesho na kesho kutwa hadi siku ya sita kunywa dawa.

-Baada ya kuja hapa kwa siku 7 kunywa dawa na kutoa vipimo, utakaa nyumbani kwa siku 7 halafu utakuja tena hapa hospitali kwaajili ya vipimo.Kila mara ukija tutamuuliza mzazi wako/mlezi kuhusu afya yako. Pia tuthitaji kutoa marone kadhaa ya damu (3-6) kwa sindano. Damu yako itapimwa kuangalia hali yako inaendeleaje ili upone vema.

-Baada ya hapo, utakuja tena mara 5 kama vile hapo juu. Utashiriki kwenye mradi huu kwa siku 42.

Nani mwingine ataambiwa vitu ambavyo tutagundua kuhusu wewe kwenye utafiti?

Taarifa tutakazo zigundua kuhusu wewe na mradi zitakuwa siri. Dakitari wa mradi atazungumza na mzazi wako/mlezi lakini hata zungumza na mtu mwingine yeyote ukiacha wafanyakazi wa mradi. Kama dakitari wako atahitaji kuzungumza na mtu mwingine kuhusu wewe, atakuomba ruhusa wewe na pia mzazi wako kama ni sawa.

Vitu gani vizuri vinaweza kutokea?

Matokeo ya utafiti yatatusaidia kuelewa vizuri malaria nchini kwako. Hii itatupa taarifa muhimu namna nzuri ya kulinda watu na malaria.

Vitu gani vibaya vinaweza kutokea?

Wakati mwingine vitu vinatokea kwenye mradi ambavyo vinasikitisha. Hivi vinaitwa "vihatarishi". Wakati wa kutoa damu, unaweza kusikia maumivu wakati wa kuchoma sindano, na kuna hatari kidogo ya kuumwa wakati wa kutoa damu.

Sio vyote hivi vinaweza kutokea kwako. Inawezakana hata moja kisitokee kwako, ama vikatoke vitu ambavyo hata watafiti hawajui vizuri. Lazima uripoti tatizo lolote unalolisikia kwa watafiti.

Vipi kama mzazi wako hataki ushiriki kwenye mradi huu?

Unaweza kuamua kuacha kushiriki kwenye mradi huu muda wowote, bila kuwa na sababu yoyote. Hakuna mtu atakae kulazimisha kubaki.

Je nitapata pesa yoyote ama zawadi kwa kushiriki kwenye mradi?

Utapata chakula wakati ukiwa umebaki hospitali na ukipata matibabu na kutoa vipimo vya mradi.

Uzungumze na nani kama una maswali?

Kama una maswali yoyote kuhusu mradi, waulize watu walioko kwenye karatasi hii mwanzoni.

Kama una maswali, manunguniko, hofu na malalamiko kuhusu haki zako wakati wa mradi, unaweza kuwasiliana na Muhimbili University of Health and allied sciences Institutional Review Board at+255 22 2121400 or Tanzania Food and Drug Authority +255 22 2452108. Ama kumpigia simu Mtafiti kiongozi Lwidiko Edward Mhamilawa, kwenye simu nambari 0712865206

Ukiweka sahihi yako hapa inamaanisha unakubali kushiriki kwenye mradi huu.

_____ _____

Weka sahihi yako hapa kama unataka kushiriki kwenye mradi Tarehe

_____

Andika jina lako hapa kama unataka kushiriki kwenye mradi

_____ _____

Sahihi ya Mtafiti anaeomba ruhusa kwako Tarehe

_____

Jina la Mtafiti anaeomba ruhusa kwako

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22 APPENDIX IV: CASE RECORD FORM (CRF):

Aiming at prolonging the therapeutic life span of artemisinin-based combination therapies in an era of imminent *Plasmodium falciparum* resistance in Bagamoyo District, Tanzania - new strategies with old tools.

Patient study No.					
Inclusion (Y/N) All must be YES!			**Exclusion (Y/N) All must be NO!**		
P. falciparum density 2000-200 000/µl			Danger signs/signs of severe malaria		
Age 1+ ≥ 65 yrs			Other disease than malaria as cause of fever		
Weight ≥ 10 kg			Serious underlying disease		
Fever/history of fever within 24 h			History of allergy to Coartem (AL)		
Screening Haemoglobin ≥ 8 g/dl			Treated with any other antimalarial drug < 14 days		
Able to ingest tablets orally					
Consent from parent/guardian			**ECG – QTc interval more than 440ms for men or more than 460ms for women**		
Willing and able to come for follow-up			Pregnant, breastfeeding, or unwilling to practice birth control during participation.		
Informed consent attached					
Demography					
Date of birth (dd. mm. yy)			Sex (M/F)		
Age (months)			Weight (Kg)		
Does the Patient meet all Inclusion Criteria			☐ YES ☐ NO		
Treatment ARMS					
Control arm: AL tablets assigned as per protocol (indicate number of tablets per dose) + Placebo			**Intervention Arm:** Prolonged AL + Primaquine arm 0.25mg/kg (indicate number of tablets per dose)		
☐			☐		
Investigators name:			Signature		Date
Confidential information:					
Patient full name:					
Phone Number and location of house:					

Parent/guardian's full name:	

