EFFECTIVENESS AND SAFETY OF ARTEMETHER-LUMEFANTRINE IN BUNGOMA COUNTY REFERRAL HOSPITAL

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DECLARATION OF ORIGINALITY

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DEDICATION

I dedicate this work my family for their support. I would also like to dedicate this to all the parents and participants for their support.

ACKNOWLEDGEMENT

First, I acknowledge the Almighty God for the gift of life and for providing me with the strength to accomplish this work.

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ABSTRACT

Background

Malaria is a worldwide healthcare issue that is causing millions of deaths. In Kenya, malaria is one of the leading causes of death especially for children under the age of 5 years and expectant mothers. There are strategies in place to try and eliminate malaria, one of which involve prompt diagnosis and treatment. Artemether and Lumefantrine are recommended first line drugs against uncomplicated malaria. With continuous exposure of drugs to the parasite, resistance is bound to occur. World Health Organization has recommended that the efficacy of Artemether and Lumefantrine be checked in endemic areas every two years. Increased screening of malaria has led to prompt treatment of malaria which has saved lives. This also has led to an increased number of people being exposed to the drugs sometimes repeatedly. With this, some rare adverse events are likely to be unmasked.

Objective

The main objective of this study is to determine the effectiveness and safety of Artemether-Lumefantrine in Bungoma County Referral Hospital.

Method

A longitudinal study was carried out involving following up of participants diagnosed with uncomplicated malaria in Bungoma County Referral Hospital. Two hundred and sixty participants on treatment with Artemether-Lumefantrine were randomly selected and followed up by calling using a mobile phone. Any adverse events were recorded in a form. Data was analyzed using STATA version 13. Both descriptive and inferential statistics were used to summarize the data at 0.05 level of significance.

Results

A total of 260 malaria participants participated in the study, of which the majority were female, 53.5%. The age range was 1 month to 61 years and median of 36 months (3years). AL was found to be effective against uncomplicated malaria. Lumefantrine was able to protect all the participants against malaria for the 28 day period irrespective of whether they protected themselves against mosquito bite or not. AL was generally well tolerated with only 23% of the participants reporting adverse events of which abdominal discomfort 43.3 %(26 participants),

cough 43.3 (26 participants) and headache 31.7 % (19 participants). 5 participants reported blisters on the body and 5 had swollen abdomen. The adverse events might be associated with the fatty meal the participant was advised to eat before taking the drugs.

Conclusion

AL is still safe and ffective against uncomplicated malaria in Bungoma County Referral Hospital. Lumefantrine is also able to protect the participants for 28 days after taking the first dose of AL. There were however strange adverse events reported during the study that requires further investigation.

Recommendations

Intense pharmacovigilance is required to identify and document adverse events associated with AL. the healthcare workers should be assured that AL is still effective against uncomplicated malaria in order to restore their faith and prevent them from using second line in place of first line. Emphasis to confirm malaria before treatment should be done to avoid overmedication and reduce drug pressure. Participants and healthcare personnel should be taught and encouraged to report adverse events.

LIST OF ABBREVATION AND ACRONYMS

AL- Artemether Lumefantrine

ALT- Alanine aminotransferase

ARV- antiretroviral

AST- Aspartate aminotransferase

AUC- Area under the curve

BUN- Blood urea nitrogen

CYP- Cytochrome P

G6PD- Glucose-6-phosphate dehydrogenase

HIV- Human Immunodeficiency Virus

PCR- Polymerase chain reaction

pfK13- *Plasmodium falciparum* kelch 13

pfmdr1- ***P.****falciparum* multidrug resistance protein 1

WHO- World Health Organisation

DEFINITION OF OPERATIONAL TERMS

Anaemia- A reduction in the quantity of the oxygen-carrying pigment haemoglobin in the blood

Anti-pyretic- A drug such as paracetamol that relieves fever without affecting the causative agent (in this case the parasite)

Endemic- Occurring frequently in a particular region or population

Fever- An increase in body temperature above the normal temperature i.e. above an oral temperature of 37.5°C

Haemolytic anaemia- Anaemia that result due to rapture of the red blood cells

Recrudescence- The recurrence of asexual parasitaemia after treatment of the infection with the same infection that caused the original illness

Treatment failure- A failure to achieve the desired therapeutic response after the initiation of therapy. It is not synonymous with drug resistance.

Treatment failure- Failure to achieve the desired therapeutic response after the initiation of therapy

Uncomplicated malaria- Symptomatic infection with malaria parasitaemia without signs of severity and/or evidence of vital organ dysfunction

CHAPTER 1

1.1: Introduction

Malaria is a preventable and treatable disease caused by plasmodium species. It, however, remains a major healthcare problem worldwide accounting for approximately 219 million cases in 2017. The African region is still the leading region with the highest burden of malaria at 92% in 2017, followed by South Asia. Of all malaria reported cases, 80% were in 15 African countries and India (1).

Malaria symptoms are non-specific making it hard to diagnose it without laboratory diagnosis. It is caused by four species of plasmodium; *Plasmodium falciparum*, *Plasmodium vivax*, *Plasmodium ovale* and *Plasmodium malariae*. Malaria is majorly transmitted by a bite of a female mosquito (anopheles) during a blood meal. It can also be transmitted through blood transfusion or organ transplant although this is rare because of screening before donation (1–3).

All species of plasmodium are found in Kenya. The most predominant species is *P. falciparum* (98.2%) and is also the most virulent. *P. vivax* accounts for 40 to 50% although it occurs as a mixed infection and it is mostly found in Northern and North Eastern Kenya. *P. malariae* and *P. ovale* account for 1.8% of the cases and also occurring as a mixed infection (2). A study done in the western region showed a prevalence of malaria to be high in children in the rural region (10.16%) compared to children in urban areas (2.93%) (4).

The clinical standard laboratory diagnosis of malaria is microscopy (2). The thick film is used for parasite detection, and quantification of the parasite in blood as well as monitoring response to treatment. Thin-film, on the other hand, is for species identification. Rapid diagnostic testing can also be used for diagnosis only. It detects the malaria parasite antigen. The shortcoming of it is that it can give positive results up to three weeks after infection. It cannot also quantify the density of the parasite in the blood. A polymerized chain reaction that detects parasite DNA can also be used. However, it is expensive to carry out the test, it requires skilled personnel and the equipment is expensive. Hence, it is used mostly for efficacy studies (1–3).

Continuous resistance to antimalarials has led to the use of combined antimalarials as opposed to a single molecule for uncomplicated malaria (1). Artemether lumefantrine (AL) is recommended as the first line for uncomplicated malaria. Treatment failure can be suspected if symptoms persist 3 to 4 days after initiation of therapy. Development of symptoms 14 days after treatment is considered reinfection according to Kenyan guidelines (2).

AL is still effective against uncomplicated malaria in endemic areas (1,2,11–20,5–10). A study done in the coastal of Kenya region has revealed that there is a reduced response of *Plasmodium falciparum* to AL (40). Several studies have also shown that people with no immunity to malaria are at higher risk of treatment

failure than those with natural immunity (4,13,14) AL is safe to use for both adults and children with 5 kilograms and above (1–3,14). However, some participants experience adverse effects after using AL. Most of the adverse effects are similar to signs and symptoms of malaria making it hard to identify the cause (1,9–11,22). There was a reported case of a participant without G6PD deficiency, was HIV positive and had severe malaria which was treated with doxycycline and quinine, who developed haemolytic anaemia 10 days after using AL (43). A systematic review of AL use shows that children experience cough as an adverse event (36). There is also evidence that AL interacts with efavirenz (anti-HIV) probably because they share a metabolic enzyme, cytochrome 3A4 with lumefantrine. As a result, malaria clearance by AL in the participant on efavirenz was reduced (5,19). The non-fatty meal has also been shown to reduce the effectiveness of AL against the malaria parasite. This has been attributed to reducing the bioavailability of lumefantrine which is better absorbed after a fatty meal (35,39,44).

Resistance to first-line antimalarials poses one of the greatest dangers to people living in malaria endemic areas and prompt treatment is recommended (22). For this reason, it is essential to monitor the effectiveness of first-line drugs. Prompt treatment of malaria means more people will be exposed to the agents hence greater chance of unmasking some of the adverse drug events. There are few studies done on the safety of the first-line antimalarial as post-market surveillance. Most importantly, there is no such study that has been done in Bungoma County Referral hospital despite being in the heart of the malaria endemic zone.