Patient ID No: **Treatment Arm:**

TREATMENT ASSESSMENT

Days of visit	**Day 0**	**Day 0**	**Day 0**	**Day 0**	**Day 1**	**Day 1**	**Day 1**	**Day 2**
Time of study (Hours)	**0**	**2**	**4**	**8**	**24**	**36**	**40**	**48**
Date (dd. mm. yy)								
Patient seen (Y/N)								
1. Lab. Parameters								
P. falciparum, asexual forms (parasites/µl) B/S								
P. falciparum, asexual forms(parasites/µl) MOMIC								
Gametocytes/1000 WBC								
Temperature (◦C)								
ECG – QTc Interval								
Hemoglobin (g/dl)								
Urine Analysis for Hematuria								
2. Symptoms: Y= Present N=Absent								
Fever								
Weakness								
Headache								
Dizziness								
Abdominal pain								
Nausea								
Vomiting								
Diarrhea								
Others (specify)								
Symptoms/signs of Severe malaria (Y/N)								
Adverse event (Y/N): If yes, fill AEF								
Serious Adverse Event (Y/N): If yes Fill the SAEF								
3. Samples Collection								
DBS for PCR -60ul (Y/N)								
Capillary blood for LAMP- 30ul (Y/N)								
Venous Blood for Pharmacokinetics -2 mls (Y/N)								
Venous blood for Biochemistry- 2 mls (Y/N)								
DBS for antimalarial PK- 60ul (Y/N)								
Concomitant drugs (Y/N)								

Patient ID No:	**Treatment Arm:**					

TREATMENT ASSESSMENT

Days of visit	**Day 2**	**Day2**	**Day 3**	**Day 3**	**Day 3**	**Day 4**	**Day4**	**Day 4**	**Day 5**	**Day 5**
Time of study (Hours)	**52**	**60**	**72**	**84**	**88**	**96**	**100**	**108**	**120**	**132**
Date (dd. mm. yy)										
Patient seen (Y/N)										
1. Lab. Parametres										
P. falciparum, asexual forms (/µl) B/S										
Gametocytes/1000 WBC										
Temperature (◦C)										
ECG – QTc Interval										
Hemoglobin (g/dl)										
Urine Analysis for haematuria										
2. Symptoms: Y= Present N=Absent										
Fever										
Weakness										
Headache										
Dizziness										
Abdominal pain										
Nausea										
Vomiting										
Diarrhea										
Others (specify)										
Symptoms/signs of Severe malaria (Y/N)										
Adverse event (Y/N): If yes, fill AEF										
Serious A. Event(Y/N):If yes Fill SAEForm										
3. Samples Collection										
DBS for PCR -60ul (Y/N)										
Capillary blood for LAMP- 30ul (Y/N)										
Venous Blood for PK -2 mls (Y/N)										
Venous blood for Biochemistry-2mls (Y/N)										
DBS for antimalarial PK- 60ul (Y/N)										

Concomitant drugs (Y/N)										
Patient ID No: **Treatment Arm:**										

TREATMENT ASSESSMENT

Days of visit	**Day5**	**Day 5**	**Day 6**	**Day 7**	**Day 14**	**Day 21**	**Day 28**	**Day35**	**Day 42**	**Any Day**
Time of study (Hours)	**134**	**136**	**144**	**168**	**336**	**504**	**672**	**840**	**1008**	
Date (dd. mm. yy)										
Patient seen (Y/N)										
1. Lab. Parameters										
P. falciparum, asexual forms (parasites/µl)										
Gametocytes/1000 WBC										
Temperature (◦C)										
ECG – QTc Interval										
Hemoglobin (g/dl)										
Urine Analysis for haematuria										
2. Symptoms: Y= Present N=Absent										
Fever										
Weakness										
Headache										
Dizziness										
Abdominal pain										
Nausea										
Vomiting										
Diarrhea										
Others (specify)										
Symptoms/signs of Severe malaria (Y/N)										
Adverse event (Y/N): If yes, fill AEF										
Serious A.Event(Y/N): If yes Fill the SAEF										
3. Samples Collection										
DBS for PCR -60ul (Y/N)										
Capillary blood for LAMP- 30ul (Y/N)										
Venous Blood for PK -2 mls (Y/N)										
Venous blood for Biochemistry-2mls (Y/N)										

DBS for antimalarial PK- 60ul (Y/N)										
Concomitant drugs (Y/N)										
4. Signature of clinician										

TREATMENT SUMMARY

Patient study No.			

Completed treatment as per protocol (Y/N/Not Known)	
Consumption of any other antimalarial drug (Y/N)	

Outcome Day 14	YES	NO	Outcome Day 42	YES	NO
Completed follow up D14			Completed follow up D42		
Adequate Clinical and Parasitological Response			Adequate Clinical and Parasitological Response		
Early Treatment Failure					
Late Clinical Failure			Clinical Failure D15-42		
Late Parasitological Failure			Parasitological Failure D15-42		

Severe malaria (Y/N) If Yes fill below	
Date of severe malaria	
Rescue treatment given (Y/N)	
Hospitalization needed (Y/N)	
Survived (Y/N/Not Known)	

Withdrawal from study (Y/N) If yes fill below	
Date of withdrawal (dd. mm. yy)	
Reason for withdrawal:	
Severe malaria (Y/N)	
Treatment failure (Y/N)	
Guardians request (Y/N)	
Lost to follow up (Y/N)	
Other reason (please state)	

ADMINISTRATION OF TREATMENT

Dose	**Date**	**Time**	**No. of tablets/mg**	**Acronym of Drug intake**			**Sign. (study nurse/Dr)**
Day 0 (0 hrs)							
Day 0 (8hrs)							