1.2 Problem statement

Malaria continues being a worldwide healthcare problem (1–3). In Kenya, many strategies have been put in place to fight the disease (1,2,22). One of the strategies in the fight is the rapid diagnosis and treatment (22). A combination of Artemether and lumefantrine is used as the first-line against uncomplicated malaria in most malaria endemic areas (1,3,16,22). Safety and effectiveness of AL must, therefore, be monitored continuously (1). If AL is no longer efficacious as a first-line agent against malaria, many lives are bound to be affected. With million cases of malaria reported and the majority of them relying on AL for treatment, resistance against AL will put us a step behind in war against malaria (1,3). AL safety also needs monitoring for pharmacovigilance purposes. Although AL is well tolerated, it is still important to monitor its safety to check for outliers that might be adversely affected by AL. There is an unpredicted drug-disease interaction that might change the way a participant reacts to AL that needs reporting.

The study was set out to investigate the prevalence and risk factors for recrudescence of malaria after using the first-line antimalarial to manage malaria infection, the prevalence and types of adverse drug events experienced by the participant with malaria on AL and associated risk factors, and the likely causes of treatment failure in a participant with malaria on AL in Bungoma County Referral Hospital. The findings are expected to reinforce the faith in AL as a first-line against uncomplicated malaria because it

has been proven to be safe and efficacious. This is because, in Kenyan malaria endemic zones, the health workers are losing faith in AL as a first-line. Some of the concerns are that it might be losing its effectiveness against malaria. The adverse events have also been documented to provide evidence of its safety.

1.3 Study justification

The safety of any drug, even the ones considered safe, needs to be established in different communities because of genetic difference. The is no single study done on the safety of Artemether Lumefantrine in participants with malaria in Bungoma county Referral Hospital (2). Bungoma County Referral Hospital, being in the center of malaria endemic area has enough population of participants using AL. Some of the adverse events of AL mimic the signs and symptoms of malaria and this might be reducing the faith in AL as a first line drug against uncomplicated malaria. The decision to order for malaria test or any disease is always based on signs and symptoms. By establishing their prevalence, it will help in reassuring the participants and healthcare workers on its effectiveness and reinforce the need to retest the participant before declaring treatment failure. Several studies have reported adverse drug events of AL that have impacted participants' lives (5,7,9). If the prevalence of such adverse events is very high or more severe adverse events are associated with AL, then the policymakers may have to review the use of AL. On the other hand, if the prevalence is not significant or the adverse events do not impact participants' life significantly then the study will help the Ministry of Health, the Pharmacy and Poisons Board and National Malaria Control Program in documenting the frequency of the expected side effects. The pharmacy and poisons Board will update their pharmacovigilance information on the safety of AL. The medical practitioners will also be able to use the results to advise participants on what to expect after they use AL and report any to the pharmacovigilance offices in their institutions. The general population will be comfortable to use AL and will also be able to anticipate the adverse drug events and report them to the nearest healthcare facility or the Pharmacy and Poisons board.

This study will also help in the fight against malaria by proving evidence of safety and effectiveness of AL as a first-line treatment. If drug resistance is detected early and reported, treatment failure will be avoided by using efficacious medicine and hence reducing treatment failure.

1.4 Research question

What is the effectiveness and safety of AL in participants with malaria in Bungoma County Referral Hospital?

1.5 Objectives

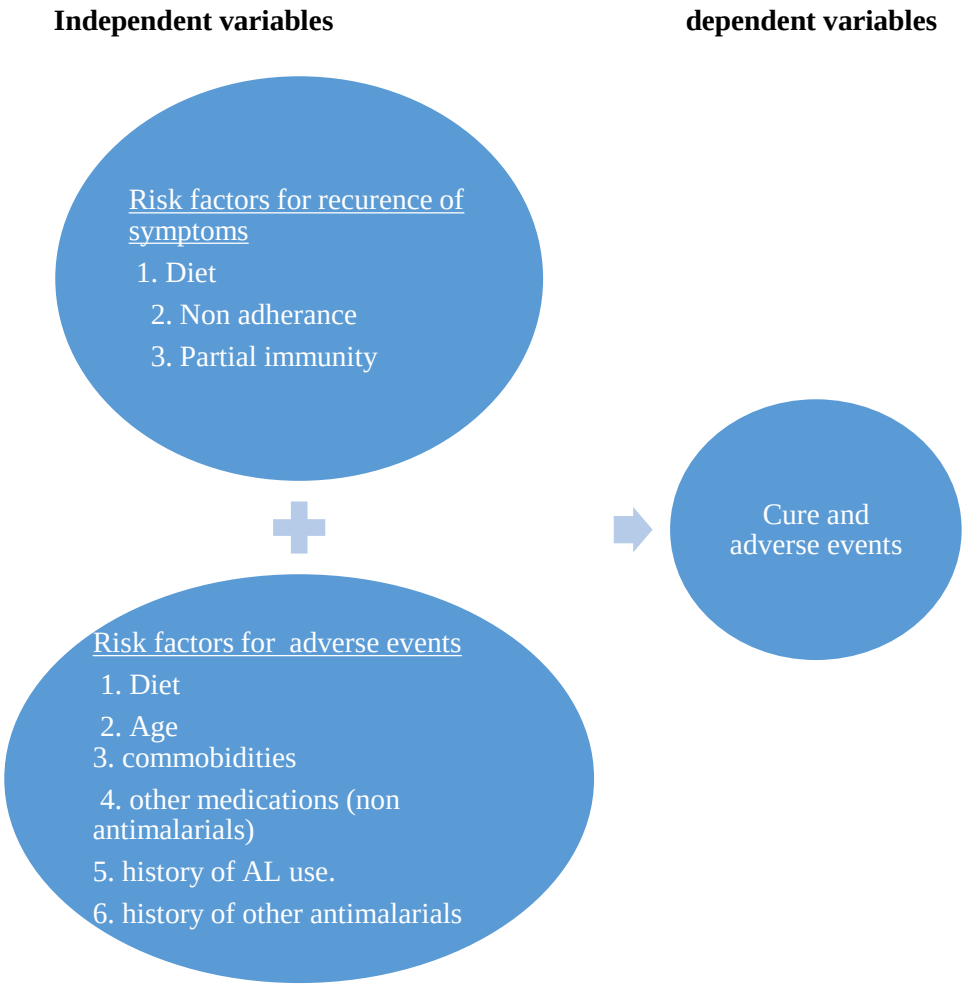
1.5.1 General objective

To determine the effectiveness and safety of AL treatment in participants with malaria in Bungoma County Referral Hospital.

1.5.2 Specific objectives

1. To determine the prevalence and risk factors of recurrence of malaria symptoms in participants after using AL at Bungoma County Referral Hospital.
2. To determine the prevalence and risk factors of adverse drug events among participants on AL at Bungoma County Referral Hospital.
3. To identify the risks of treatment failure in participants on AL at Bungoma County Referral Hospital.

1.6 Conceptual Framework



The fatty diet will increase the solubility of Lumefantrine, increasing its absorption which will ensure cure from malaria but also predispose the participant to adverse events because of increased exposure. Children below the age of five and non-immune participants have been found to have high parasitic density. Their cure rate will, therefore, be reduced. Children are at risk of developing adverse events than adults due to immature organs that metabolise the drug. Non- adherent participants are less likely to achieve a cure rate than adherent ones. They will, however, have less exposure to the drug hence experience less adverse events. The previous history of AL use and use of other antimalarial will predispose participants to adverse drug reaction.

CHAPTER 2: LITERATURE REVIEW

2.1: Introduction

This section of the proposal is about studies done on the safety and effectiveness of artemether and Lumefantrine. This involves studies done on the effectiveness of artemether and lumefantrine against uncomplicated malaria. The studies are done in both endemic and non-endemic areas. Artemether and lumefantrine are still efficacious against uncomplicated malaria although their effectiveness is reduced in some areas. There is no reported resistance yet. Both agents are well tolerated. There has been reported severe adverse events but the incidences as very low.