Day 1 morning							
Day 1 evening							
Day 2 morning							
Day 2 evening							
Dose	**Date**	**Time**	**No. of tablets/mg**	**Acronym of Drug intake**			**Sign. (study nurse/Dr)**
Day 3 morning							
Day 3 evening							
Day 4 morning							
Day 4 evening							
Day 5 morning							
Day 5 evening							

Vomiting within 30 minutes after any drug administration (Y/N), if yes indicate after which dose
Replacement dose given (Y/N), if yes state after which dose
Study treatment permanently withdrawn (Y/N), if yes specify reasons
Any severe adverse event requiring treatment withdrawal (Y/N)

23 APENDIX IV: SERIOUS ADVERSE EVENT REPORT FORM:

STUDY -Aiming at prolonging the therapeutic life span of artemisinin-based combination therapies in an era of imminent *Plasmodium falciparum* resistance in Bagamoyo District, Tanzania - new strategies with old tools

Serious adverse event report form	
Health center name: District: Region:	**Visit Type; Initial** **Follow up** Patient identity number: Date of visit (dd-mm-yy): Follow-up day:
Demographic data	
Date of birth (dd-mm-yy): Or estimated age: in: ☐ months or ☐ years Height (cm): Weight (kg): Sex: ☐ Male ☐ Female	
Serious adverse event	
Type of event: ☐ Death ☐ Life-threatening ☐ Hospitalization or prolongation of hospitalization ☐ Permanent disability	
Describe the serious adverse event (include all relevant laboratory results):	
Reaction/ Event Start date (dd-mm-yy) **Reaction /Event End date (dd-mm-yy)**	
Describe how the reaction was treated:	

Serious adverse event report form (page 2)

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

Outcome

☐ Recovered completely

☐ Not yet recovered

☐ Recovered with long-term consequences

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

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

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

Reporting officer

Name: Qualification:

Address: Phone:

Fax: Email:

Signature: Date:

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24 APENDIX V: ADVERSE EVENT FORM

STUDY -Aiming at prolonging the therapeutic life span of artemisinin-based combination therapies in an era of imminent *Plasmodium falciparum* resistance in Bagamoyo District, Tanzania - new strategies with old tools

Patient study No.				
Date	1st AE (dd. mm. yy)		2nd AE (dd. mm. yy)	
Day in Study	of 1st AE		of 2nd AE	
Describe AE (symptoms, signs, diagnosis and treatment & action)				
Date start/end				
Intensity [Tick ONE] OR Urine color chart: Hillmen Grade [____]	Mild		Mild	
	Moderate		Moderate	
	Severe		Severe	
	Very Severe		Very Severe	
	Unknown		Unknown	
Drug-event relationship [Tick ONE]	None		None	
	Unlikely		Unlikely	
	Possible		Possible	
	Probable		Probable	
	Definite		Definite	
	Unknown		Unknown	
Outcome [Check ONE]	Complete recovery		Complete recovery	
	Still present		Still present	
	Sequelae		Sequelae	
	Death		Death	
	Unknown		Unknown	
Action taken [Tick all applicable]	None		None	
	Study treatment stopped		Study treatment stopped	
	Hospitalization required		Hospitalization required	

	Concomitant drug therapy		Concomitant therapy	

24.1.1 Appendix Vb

Data Collection Form for Safety Assessment

INSTRUCTIONS:

Complete this form for all cases of confirmed, uncomplicated *P. falciparum* malaria that

Barcode/Unique ID

1. Today's Date (dd/mm/yy) _ _ / _ _ / _ _
2. Family Name |__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|
3. First (Given) Name |__|__|__|__|__|__|__|__|__|__|__|__|
4. Nationality: ☐ Tanzania Other (specify): _____
5. Is Tanzania your country of residence? ☐ Yes ☐ No 6. Age: |__|__| ☐ yrs ☐ mths 7. Sex ☐ M ☐ F
8. Mobile No. 1 |__|__|__|__|__|__|__|__|__|__|__|__| 9. Mobile No. 2 |__|__|__|__|__|__|__|__|__|__|__|__|
10. Pregnant: ☐ Y (Trimester |__|) ☐ N ☐ Uncertain ☐ N/A 11. Weight: _ _ _. _ kg
12. Does this patient have a family history of hemolysis (severe anemia)? ☐ Yes ☐ No ☐ Uncertain

If yes, was it in response to: ☐ Medication ☐Food ☐ Infection ☐ Other

13. Does this patient have a family history of G6PD deficiency? ☐ Yes ☐ No ☐ Uncertain
14. Has this patient ever had a blood transfusion? ☐ Yes ☐ No
15. Diagnostic test type: ☐RDT ☐ Microscopy ☐Both
16. Diagnosis: ☐Pf ☐ Pv ☐ Mixed ☐Other (specify): _____
17. Antimalarial Prescribed (check all given):

☐AL ☐Oral QN ☐IV QN ☐IM QN ☐SP/Fandisar ☐CQ ☐Other (specify): _____☐Unknown

18. Primaquine dose prescribed and # of days:

Daily dose: ☐15mg ☐45mg ☐Other (specify): _____ mg/dose

For how many days: ☐1 day ☐14 days ☐1x weekly for 8 weeks ☐Other (specify):

_____

19. Day 0: ☐Hemoglobin: _ _ _ . _ g/dl
20. Blood Spot: ☐Taken ☐Not taken (INSTRUCTIONS: Add Barcode No. to blood spot if taken.)

24.1.1.1

Patient Information Card

Family Name |__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|

First (Given) Name |__|__|__|__|__|__|__|__|__|__|__|__|

Barcode/Unique ID

Patient Instructions

You have received treatment for malaria. Please return if you do not improve or notice new problems. Please check the color of your urine (by passing urine into a white or clear container) while taking malaria medications. If you notice dark to very dark yellow-orange urine or experience nausea, vomiting, stomach or back pain, please return to the health facility with this card or call the following mobile number: |__|__|__|__|__|__|__|__|__|__|__|__|

----------perforation----------

Maelekezo kwa mgonjwa

Umepata matibabu ya malaria. Tafadhali rudi hapa kituoni kama hutapata nafuu ama utapata tatizo. Tafadhari chunguza rangi ya mkojo (kwa kukojoa kwenye chupa angavu) wakati ukitumia dawa za malaria. Ukiona mkojo wa njano iliyoiva

ama njano ya machungwa iliyoiva sana, ama ukipata kichefuchefu, kutapika, maumivu ya tumbo au mgongo, tafadhali rudi hapa kituoni na kadi hii ama piga simu kwa namba hizi: |__|__|__|__|__|__|__|__|__|__|__|__|__|

----------perforation----------

Barcode/Unique ID

Provider Instructions

Health Facility Name: _____ Contact No. |__|__|__|__|__|__|__|__|__|__|__|__|__|

Should the patient return with signs or symptoms of commonly reported adverse events associated with Primaquine, please complete a patient encounter form. If patient presents to a different health facility from the health facility where original treatment was provided, please contact the treating facility

Patient Encounter Forms

Patient Encounter 1

1. Date of return visit (dd/mm/yy) _ _ / _ _ / _ _ 2. Is this a scheduled day 7 visit? ☐Yes ☐No

3. ☐Hemoglobin: _ _ _ . _ g/dl

4. # of PQ taken per day: _____ 5. # of days PQ tablets taken: _____

6. Did the patient experience an adverse event since being treated with PQ? ☐Yes ☐No

If yes, complete adverse event report. Otherwise, leave blank.

Type of AE (check all that apply)	Onset Date	Severity Grade (check one)	Actions Taken? (specify below if needed)	Is AE related to PQ? (check one)	Date Resolved	Outcome of AE (check one)	Serious AE?
☐ Rash	_ _ / _ _ / _ _	☐ Mild ☐ Moderate ☐ Severe ☐ Life-threatening	☐ None ☐ Stopped PQ ☐ Prescribed drug ☐ Blood Transfusion ☐ Hospitalization ☐ Other**	☐ Unrelated ☐ Unlikely ☐ Possible ☐ Probable ☐ Definite	_ _ / _ _ / _ _ or ongoing ☐	☐ Recovered/resolved ☐ Recovered/resolved with sequelae ☐ Recovering/resolving ☐ Not recovered/not resolved ☐ Fatal ☐ Unknown	☐ No ☐ Yes*
☐ Nausea	_ _ / _ _ / _ _	☐ Mild ☐ Moderate ☐ Severe ☐ Life-threatening	☐ None ☐ Stopped PQ ☐ Prescribed drug ☐ Blood Transfusion ☐ Hospitalization ☐ Other**	☐ Unrelated ☐ Unlikely ☐ Possible ☐ Probable ☐ Definite	_ _ / _ _ / _ _ or ongoing ☐	☐ Recovered/resolved ☐ Recovered/resolved with sequelae ☐ Recovering/resolving ☐ Not recovered/not resolved ☐ Fatal ☐ Unknown	☐ No ☐ Yes*

☐ Vomiting	_ _/_ _/_ _	☐ Mild ☐ Moderate ☐ Severe ☐ Life-threatening	☐ None ☐ Stopped PQ ☐ Prescribed drug ☐ Blood Transfusion ☐ Hospitalization ☐ Other**	☐ Unrelated ☐ Unlikely ☐ Possible ☐ Probable ☐ Definite	_ _/_ _/_ _ or ongoing ☐	☐ Recovered/resolved ☐ Recovered/resolved with sequelae ☐ Recovering/resolving ☐ Not recovered/not resolved ☐ Fatal ☐ Unknown	☐ No ☐ Yes*
☐ Anemia	_ _/_ _/_ _	☐ Mild ☐ Moderate ☐ Severe ☐ Life-threatening	☐ None ☐ Stopped PQ ☐ Prescribed drug ☐ Blood Transfusion ☐ Hospitalization ☐ Other**	☐ Unrelated ☐ Unlikely ☐ Possible ☐ Probable ☐ Definite	_ _/_ _/_ _ or ongoing ☐	☐ Recovered/resolved ☐ Recovered/resolved with sequelae ☐ Recovering/resolving ☐ Not recovered/not resolved ☐ Fatal ☐ Unknown	☐ No ☐ Yes*
☐ Dark Urine	_ _/_ _/_ _	☐ Mild ☐ Moderate ☐ Severe ☐ Life-threatening	☐ None ☐ Stopped PQ ☐ Prescribed drug ☐ Blood Transfusion ☐ Hospitalization ☐ Other**	☐ Unrelated ☐ Unlikely ☐ Possible ☐ Probable ☐ Definite	_ _/_ _/_ _ or ongoing ☐	☐ Recovered/resolved ☐ Recovered/resolved with sequelae ☐ Recovering/resolving ☐ Not recovered/not resolved ☐ Fatal ☐ Unknown	☐ No ☐ Yes*
☐ Diarrhea	_ _/_ _/_ _	☐ Mild ☐ Moderate ☐ Severe ☐ Life-threatening	☐ None ☐ Stopped PQ ☐ Prescribed drug ☐ Blood Transfusion ☐ Hospitalization ☐ Other**	☐ Unrelated ☐ Unlikely ☐ Possible ☐ Probable ☐ Definite	_ _/_ _/_ _ or ongoing ☐	☐ Recovered/resolved ☐ Recovered/resolved with sequelae ☐ Recovering/resolving ☐ Not recovered/not resolved ☐ Fatal ☐ Unknown	☐ No ☐ Yes*
☐ Other (describe): _____ _____	_ _/_ _/_ _	☐ Mild ☐ Moderate ☐ Severe ☐ Life-threatening	☐ None ☐ Stopped PQ ☐ Prescribed drug ☐ Blood Transfusion ☐ Hospitalization ☐ Other**	☐ Unrelated ☐ Unlikely ☐ Possible ☐ Probable ☐ Definite	_ _/_ _/_ _ or ongoing ☐	☐ Recovered/resolved ☐ Recovered/resolved with sequelae ☐ Recovering/resolving ☐ Not recovered/not resolved ☐ Fatal ☐ Unknown	☐ No ☐ Yes*