2.2 Plasmodium parasite

Malaria continues to claim the lives of the millions worldwide (1). A Vaccine against it is currently in a clinical trial and showing promising results (46). Partial immunity towards malaria has been found to contribute to the efficacy of drugs against multidrug-resistant malaria, thus a confounder (13). In the meantime, prompt diagnosis and treatment remain one of the cornerstones in the fight against malaria.

Safety of any drug is paramount. Most drugs fail to be approved because of safety. Some drugs like Thalidomide, once thought to be safe, was withdrawn from the market because of safety. Effectiveness of a drug is proven during the clinical trial but the drug can become less efficacious because of resistance, drug-drug interaction, participant factors among other causes.

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The life cycle starts with a bite from a female anopheles mosquito (such as *Anopheles gambiae*) bite humans during a blood meal. The mosquito regurgitates the gut content, which contains sporozoites, then feeds on blood. The sporozoites invade the hepatocytes and mature into schizonts (3). This is called the exoerythrocytic stage. This stage is not clinically important to *P.malariae* and *P. falciparum* because they do not remain dormant in the liver. *P.vivax* and *P. ovale*, on the other hand, can form hypnozoites which remain dormant and can cause relapses hence require medicine that target this stage specifically. The hepatocytes then rupture to release merozoites into the bloodstream (3). The merozoites then infect the red blood cell (ring stage). The trophozoites mature into either schizont or gametocytes. The red blood cell then ruptures to release schizont which infects another red blood cell or gametocyte which when taken by the

female mosquito reproduce in the mosquito. This blood stage is called the erythrocyticytic stage and is the stage where the participant will experience the signs and symptoms of malaria such as fever and chills (3).

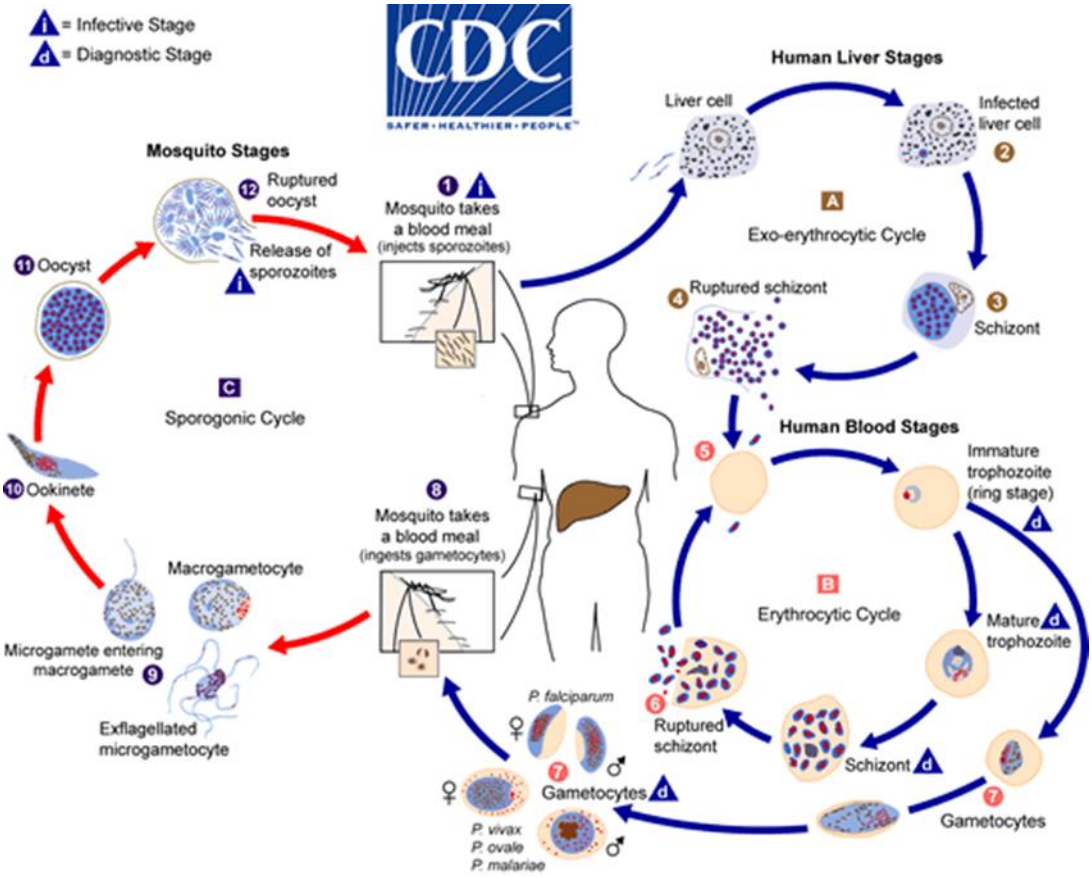

Figure 1: The life cycle of plasmodium parasite (3).

2.3 Classification of Antimalarial

Antimalarials are grouped according to the stage of parasite they act on. Those that kill dormant hypnozoites in the liver are called tissue schizonticides. An example is primaquine. Blood schizonticides affect the plasmodium in their erythrocytic stage (1,16,47). Examples are chloroquine, artemisinin and its derivatives and halofantrine. Gametocides kill gametocyte preventing sexual reproduction, hence preventing reinfection, therefore, are preventative in nature. Chloroquine is only moderately effective against *P.vivax, P.ovale* and *P. malariae* but does not affect *P. falciparum* gametocyte (47). Artemether is also a gametocidal in nature. Antimalarials can also be classified according to their derivative compounds and their chemical structure (47).

2.3.1 Artemisinin and its Derivatives

Artemisinin is derived from a Chinese herb called *Artemisia annua*. The Chinese used the herb for management of fever (48). Artemisinin is slightly soluble in both oil and water hence the need to synthesise

soluble compounds. Artemether and other derivatives are derived by reducing the carbonyl group of the artemisinin compound (47,48).

Artemether is readily absorbed after oral administration reaching its peak plasma in 1-2 hours. Its half-life is 1-3 hours after oral administration. Artemether is a prodrug that needs to be activated to active dihydroartemisinin. It is then metabolized in the liver by glucuronidation. Artemether affects all human plasmodium species in their erythrocytic stage. It, however, does not have any effect against hypnozoites hence the need for a second molecule in case of their presence (47).

Artemether mechanism of action is not yet well understood. It has been stipulated to be due to free radicals that are produced during iron catalyzed cleavage of artemisinin endoperoxide bridge in the plasmodium food vacuole. Alternatively, it can be due to the inhibition of plasmodium calcium ATPase (47).

2.3.2 Lumefantrine

Oral absorption of Lumefantrine is variable and improves if taken with meals especially a fatty meal. Lumefantrine, unlike halofantrine, is safe to be taken after a meal because it has fewer adverse effects. It has a half-life of about 4 days (47).

Lumefantrine has been shown to prolong the QT interval asymptomatically. During the clinical trial, some of the adverse events associated include gastrointestinal disturbances, headaches, dizziness, rash and itchiness (47).

2.3.3 Effectiveness of Artemether and Lumefantrine

Artemether and Lumefantrine are effective and has been approved by most countries and WHO as one of the first lines against uncomplicated malaria (1,2). Worldwide, there have been reported cases of minor concerns over the effectiveness of artesunate and its derivatives. Travellers have also reported unsatisfactory response to AL. A Japanese traveller reported recurring of symptoms after six doses of AL (49). In Sweden, imported uncomplicated malaria is managed by Artemether Lumefantrine combination (44). A study done there showed that uncomplicated malaria caused by *Plasmodium falciparum* was managed with AL which was found to be efficacious. 5 out of 95 participants had a recrudesce of malaria within 20 to 28 days after the AL administration. These participants were found to have Lumefantrine levels below the expected amount (2microgram/dl) (44). In the United States of America, a study on imported malaria was carried out for 5 years. 61.1% of the participants had a history of travelling from West Africa while 38.9% were from other malaria endemic areas. AL was used to manage the malaria cases with a cure rate of 91.5% which is above WHO recommendation as a first line (1,14). Despite the successful cure rate with AL, 10 out of 203 participants had malaria parasite by day 7. Seven of these participants were misdiagnosed to have uncomplicated malaria when they had severe malaria hence the reason for early

treatment failure (14). In Cambodia, an area known for multidrug resistance malaria parasite reported cases of reduced effectiveness of artemisinin after using it as a monotherapy (30). However, AL was found to be still efficacious against uncomplicated malaria in this area (30). East Myanmar, some reports support AL to be effective against uncomplicated malaria even after K13 mutation being reported to be prevalent in the area. The C550Y mutation was also isolated and was associated with late treatment failure in the area (35).

So far, no resistance to AL has been reported in Africa. Several studies have been carried out in different countries to support this. In Angola, a study proved the effectiveness of AL against uncomplicated malaria in the country. Efficacy was reported to be at 96% in one area and 97% in another area of the country (9). Although there were no mutated genes that were isolated that would suggest reduced susceptibility of the malaria parasite to artemisinin, wild type *pfK13* caused reinfection that resulted in late treatment failure (11). This group was also found to have lumefantrine levels lower than 0.2 µg/ml by day 7 which is below recommended levels by WHO (11). A comparison of AL and Amodiaquine in Gabon claimed that there was no difference in effectiveness between the two groups. AL was found to have 95% parasite clearance on day two and a 74% fever clearance in 24 hours. Late therapeutic failure was however reported to be at 3.6% in children below 12 years (9). A study in Zambia reported that AL caused a drastic drop in malaria parasite in participants with partial immunity compared to non-immune participants. The Late failure rate of 3.5% was reported in children below 15 years. AL was however found to be still effective against uncomplicated malaria in Zambia (5).

Tanzanian study proved that unsupervised administration of AL for uncomplicated malaria, with good adherence, can effectively clear malaria parasite (20). Post treatment prophylaxis was found to be shorter which concurs with other endemic areas study. Non-immune participants were found to be less protected after seven days than immune participants. The cure rate of AL was found to be at 93% proving that it is still effective and should still be considered as the first line against uncomplicated malaria. 0.3% of the cases had early treatment failure, 6.3% of the cases had a late clinical failure with recrudesce of fever before day 28 and 5.3% of the cases having the mutation. All cases that had parasite at day 3 had wild type *pfk13* but was not associated with resistance against AL(11).

In Kenya, there is a study done in the coastal region which showed reduced parasite clearance in participants who used AL (40). A study in Kenyan children claimed that AL and Pyronaridine artesunate had the same effectiveness (34). There is two-year monitoring of AL in Kenya that so far proves that AL is efficacious against uncomplicated malaria and still qualify as a first line (1). Overall, AL is still efficacious against all types of malaria parasite found in Africa and still qualifies as the first line against uncomplicated malaria. Late treatment failure, although less common, should be looked in further to try to make sense of it. Some

studies have attempted to tie late treatment failure to endemic areas and non-immune participants but this needs more investigation.

Molecular markers are important in monitoring antimalarial resistance. Mutation in *P.falciparum* multidrug resistance protein 1 (*Pfmdr1*) has been linked to resistance to mefloquine and artemisinin derivatives including artemether and also halofantrine and lumefantrine in vitro (8,9,11).

Participants with HIV whether on Antiretroviral drugs or not that get infected with uncomplicated malaria are generally managed with AL. Generally, AL is efficacious against uncomplicated malaria in participants on NNRT. There is, however, a possibility that NNRT, being cytochrome enzyme inducers and inhibitors, to interact with AL pharmacokinetics. Participants on efavirenz, nevirapine and ARV naive who had uncomplicated malaria were found to have varying level of lumefantrine in blood. Efavirenz group had low Lumefantrine level in blood compared to ARV naive participants which increased chances of treatment failure in participants on efavirenz. This was associated with CYP 3A4 enzyme induction properties of efavirenz which possibly sped up the metabolism of Lumefantrine. This was observed in participants who received half a dose of lumefantrine. The half-life of lumefantrine was also found to be reduced with lower C_{max} and AUC $_{0\text{-}14day}$. At a full dose of Lumefantrine, there was no difference between the efavirenz group and those not ARVS (19,37).

Nevirapine and lopinavir boosted ritonavir group showed increased lumefantrine levels both at the half and the full dose of lumefantrine. The possible explanation is that nevirapine and lopinavir inhibit CYP 450 enzyme causing an increasing level of lumefantrine (19).

A study in these children and pregnant women suggests that the group get underexposed to lumefantrine levels leaving them vulnerable to treatment failure and selective resistance. The children were found to be underexposed because the current dose does not account for the non-linear relation between body weight and systemic exposure. Pregnant women were underexposed because of the change in distribution kinetics during pregnancy. This calls for further studies in these groups so that they can establish if there is a need to evaluate dose in these groups (39).

When AL dose was based on body weight, the cure rate was found to be at 97%. Participants of weight between 5 to less 10 kg were found to have high levels of active pharmaceutical ingredients although no associated toxicities were reported. There were no reported cases of drug levels in plasma being below the therapeutic window (50).

Comparison of AL to other antimalarials proves that AL is equally safe and effective against uncomplicated malaria. A comparison of AL to other antimalarial, AL had a slightly lower cure rate of 92% while

artesunate +sulphurmethoxypyrazine-pyrimethamine (93%) and artesunate + amodiaquine (100%). These differences were not however statistically significant. Therefore, all antimalarials were found to be efficacious against uncomplicated malaria (51). In Zambian children, recurrent infections observed after day 28 were lower participants who had used dihydroartemisinin-piperaquine than in those who used AL. Participants on dihydroartemisinin-piperaquine, however, were fewer than those on AL. Another explanation is that piperaquine has a longer half-life (2 to 3 weeks) compared to lumefantrine (4 to 10 days). Day 42, on the other hand, had similar finds in both groups (52). In Kenyan children and infants, AL PCR corrected cure rate (97.8%) on day 28 was found to be lower than dihydroartemisinin-piperaquine arm (99%). Cure rate on day 14 was found to be equal in both arms (100%). Parasite clearance was found to be 50% in 24 hours and 90% in 40 hours (53).

2.3.4 Possible causes of and risk factors for treatment failure.

Participants with no immunity have been found to have a high parasitic burden (4). These same participants have also been found to have a poor response to AL. Lack of immunity has thus been associated with treatment failure of AL (11,26,32). Reduced CD4 cell count has been associated with increased malaria parasite level which in turn contributes to AL treatment failure (19).

Food has also been associated with treatment failure. Participants who took AL on an empty stomach or after consuming food low in fat were found to have a poor response (30). This can be associated with the pharmacokinetics of lumefantrine which is lipophilic (47).

In Cambodia, treatment failure was observed after using artemisinin alone. The cause of reduced effectiveness here can be attributed to monotherapy which is also observed in other infections such as Human Immunodeficiency Virus and tuberculosis (30).

2.3.5 Safety of Artemether and Lumefantrine

Adverse events were reported to be due to AL are similar to the signs and symptoms of malaria (1,16,54) hence they are confounders. A clinical trial by Novartis has shown anaemia and thrombocytopenia to be common severe adverse events. The parameters, however, normalized after the participant finished the dose. When compared to others, AL had varied outcomes. Children on AL had a lower risk of developing anorexia and weakness compared to those on Artesunate-amodiaquine. Those on AL, however, had a high risk of developing fever. This was probably due to the antipyretic effect of amodiaquine. Urticaria was the most common adverse event that was linked to the drug (54). AL is regarded as safe for everyone above 5kg and pregnant women from 2nd trimester (16,39,55). However, after the thalidomide disaster, the safety of any drug even those regarded as well tolerated are monitored through pharmacovigilance. There have been reported cases of nausea and vomiting that has warranted AL to be discontinued (38). Anaemia, which

a severe adverse effect is also being reported although the prevalence is not high enough to cause concerns (36,43). Liver and kidney enzymes have been reported to be elevated without the participant having any signs. There was a slight elevation of AST, ALT, bilirubin, BUN, and creatinine which normalised after the drug was stopped (36,43). It is not clear which drug between the two is responsible for elevation but lumefantrine seems to be the likely cause. Other adverse events reported in this group were nausea, vomiting, headache and dizziness (2). A study done in Tanzania reported one death after one dose of AL although it was not proven if AL caused it. The cough was the most reported adverse events in this group (49.4%). majority of the cough was experienced in children. Other adverse events reported from Tanzanians include fever (20.2), abdominal pain (10.1%), diarrhoea (1.3%), headache (1.3%), skin rash (1.3%). Children under five years, in this group, were more susceptible to adverse events than adults (20).