☐ Other (describe): _____ _____	_ _/ _ _/ _ _	☐ Mild ☐ Moderate ☐ Severe ☐ Life-threatening	☐ None ☐ Stopped PQ ☐ Prescribed drug ☐ Blood Transfusion ☐ Hospitalization ☐ Other**	☐ Unrelated ☐ Unlikely ☐ Possible ☐ Probable ☐ Definite	_ _/ _ _/ _ _ or ongoing ☐	☐ Recovered/resolved ☐ Recovered/resolved with sequelae ☐ Recovering/resolving ☐ Not recovered/not resolved ☐ Fatal ☐ Unknown	☐ No ☐ Yes*
☐ Other (describe): _____ _____	_ _/ _ _/ _ _	☐ Mild ☐ Moderate ☐ Severe ☐ Life-threatening	☐ None ☐ Stopped PQ ☐ Prescribed drug ☐ Blood Transfusion ☐ Hospitalization ☐ Other**	☐ Unrelated ☐ Unlikely ☐ Possible ☐ Probable ☐ Definite	_ _/ _ _/ _ _ or ongoing ☐	☐ Recovered/resolved ☐ Recovered/resolved with sequelae ☐ Recovering/resolving ☐ Not recovered/not resolved ☐ Fatal ☐ Unknown	☐ No ☐ Yes*

** Yes should be answered when the adverse event results in death, is life-threatening, requires in-patient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect.*

~~Definitions~~

Severity – Mild (easily tolerated; no or minimal interference with daily activities); Moderate (low level of inconvenience; greater than minimal interference with daily activities); Severe (interrupts normal daily activities; usually incapacitating); Life-threatening (life-threatening consequences; urgent intervention indicated); Fatal (death)

**Other information (actions taken): _____

_____

OPTION 1:

7. Did the patient take any other drugs along with PQ at the time of treatment or in the two-week period prior to the onset of the event? *If yes, please specify the following:*

Name of Drug	Dose	Unit	Frequency (number of times per day)	Route	Date Started (dd/mm/yy)	Date Stopped (dd/mm/yy) Or Continuing?	Indication
		☐ mg ☐ g ☐ ml ☐ mcg ☐ drops ☐ other:_____ ☐ tsp ☐ don't know		☐ oral ☐ topical ☐ IM ☐ rectal ☐ IV	_ _/ _ _/ _ _	_ _/ _ _/ _ _ ☐	

		☐ tablet/capsule		☐ other:_____ ☐ don't know			
If AL is given, complete information above. Include all other concomitant medicines below.							
		☐ mg ☐ g ☐ ml ☐ mcg ☐ drops ☐ other:_____ ☐ tsp ☐ don't know ☐ tablet/capsule		☐ oral ☐ topical ☐ IM ☐ rectal ☐ IV ☐ other:_____ ☐ don't know	_ _ / _ _ / _ _	_ _ / _ _ / _ _ ☐	
		☐ mg ☐ g ☐ ml ☐ mcg ☐ drops ☐ other:_____ ☐ tsp ☐ don't know ☐ tablet/capsule		☐ oral ☐ topical ☐ IM ☐ rectal ☐ IV ☐ other:_____ ☐ don't know	_ _ / _ _ / _ _	_ _ / _ _ / _ _ ☐	

8. Did the patient take any traditional medicines along with PQ at the time of treatment or in the two-week period prior to the onset of the event? *If yes, give details if known:*
_____
_____

INSTRUCTIONS: If patient presents with additional adverse events, attach and complete another form.