Safety of AL in children below 17 years has already been established (2). The most common adverse events in this group are cough and or coryza. Other adverse events reported include nausea, vomiting, diarrhoea, abdominal pain and anaemia. One participant developed severe anaemia that was not linked to AL. AL compared to amodiaquine causes general body malaise (9). Children with HIV who used AL showed the same safety profile as those without HIV when they used AL. The adverse events reported included cough, diarrhoea, vomiting and anaemia (12). Participants on nevirapine antiretroviral regimen, using lumefantrine have been found to have neutropenia. The cause of neutropenia has not been well established but associated with increased lumefantrine level in the group, increased nevirapine level in the group on the synergistic effect of both high lumefantrine and nevirapine levels. Thrombocytopenia was reported in participants receiving nevirapine and was given lumefantrine at the half-normal dose. This was not experienced in the same participants at a full dose of lumefantrine hence thrombocytopenia was seen by chance (19).

One participant was found to have hemolytic anaemia on day 10 after using AL. The participant had a history of severe malaria that was managed with quinine and doxycycline and later discharged on AL. the participant was non-immune to malaria (43).

A study on the safety of AL in infants and children when the dose was based on weight reported adverse events similar to signs and symptoms of malaria. Pyrexia was reported in 36.96% of the participants. Other adverse events include cough and vomiting. Headache was experienced more with an increase in body weight. 2.2 % of the participants had to discontinue treatment because of adverse events. One developed severe malaria on day 31 and died while the other died because of dehydration secondary to uncontrolled vomiting (50).

In Central Africa, vomiting, diarrhoea, abdominal pain and anorexia were reported after AL use (51). Nigerian children tolerated AL well. Anaemia was the laboratory most reported adverse event while cough

was the most volunteered adverse event. Other most recorded adverse events include diarrhoea, vomiting, a transient rash that cleared after the dose was done, clonus and insomnia. Hypothermia, hyperreflexia and distended abdomen were reported. PR and QT intervals were slightly elevated but participants had no symptoms (56).

In Ugandan children, AL was found to be better tolerated than amodiaquine+sulphadoxine-pyrimethamine (participants complained of weakness and anorexia). AL arm, however, had a high risk of developing fever and diarrhoea (57). Zambian children tolerated both AL and dihydroartemisinin-piperaquine well. The most severe adverse events experienced were anaemia on day 3 and jaundice. Cough due to respiratory infection was observed more in the dihdroartemisinin-piperaquine arm (52). In Liberia, participants experienced mild to moderate adverse events that did not warrant drug to be stopped. Fatigue was the most reported adverse event (16.3%). Other adverse events experienced include abdominal pain, anorexia and vomiting. Laboratory recorded adverse events included eosinophilia which was linked to parasitic infection, neutropenia, anaemia and asymptomatic elevation of AST and ALT (58). In Kenyan children below 5 years, the cough was the most experienced adverse event (15.5%). One participant had severe anaemia which was linked to malaria. Adherence to AL was better than dihdroartemisinin-piperaquine because it was considered easy to give and better in taste (53).

2.3.6 Literature Gap

Artemether and Lumefantrine were proved to be effective against uncomplicated malaria and well tolerated during the clinical trial. Further studies continue to prove that both agents are efficacious and well tolerated. There have been cases of the agents causing life threatening adverse events. Effectiveness of both agents was also shown to be reduced especially in endemic areas. For this reason, it is paramount to be vigilant for resistance and tolerability of artemether and lumefantrine. Bungoma County Referral Hospital, despite being a referral hospital in a malaria endemic area, has limited data on safety and tolerability of antimalarials.

CHAPTER 3: METHODOLOGY

3.1 Introduction

This chapter highlights the methodological details of the study. They include study design and site, target and study population, inclusion and exclusion criteria, sample size, and sampling technique. Other components include data collection and analysis as well as ethical considerations.

3.2 Study design

The study was a longitudinal prospective study that involved following up with participants to identify adverse events that the participants might experience. We also identified risk factors for treatment failure and adverse events. Such data does not exist hence the reason for doing the longitudinal study. The prospective study design was used because adverse events are rarely reported or documented in the participant file. The study involved following up of participants with malaria for 28 days. The 28-day period was chosen because Lumefantrine is protective against malaria for this duration. The study was conducted between November 2020 and January 2021.

3.3 Study area

The study area was Bungoma County Referral Hospital which is located in the heart of Bungoma town and it is the referral hospital in Bungoma county. It is located on Bungoma Malaba highway, Kanduyi constituency, Bungoma South district, and Kanduyi location. It is located in the heart of the malaria-endemic area with malaria being reported to be high throughout the year. The hospital has a bed capacity of 250. Malaria prevalence in the Hospital was reported to be 21.6% in 2017(55). There is, however, inadequate data on safety and effectiveness of AL in the hospital.

3.4 Inclusion and exclusion criteria

The study excluded participants presenting with severe malaria or cerebral malaria for the first time because they were not managed with AL. Participants who were on or required the second line for the first time after malaria diagnosis for other reasons other than the first reason. Those who did not consent or their guardian did not consent to be in the study or chose to withdraw before the initiation of the first treatment. Those who could not speak, understand or converse in either English, Kiswahili, or Luhya to avoid miscommunication that may arise due to the language barrier. Participants without a working phone and no relative with a phone in the immediate proximity because follow-up will be done over the phone.

3.6 Sample

3.6.1 Sample size determination

The prevalence of malaria in Bungoma county Referral hospital was found to be 21.6% (18). The Cochran sample formula was used to estimate the sample size at a 95% confidence interval, the z value of 1.96 at 5% significance level. The formula was;

$$n_0 = \frac{Z^2pq}{e^2}$$

$n_0 = \frac{1.96^2 \times 0.216 \times (1-0.216)}{0.05^2} = 260.22$

Where; e is the desired level of precision (i.e. the margin of error) for categorical value set at 0.05,

p is the expected prevalence of malaria in Bungoma county

q is $1 - p$.

z is z-score which is set at 1.96 for an α value of 0.05

n_0 is the sample size

3.6.2 Sampling technique

Simple random sampling was used to select the participants. This was accomplished by tossing a coin. The potential participants were approached and after explaining the purpose of the study, a coin was tossed and whoever coincided with the head was selected. The activity was repeated until the desired sample size was achieved.

3.7 Research Instruments

The research tools used include consent forms for both adults and minors as shown in appendix 1 and appendix 2 respectively. Participants were chosen for the study using the eligibility criteria checklist (appendix 3). The data collection form (appendix 4) was used as a guide for extracting data from the participants.

3.8 Pilot Study or Pre-Testing

A pilot study was carried out on participants who were diagnosed with malaria in Kenyatta National Hospital. Recruitment was done when the participant was being discharged from the ward and follow-up was done over the phone. This helped the principal investigator to identify ambiguous and repeated questions and make them clear and remove them respectively. The data collected were analyzed to check if the data collected was enough or more questions needed to be added.

3.9 Validity and reliability of research instruments

The reliability of the research instrument was established by determining the stability and consistency of the instruments. Stability was established by doing test-retest reliability testing in Kenyatta National Hospital. The coefficiency was expected to be above 0.7. Consistency was established using inter-rater reliability testing. The second observer was given the same training and qualifications as the first observer. Consistency was measured using Cronbach's alpha. The alpha values were expected to be above 0.7.

The validity of the instruments was established by determining the internal and external validity. The internal validity was established after the experts (who are the supervisors) reviewed the instruments and approved them after necessary corrections if any. The external validity was, on the other hand, established by randomly selecting participants with malaria.

3.10 Data collection process

Before commencing data collection, approval was sought from the University of Nairobi- Kenyatta National Hospital Ethics and Research committee and management of Bungoma County and Referral Hospital (P172/03/2020) included as *appendix 10*. Only those who had consented directly or through proxy were included. Data collection was done using a questionnaire and data abstraction form. Prospective participants were approached in the hospital and taken through the consenting process in a face to face interview. Eligible participants were picked according to the eligibility criteria checklist (appendix 3). They were then requested to sign the document (appendix 1).

Data on sociodemographic characteristics were collected during the interview while those on drugs and diseases abstracted from the records. The collection was done by a trained and qualified pharmacist who is also a principal investigator using the data collection form (appendix 4). The data collection was carried out for eight weeks.

The first dose was administered on-site by the pharmacist and instructions on how to take or administer the remaining drugs were given by the pharmacist in the hospital. If the participant was unable to take the

first dose on-site, they were taught how to send a flashback massage or how to make a reverse call to the pharmacist when they are comfortable taking the first dose. The participant was reminded every day over the phone on how and when to take their medicine by the pharmacist until the dose was done. Those in the in-participant department were supervised for the whole 6 doses by the pharmacist at the interval recommended by the Kenyan Malaria Treatment guideline. Vomiting within the first 30 minutes warranted re-administration of the dose. In the event any participant did not improve after 3 days or deteriorate, they were asked to report back immediately and be put on the second line after laboratory confirmation of persistent malaria. If no major events were observed, then participants were followed up every week afterward for four weeks. Those lost to follow-up were treated with intent to treat

3.11 Data management

Data were managed using Open clinica® software. The software was set for real-time data entry by multiple users. The system was password protected and set to automatically backup the data every 12 hours. Unique participant codes were used instead of the participant's name. Any participant information and data were stored under lock and key and the principal investigator was in charge of the key. The principal investigator double-checked the data obtained during data entry.

3.12 Data analysis plan

We assumed that self-administered AL treatment will result in less than 85% PCR uncorrected parasitological cure rate by day 28 and will be well tolerated. According to the WHO protocol (1), with an estimated treatment failure lower than 15%, confidence interval of 95%, a precision of 10% and a 20% drop out rate, the minimum sample size needed was at least 260 participants

Data was double-entered and validated using EpiData software and analysed using STATA version 16 software at 95% confidence level. Proportions were compared with the X2 test or Fisher's exact test as appropriate. Summary statistics are presented for quantitative variables, and counts and percentages were calculated for categorical data. The proportion of cured participants was based on all participants with available effectiveness information. Effectiveness data were further stratified by age (≤16 years, 17–64 years, ≥65 years), likely malaria immune status, and malaria species (P. falciparum, other, undetermined). (appendix 9).

3.13 Ethical consideration

The study was approved by the Kenyatta National Hospital- University of Nairobi Ethics Committee. Further approval was obtained from Bungoma County Referral Hospital. Oral and written informed consent was obtained from all study participants in either English, Kiswahili, or Bukusu. Participants and guardians had the study objectives and procedures explained to them before signing written consent forms. Study

participants were given the option to withdraw from the study at any time they wished. Data obtained were coded and kept strictly confidential. The results will be shared with the individuals who wished to know after publication. Any participant who develop severe malaria or severe adverse events were asked to report back to the hospital immediately and they were managed according to the Kenyan guideline appropriately.

3.14 Study dissemination plan.

Data from this study will be shared with various bodies. It will be shared with the Pharmacy and Poisons Body so that they can update their pharmacovigilance data on AL. Bungoma county referral hospital will be given results so that they can update their pharmacovigilance data on AL and they can know its status on safety and effectiveness against malaria. The data will be presented in a conference so that the healthcare practitioners can benefit from my research. The study findings have been disseminated at the International Society of Pharmacoepidemiology Africa conference which was held on 28th to 30th June this year. Finally, I will publish the finds in a journal so that the data can reach local and international audience.

3.15 Quality assurance

The principal investigator, who is a qualified pharmacist, was the one responsible for recruitment, follow-up, and supervision of the project. Malaria diagnosis, parasite density, and species were confirmed by a qualified laboratory technician using a light microscope. The participant retained the right to withdraw at any time. Those who deteriorate or experience severe adverse events were switched to an appropriate drug.

CHAPTER 4: RESULTS

4.1 Social demographic

A total of 260 participants with a diagnosis of malaria based on microscopy were enrolled in the study (Table 1). Females were slightly more than males. The age range was 1 month to 61 years and median of (3years). The largest group comprised of those below 16 years old. Most participants had attained primary or secondary education level. The majority (159, 61.2%) of the participants came from a household with a reliable source of income, and 218(83.8%) had malaria infection in the past five years. 186 (71.5%) participants used treated mosquito nets to prevent mosquito bites.

Table 1: Social demographic characteristics (n=260)

Biodata	**Category**	**Frequency**	**Percentage (%)**
Gender	Male	121	46.5
	Female	139	53.5
Age (months)	≤60	186	71.5
	61-200	42	16.2
	>201	35	13.5
Marital status	Too young	237	91.2
	Single	4	1.5
	Married	17	6.5
	Does not want to disclose	1	0.4
	Divorced/Separated	1	0.4
Education	Informal/none	21	8.1
	Primary	99	38.1
	Secondary	97	37.3
	Tertiary	43	16.5
Malaria prevention	Yes	186	71.5
	No	74	28.5

History of malaria	Yes	218	83.8
In past 5 years	No	42	16.2
Medication used	AL	232	89.2
	Others	18	6.9
	Not sure	10	3.8
Reliable income	Yes	159	61.2
	No	101	38.8

4.2 Past Medical History

The majority of the participants (227, 87.7%) did not have an underlying chronic condition (87.3%) or were not using more than five types of medicines. The main co-morbidity was sickle cell anaemia (19,7.3%) while others were grouped together (5.4%) and the others were hypertension, diabetes, gout arthritis, and asthma.

4.3 Prevalence of adverse events of AL

Of the 260 participants, only (60, (23%)) reported adverse reactions. The most common included abdominal discomfort (26, (43.3%)), cough (26, (43.3%)) and headache (19, (31.7%)) as shown in **Table 2** below. All of the symptoms were reported during the first week of taking AL and they recovered with the first week.

Table 2: Adverse events after taking AL

Symptoms after taking AL	**Frequency**	**Percentage (%)**
Palpitation	10	16.7
Constipation	1	1.7
abdominal discomfort	26	43.3
cough	26	43.3
blisters on legs	5	8.3

diarrhoea	15	25
disturbed sleep	6	10
swollen abdomen	5	8.3
headache	19	31.7

4.4 Risk for treatment failure

Almost all participants (259,99.6%) used the medication provided but 36 (13.8%) vomited (**Table 3**). Majority (253,97.3%) of them ingested medicines after a fatty meal (97.3%).

Table 3: Risk for treatment failure

Risk of treatment failure	Response	Frequency	Percentage (%)
Medication taken	Yes	259	99.6
	No	1	0.4
Had to be reminded to take medication	Yes	24	9.2
	No	235	90.4
Medicines vomited	Yes	36	13.8
	No	224	86.2
Medicines taken after fatty meal	Yes	253	97.3
	No	7	2.7
Palatability	Okay	24	9.2
	Indifferent	1	0.4
	Bitter	235	90.4

4.5 Risk factors for adverse drug reaction

Only two participants reported having a history of developing an adverse drug to AL. Seven (2.7%) participants reported being using alcohol or cigarette smoking. Every participant was taking another drug other than AL (**image 1**). The majority of the drugs were to relieve the signs and symptoms of malaria. The most commonly used drug was paracetamol.

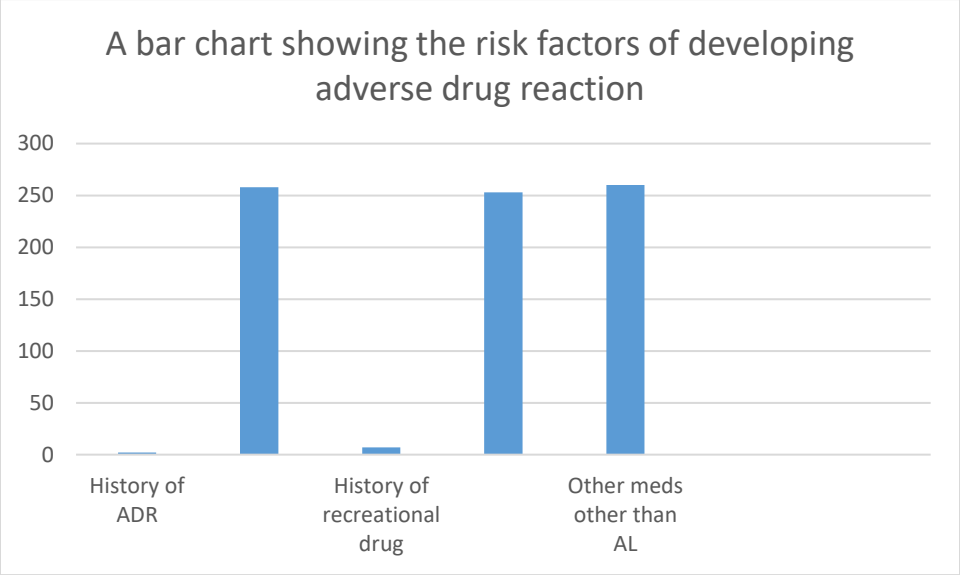

Figure 1: Risk for developing adverse reaction

4.6 Cure chart

All the participants recovered within the first week after taking AL. There were no signs or symptoms of malaria during the 28 days of the study period following treatment.