24.1.3 Appendix Vb

Fomu ya kukusanyia taarifa za usalama wa dawa

Maelekezo:

Jaza fomu hii kwa wagonjwa wote waliothibitishwa kuwa na malaria kawaida itokanayo

Namba ya mgonjwa

1. Tarehe ya leo (sk/mz/mk) _ _ / _ _ / _ _

2. Jina la familia |__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|

3. Jina la kwanza |__|__|__|__|__|__|__|__|__|__|__|__|

4. Utaifa: ☐ Tanzania. Mwingineo (Taja): _____

5. Je Tanzania ni nchi yako ya ukazi? ☐ Ndiyo ☐ Hapana 6. Umri: |__|__| ☐ miaka ☐ miezi 7. Jinsia ☐Kiume ☐Kike

8. Namba ya simu ya mkononi. 1 |__|__|__|__|__|__|__|__|__|__|__|__|__| 9. Namba nyingine. 2 |__|__|__|__|__|__|__|__|__|__|__|__|__|

10. Mjamzito: ☐ N (Trimester |__|) ☐ H ☐ Haijulikani ☐ N/A 11. Uzito: _ _ _. _ kg

12. Je mgonjwa anahistoria ya kupungukiwa damu (kupungukiwa damu sana)? ☐ Ndiyo ☐ Hapana ☐ Haijulikani

Kama ndiyo, ilisababishwa na: ☐Dawa ☐Chakula ☐ Maambukizi ☐ Mengineyo

13. Je mgonjwa ana historia ya familia kuwa na upungufu wa kimengénya kiitwacho G6PD? ☐ Ndiyo ☐Hapana ☐ Haijulikani

14. Je mgonjwa amewahi kuwekewa damu? ☐ Ndiyo ☐Hapana

15. Aina ya kipimo: ☐RDT ☐Darubini ☐Vyote

16. Majibu: ☐Pf ☐ Pv ☐ Mchanganyiko ☐Mengineyo (Taja): _____

17. Dawa ya malaria iliyotolwa (Tiki zote zilizotolewa):

☐AL ☐Oral QN ☐IV QN ☐IM QN ☐SP/Fandisar ☐CQ ☐Nyinginezo (Taja): _____☐Haifahamiki

18. Dozi ya Primaquine iliyotolewa na idadi ya siku:

Dozi ya siku: ☐15mg ☐45mg ☐Nyinginezo (Taja): _____ mg/dozi

Kwa siku ngapi: ☐ siku 1 ☐ siku 14 ☐mara 1 kwa wiki kwa wiki 8 ☐Mengineyo (Taja): _____

19. Siku 0: ☐Uwingi wa damu: _ _ _ . _ g/dl

20. Damu kwenye karatasi: ☐Imechukuliwa ☐Haijachukuliwa (Maelekezo:Weka namba ya mgonjwa kama damu imechukuliwa kwenye kikaratasi)

Kadi ya maelekezo kwa mgonjwa

Jina la mgonjwa |__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|

Jina la kwanza |__|__|__|__|__|__|__|__|__|__|__|__|

----------mkato----------

Namba ya mgonjwa

Maelekezo kwa mgonjwa

Umepata matibabu ya malaria. Tafadhali rudi hapa kituoni kama hutapata nafuu ama utapata tatizo. Tafadhari chunguza rangi ya mkojo (kwa kukojoa kwenye chupa angavu) wakati ukitumia dawa za malaria. Ukiona mkojo wa njano iliyoiva ama njano ya machungwa iliyoiva sana, ama ukipata kichefuchefu, kutapika, maumivu ya tumbo au mgongo, tafadhali rudi hapa kituoni na kadi hii ama piga simu kwa namba hizi: |__|__|__|__|__|__|__|__|__|__|__|__|

----------mkato----------

Maelekezo kwa mtoa huduma

Jina la zahanati: _____ Namba ya simu.
|__|__|__|__|__|__|__|__|__|__|__|__|

Ikitokea mgonjwa akarudi na dalili za madhara ya kawaida yatokanayo na matumizi ya Primaquine, tafadhali jaza fomu ya mgonjwa. Kama mgonjwa ataenda hospitali nyingine tofauti na hospitali ambako alipewa matibabu ya kwanza, tafadhali wasiliana na hiyo hospitali.

Namba ya mgonjwa

Fomu ya mgonjwa aliyepata madhara

Fomu ya mgonjwa aliyedhurika 1

1. Tarehe ya kurudi (sk/mz/mk) _ _ / _ _ / _ _ 2. Hii ni siku ya 7 uliyopangiwa? ☐Ndiyo ☐Hapana

3. ☐Uwingi wa damu: _ _ _ . _ g/dl

4. Idadi ya vidonge vilivyomezwa kwa siku: _____ 5. Idadi ya siku PQ imenywewa: _____

6. Mgonjwa alipata madhara tangu alipokuwa akitibiwa kwa PQ? ☐Ndiyo ☐Hapana

Kama ni ndiyo, jaza fomu yaripoti ya madhara makubwa.