4.7 Association between biodata and risk of developing adverse drug reaction

The table below (Table 4) shows an association between biodata and adverse drug reaction at 95% confidence interval. There was no significant association between the biodata and adverse drug reaction.

Table 4: Association between biodata and risk of getting adverse events

Biodata			
	Category	**History of ADR (%)**	**P value**

Gender	Male	46.5	
	Female	53.5	0.06
	Single	1.5	
	Married	6.5	0.316
	Does not want to disclose	0.4	
	Divorced/Separated	0.4	
Education	Informal/none	8.1	
	Primary	38.1	0.435
	Secondary	37.3	
	Tertiary	16.5	
Reliable income	Yes	61.2	0.645
	No	38.8	

Table 5: history of adverse events, using more than 5 drugs and adverse events.

	Yes	**No**	**P value**
History of ADR	2(0.8%)	258(99.2)	0.994
Recreational drugs	7(2.7%)	253(97.3)	0.994
More than five medication	228(12.3%)	32(87.7%)	0.404
Recreational drugs	4		0.801

CHAPTER FIVE: DISCUSSION, CONCLUSION, AND RECOMMENDATIONS

5.1 Discussion

The study aimed to determine if AL is still effective in treating uncomplicated malaria, reinfection for 28 days after the initial dose and to identify some of the adverse events experienced by the participants after they use AL. This is following a study that was conducted in the Kenyan coastal region which found a decline in plasmodium responsiveness to the artemisinin-based regimen(40). There have been reported cases of resistance or reduced effectiveness of artemisinin-based drugs that have led WHO to recommend studies to be done every 2 years on the effectiveness of the drugs(59).

All participants recovered within the first seven days of treatment. This has a positive comparison with the study that was done in the USA(14) and it is in line with WHO guideline recommendation for effectiveness and it is in line with WHO guideline recommendation for effectiveness (59). There was no reported reinfection within 28 days for all participants which also relates positively with the study on the efficacy of Artemether-Lumefantrine in Tanzania(20,33). The recovery and prophylaxis seen in all participants confirm that AL is still effective against uncomplicated malaria. The advice to take the dose after a fatty meal might have contributed to the observation (59) although background immunity might have contributed too (13). One cautionary note, all participants had some residual symptoms on day 3 after completing the dose which can either be due to adverse events (2) or signs and symptoms of uncleared parasitemia (9). Prevention of malaria, although it has been proven effective, did not have any significant difference in malaria recurrence. This can be attributed to the prophylaxis of Lumefantrine that protects participants up to 28 days(3) .

Generally, AL was well tolerated with mild adverse events. Some participants however reported uncharacteristic adverse events; swollen abdomen, blisters on the legs, and yellow/blood in the urine. The symptoms resolved on their own after a few days. Other participants experienced mild pallor that resolved after a week. This was not clear if it was a normal course of malaria disease(16) or a new adverse event of AL. There was no significant difference between participants with co-morbidity or those taking more than five different drugs and the number of adverse events experienced despite evidence that more than five drugs increase the risk of adverse events. The level of education, reliable source of income, and the number of siblings did not have any significant influence on the rate of reporting adverse events. This can be because antimalarials and mosquito nets are given for free.

Among participants below 5 years old, the most reported symptoms were cough and abdominal pain which is consistent with a study done in Nigerian and Kenyan children. This can be due to the condition or other conditions (53,56). This can be corroborated by a study done in children in western Kenya where

anaemia was detected during a routine check and not reported by the guardian (60). The most common reported symptom in participants above 16 years was headache which could have been due to disease or drug (16).

5.2 Conclusion

AL is still effective in treating uncomplicated malaria, prevents reinfection for 28 days after the initial dose and it is relatively well tolerated. The Lumefantrine prophylaxis used concurrently with the mosquito net seems to help prevent malaria. The most reported symptom in children below five years was cough and abdominal pain. The adults on the other hand essentially recorded headaches.

5.3 Study recommendation

5.3.1 5.3.1 Recommendations for policy and practice

AL should be recommended as a first-line in treating uncomplicated malaria. Its safety should be looked into further because some of the adverse events were moderately severe.

5.3.2 Further research

Pharmacovigilance needs to be the key activity in malaria management. AL is well tolerated but there were however some adverse events that required further investigations and follow-up. Some of them include blisters on the body and swollen abdomen.

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Appendix 1 informed consent

KNH-UON Research Ethics Review Committee

(English)

Name of Principal Investigator: Wakoli Phidelis Lutomia

Name of Organization: University of Nairobi

Name of Proposal: Effectiveness and safety of artemether lumefantrine in participants with malaria in Bungoma County Referral Hospital.

This Informed Consent Form has two parts:

- **Information Sheet (to share information about the research with you)**
- **Certificate of Consent (for signatures if you agree to take part)**

You will be given a copy of the full Informed Consent Form

PART I: Information Sheet

Introduction

I am Dr Wakoli Phidelis, a master's student in Clinical Pharmacy from the University of Nairobi. We are doing research on malaria, which is very common in this country. I am going to give you information and invite you to be part of this research. Before you decide, you can talk to anyone you feel comfortable with about the research.

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 them of me, the study doctor or the staff.

Participant selection

We are inviting all participants with malaria who seek medical care from Bungoma County Referral Hospital to participate in the research on effectiveness and safety of Artemether Lumefantrine.

Purpose of the research

Malaria is one of the most common and dangerous diseases in this region. Artemether Lumefantrine is currently being used to treat uncomplicated malaria. We are going to taste if it is safe and still able to kill malaria parasite.

Type of Research Intervention

This research involves swallowing of the four tablets after a meal then you will be followed up over the phone.

Voluntary Participation

Your participation in this research is entirely voluntary. It is your choice whether to participate or not. Whether you choose to participate or not, all the services you receive at this hospital will continue and nothing will change. If you choose not to participate in this research project, you will be offered the treatment that is routinely offered in this hospital for malaria, and we will tell you more about it later. You may change your mind later and stop participating even if you agreed earlier.

Procedures and Protocol

You will receive the treatment of your condition according to national guidelines. This means that you will be required to swallow tablets according to your weight. A pharmacist will then be calling you to ask you some questions for 28 days.

Duration

The research takes place over 28 days in total. During that time, it will be necessary for you to answer our call every 12 hours a day for the first three days then every week, for one hour each day. You will not incur any charges.

In total, you will be asked to answer our call 10 times 28 days. At the end of 28 days, the research will be finished.

Confidentiality

The information that we collect from this research project will be kept confidential. Information about you that will be collected during the research will be put away and no-one but the researchers will be able to see it. Any information about you will have a number on it instead of your name. Only the researchers will know what your number is and we will lock that information up with a lock and key.

Sharing the Results

The knowledge that we get from doing this research will be shared with you through the phone or email before it is made widely available to the public. Confidential information will not be shared. We will publish the results so that other interested people may learn from our research.

Right to Refuse or Withdraw

You do not have to take part in this research if you do not wish to do so and refusing to participate will not affect your treatment at this hospital in any way. You will still have all the benefits that you would otherwise have at this clinic. You may stop participating in the research at any time that you wish without losing any of your rights as a participant here. Your treatment at this hospital will not be affected in any way.