Aina ya madhara (Tiki inayohusika)	Siku yalipoanza	Kiwango (Tiki moja)	Hatua iliyochukuliwa? (Elezea)	Madhara yanahusiana na PQ? (Tiki moja)	Tarehe yalipokwisha	Matokeo ya madhara (Tiki moja)	Serious AE?
☐ Upele	_ _ / _ _ / _ _	☐ Kidogo ☐ Wastani ☐ Mbaya ☐ Yanatishia uhai	☐ Hakuna ☐ PQ Imesitishwa ☐ Amepewa dawa ☐ Kaongezwa damu ☐ Kalazwa ☐ Mengineyo**	☐ Hamna uhusiano ☐ Nadra ☐ Yawezekana ☐Hakika	_ _ / _ _ / _ _ au inaendelea ☐	☐ Amepona/amepata nafuu ☐ Amepona na kubaki na ulemavu ☐Anapata nafuu ☐ Hajapona/hajapata nafuu ☐ Hali ni mbaya ☐ Haifahamiki	☐ No ☐ Yes*
☐ Kichefuchefu	_ _ / _ _ / _ _	☐ Kidogo ☐ Wastani ☐ Mbaya ☐ Yanatishia uhai	☐ Hakuna ☐ PQ Imesitishwa ☐ Amepewa dawa ☐ Kaongezwa damu ☐ Kalazwa ☐ Mengineyo**	☐ Hamna uhusiano ☐ Nadra ☐ Yawezekana ☐Hakika	_ _ / _ _ / _ _ au inaendelea ☐	☐ Amepona/amepata nafuu ☐ Amepona na kubaki na ulemavu ☐Anapata nafuu ☐ Hajapona/hajapata nafuu ☐ Hali ni mbaya ☐ Haifahamiki	☐ No ☐ Yes*
☐ Kutapika	_ _ / _ _ / _ _	☐ Kidogo ☐ Wastani ☐ Mbaya ☐ Yanatishia uhai	☐ Hakuna ☐ PQ Imesitishwa ☐ Amepewa dawa ☐ Kaongezwa damu ☐ Kalazwa ☐ Mengineyo**	☐ Hamna uhusiano ☐ Nadra ☐ Yawezekana ☐Hakika	_ _ / _ _ / _ _ au inaendelea ☐	☐ Amepona/amepata nafuu ☐ Amepona na kubaki na ulemavu ☐Anapata nafuu ☐ Hajapona/hajapata nafuu ☐ Hali ni mbaya ☐ Haifahamiki	☐ No ☐ Yes*
☐ Anemia	_ _ / _ _ / _ _	☐ Kidogo ☐ Wastani ☐ Mbaya ☐ Yanatishia uhai	☐ Hakuna ☐ PQ Imesitishwa ☐ Amepewa dawa ☐ Kaongezwa damu ☐ Kalazwa ☐ Mengineyo**	☐ Hamna uhusiano ☐ Nadra ☐ Yawezekana ☐Hakika	_ _ / _ _ / _ _ au inaendelea ☐	☐ Amepona/amepata nafuu ☐ Amepona na kubaki na ulemavu ☐Anapata nafuu ☐ Hajapona/hajapata nafuu ☐ Hali ni mbaya ☐ Haifahamiki	☐ No ☐ Yes*

☐ Mkojo mweusi	_ _/_ _/_ _	☐ Kidogo ☐ Wastani ☐ Mbaya ☐ Yanatishia uhai	☐ Hakuna ☐ PQ Imesitishwa ☐ Amepewa dawa ☐ Kaongezwa damu ☐ Kalazwa ☐ Mengineyo**	☐ Hamna uhusiano ☐ Nadra ☐ Yawezekana ☐Hakika	_ _/_ _/_ _ au inaendelea ☐	☐ Amepona/amepata nafuu ☐ Amepona na kubaki na ulemavu ☐Anapata nafuu ☐ Hajapona/hajapata nafuu ☐ Hali ni mbaya ☐ Haifahamiki	☐ No ☐ Yes*
☐ Kuharisha	_ _/_ _/_ _	☐ Kidogo ☐ Wastani ☐ Mbaya ☐ Yanatishia uhai	☐ Hakuna ☐ PQ Imesitishwa ☐ Amepewa dawa ☐ Kaongezwa damu ☐ Kalazwa ☐ Mengineyo**	☐ Hamna uhusiano ☐ Nadra ☐ Yawezekana ☐Hakika	_ _/_ _/_ _ au inaendelea ☐	☐ Amepona/amepata nafuu ☐ Amepona na kubaki na ulemavulae ☐Anapata nafuu ☐ Hajapona/hajapata nafuu ☐ Hali ni mbaya ☐ Haifahamiki	☐ No ☐ Yes*
☐Mengineyo (Elezea): _____ _____	_ _/_ _/_ _	☐ Kidogo ☐ Wastani ☐ Mbaya ☐ Yanatishia uhai	☐ Hakuna ☐ PQ Imesitishwa ☐ Amepewa dawa ☐ Kaongezwa damu ☐ Kalazwa ☐ Mengineyo**	☐ Hamna uhusiano ☐ Nadra ☐ Yawezekana ☐Hakika	_ _/_ _/_ _ au inaendelea ☐	☐ Amepona/amepata nafuu ☐ Amepona na kubaki na ulemavulae ☐Anapata nafuu ☐ Hajapona/hajapata nafuu ☐ Hali ni mbaya ☐ Haifahamiki	☐ No ☐ Yes*
☐Mengineyo (Elezea):_____ _____ ____	_ _/_ _/_ _	☐ Kidogo ☐ Wastani ☐ Mbaya ☐ Yanatishia uhai	☐ Hakuna ☐ PQ Imesitishwa ☐ Amepewa dawa ☐ Kaongezwa damu ☐ Kalazwa ☐ Mengineyo**	☐ Hamna uhusiano ☐ Nadra ☐ Yawezekana ☐Hakika	_ _/_ _/_ _ au inaendelea ☐	☐ Amepona/amepata nafuu ☐ Amepona na kubaki na ulemavulae ☐Anapata nafuu ☐ Hajapona/hajapata nafuu ☐ Hali ni mbaya ☐ Haifahamiki	☐ No ☐ Yes*
☐Mengineyo (Elezea): _____ _____	_ _/_ _/_ _	☐ Kidogo ☐ Wastani ☐ Mbaya ☐ Yanatishia uhai	☐ Hakuna ☐ PQ Imesitishwa ☐ Amepewa dawa ☐ Kaongezwa damu ☐ Kalazwa ☐ Mengineyo**	☐ Hamna uhusiano ☐ Nadra ☐ Yawezekana ☐Hakika	_ _/_ _/_ _ au inaendelea ☐	☐ Amepona/amepata nafuu ☐ Amepona na kubaki na ulemavulae ☐Anapata nafuu ☐ Hajapona/hajapata nafuu ☐ Hali ni mbaya ☐ Haifahamiki	☐ No ☐ Yes*

** Iwe ndiyo endapo madhara yamepelekea kifo, inatishia uhai, inahitajika kulazwa au kuongeza muda wa kulazwa, inapelekea kuendelea au kupata ulemavu/kupoteza uwezo, au madhara ya kuzaliwa nayo.*

7. Mgonjwa alikunywa dawa wakati akitumia PQ au ndani ya wiki mbili kabla ya kutokea kwa madhara? Kama ndiyo, tafadhari elezea yafuatayo*:*

Jina la dawa	Dozi	Kipimo	Frequency (number of times per day)	Njia	Tarehe ya kuanza (sk/mz/mk)	Tarehe ya kusitisha (sk/mz/mk)	Indication
		☐ mg ☐ g ☐ ml ☐ mcg ☐ matone ☐ Mengine:_____ ☐ K/chai ☐ Sifahamu ☐ Kidonge/tembe		☐ Mdomo ☐ Kupaka ☐ IM ☐ Haja kubwa ☐ IV ☐ Nyingine:_____ ☐ Sifahamu	_ _ / _ _ / _ _	_ _ / _ _ / _ _ ☐	
If AL is given, complete information above. Include all other concomitant medicines below.							
		☐ mg ☐ g ☐ ml ☐ mcg ☐ matone☐ Mengine:_____ ☐ K/chai ☐ Sifahamu ☐ Kidonge/tembe		☐ Mdomo ☐ Kupaka ☐ IM ☐ Haja kubwa ☐ IV ☐ Nyingine:_____ ☐ Sifahamu	_ _ / _ _ / _ _	_ _ / _ _ / _ _ ☐	
		☐ mg ☐ g ☐ ml ☐ mcg ☐ matone☐ Mengine:_____ ☐ K/chai ☐ Sifahamu ☐ Kidonge/tembe		☐ Mdomo ☐ Kupaka ☐ IM ☐ Haja kubwa ☐ IV ☐ Nyingine:_____ ☐ Sifahamu	_ _ / _ _ / _ _	_ _ / _ _ / _ _ ☐	

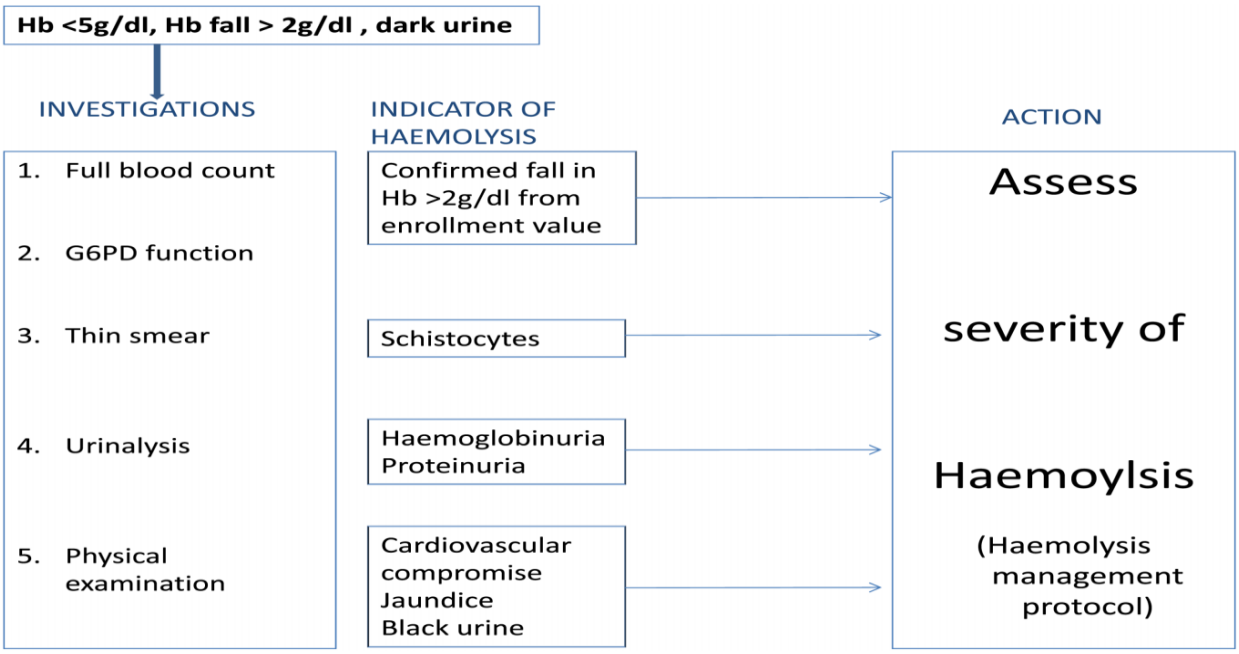
8. Je, mgonjwa alitumia dawa zozote za asili pamoja na PQ wakati wa matibabu au ndani ya wiki mbili kabla ya kutokea kwa madhara? Kama ndiyo, elezea:

_____

_____

Maelekezo: Kama mgonjwa atapata madhara zaidi, ambatanisha na jaza fomu nyingine.

24.1.4 Procedure for investigation of suspected hemolysis



24.1.5 Procedure for management of hemolysis