Whom to Contact

If you have any questions you may ask them now or later, even after the study has started. If you wish to ask questions later, you may contact any of the following:

Name: Dr Wakoli Phidelis

Mobile number: +254700479805

e-mail: lutomiawakoli@yahoo.com

or

KNH-UON ERC

EMAIL: uonknh_erc@uonbi.ac.ke

Part II

I voluntarily agree to participate in this research study: **Yes** **No**

I agree to provide contact information for follow-up: **Yes** **No**

signature /Thumb stamp: _____ **Date** _____

Printed name: _____

Researcher's statement; I, the undersigned, have fully explained the relevant details of this research study to the participant named above and believe that the participant has understood and has knowingly given his/her consent.

Printed Name: _____ **Date**: _____

Signature: _____

Appendix 2 Adult informed consent

(Swahili)

Jina la mtafiti mkuu: Dr Wakoli Phidelis Lutomia

Majina ya manaibu watafiti: Dr Sylvia Opanga Dr Peter Karimi

Utaratibu wa kukubali

Habari, Jina langu ni Dr Phidelis Wakoli. Ninasomea shahada ya pili katika chuo kikuu cha Nairobi. Nataka kudhibitisha kuwa dawa ya AL inaua Malaria na madhara yake kwa binadamu anayeugua malaria.

Maelzo haya ndiyo fomu yako ya kukubali kushiriki na yana maelezo kuhusu utafiti. Tafandhali yasome kwa makini na uombe kufafanuliwa hasa maneno, msamiati au taratibu ambazo huelewi. Ukielewa na kukubali kushiriki katika utafiti huu, nakuomba uandike jina lako na sahii kwenye fomu hii. Unafaa kuelewa yafuatayo yatakayotumika na kuzingatiwa na kila mshiriki katika utafiti huu wa kimatibabu;

1. Kukubali kwako kushiriki ni kwa hiari au kujitolea.
2. Unaweza kujiondoa wakati wowote hata bila ya kutoa sababu ya kujiondoa
3. Kukataa kushiriki katika utafiti huu hautaadhiri kwa vyovyote huduma unazostahili kupokea katika kliniki hii.

Sababu ya utafiti

Malaria ni mingioni mwa magonjwa ya kawaida na hatari kwa sehemu hii ya nchi. AL ni dawa inayotumika kwa sasa kutibu malaria ambayo si ngumu kutibu. Tunaenda kudhibitisha kama ni salama na bado inaweza kuua malaria.

Aina ya matibabu

Uchunguzi huu utahitaji umeze tembe nne baada ya chakula halafu utafwatiliwa kwa njia ya simu.

Muda

Utafiti huu utachukua siku 28. Utahitajika kuchua simu zetu katika huu muda kila masaa 12 kwa siku tatu za kwanza mtawalia kisha kila wiki kwa masaa moja. Hautatumia pesa zozote. Kwa jumla, utajibu simu10

Dhihirisho la usiri

Uangalifu wa dhati utachukuliwa kuhakikisha kushiriki kwako katika utafiti huu umepewa usiri. Habari zote zitakazotolewa kwenye faili yako zitahifadhiwa vyema na kutumika kwa madhumuni ya utafiti pekee. Jina lako halitatumika katika kushughulikia data ama uchapishaji wowote bali nambari za siri zitatumika. Rekodi zako za matibabu zitafungiwa na ripoti itatumiwa tu na mtafiti aliyekusanya data na wakaguzi wa utafiti huu.

Mawasiliano

Kwa maelezo Zaidi kuhusu utafiti huu, unaweza kuwasiliana nami ama Hospitali kuu ya Bungoma au K amati ya utafiti na Maadili ya Chuo Kikuu cha Nairobi kupitia

Wakoli Lutomia Wakoli

Kitengo cha famasia

Chuo kikuu cha Nairobi

SLP 19676, Nairobi

Simu- 0700479805

Dkt Sylvia Opanga-mkaguzi

Idara ya utendakazi wa famasia,

Chuo kikuu cha Nairobi

Simu-0721296448

Dkt Peter Karimi

Idara ya utendakazi wa famasia

Chuo Kikuu cha Nairobi

Simu-0722436019

Thibitisho la kushiriki

Mgonjwa

Nimeelea ujumbe ulio katika fomu hii. Nimepata nafasi ya kujadiliana na mtafiti na maswali yangu yameshugulukiwa. Nimeelezwa hatari zilizoko na faida. Naelewa kuwa kushiriki kwangu katika utafiti huu ni kwa hiari na ninaweza kujiondoa wakati wowote. Nimekubali kushiriki kwa hiari katika utafiti huu. Kwa kutia sahihi katika fomu hii, sijapeana haki yoyote ya kisheria niliyo nayo kama mshirika katika utafiti huu.

Sahihi ya mshirika……. Tarehe……..

Nakubali kuwa nieeleza hali na athari za utafiti kwa mshiriki aliyetajwa hapo juu na nimaamini kua mshirika ameelewa na kwa hiari ametoa udhuru wake.

Jina……. Tarehe……

Sahihi……. Tarehe……

Kwa maelezo Zaidi kuhusu utafiti huu, unaeza kuasiliana name ama Hospitali Kuu ya Bungoma ama Kamati ya Utafiti na Maadili ya Chuo kikuu cha Nairobi kupitia

Wakoli Phidelis Lutomia- 0700479805

Dr Sylvia Opanga- 0721296448

KNH/UON 2726300 EXT 44102

Appendix 3

STUDIES INVOLVING CHILDREN

PARTICIPANT INFORMATION AND CONSENT FORM

PARENTAL CONSENT

Title of study: Effectiveness and safety of artemether lumefantrine in participants with malaria in Bungoma County Referral Hospital

Principal Investigator and institutional affiliation: Wakoli Phidelis Lutomia

Co-Investigators and institutional affiliation: Dr Sylvia Opanga, Senior lecturer University of Nairobi. **Dr Peter Karimi Senior lecture, University of Nairobi.**

Introduction

I would like to tell you about a study being conducted by the above-listed researchers. The purpose of this consent form is to give you the information you will need to help you decide whether or not your child should participate in the study. Feel free to ask any questions about the purpose of the research, what happens if your child participates in the study, the possible risks and benefits, the rights of your child as a volunteer, and anything else about the research or this form that is not clear. When we have answered all your questions to your satisfaction, you may decide if you want your child to be in the study or not. This process is called 'informed consent'. Once you understand and agree for your child to be in the study, I will request you to sign your name on this form. You should understand the general principles which apply to all participants in medical research:

i) Your child's decision to participate is entirely voluntary

ii) Your child may withdraw from the study at any time without necessarily giving a reason for his/her withdrawal

iii) Refusal to participate in the research will not affect the services your child is entitled to in this health facility or other facilities.

May I continue? **YES** **NO**

For children below 18 years of age, we give information about the study to parents or guardians. We will go over this information with you and you need to permit for your child to participate in this study. We will

give you a copy of this form for your records. A child above 8 years will also need to give verbal assent to participate in the study.

WHAT IS THE PURPOSE OF THE STUDY?

The researcher listed above is interviewing individuals who have been diagnosed with Malaria. The purpose of the interview is to find out if participants will be willing to take artemether-lumefantrine for their malaria. There will be approximately 260 participants in this study. We are asking for your consent to consider your child to participate in this study.

WHAT WILL HAPPEN IF YOU DECIDE YOU WANT YOUR CHILD TO BE IN THIS RESEARCH STUDY?

If you agree for your child to participate in this study, the following things will happen: You will be interviewed by a trained interviewer in a private area where you feel comfortable answering questions. The interview will last approximately 30 minutes. The interview will cover topics such as the age of the participant, diet of a typical participant, any other drug the participant might be on and any other condition the participant has. After the interview has finished, you will be guided on how and when to administer the drug. You will be called on your cell phone periodically for 28 days to answer some questions. You will be informed about the results. We will ask for a telephone number where we can contact you. If you agree to provide your contact information, it will be used only by people working for this study and will never be shared with others.

ARE THERE ANY RISKS, HARMS, DISCOMFORTS ASSOCIATED WITH THIS STUDY?

Medical research has the potential to introduce psychological, social, emotional and physical risks. Effort should always be put in place to minimize the risks. One potential risk of being in the study is the loss of privacy. We will keep everything you tell us as confidential as possible. We will use a code number to identify your child in a password-protected computer database and will keep all of our paper records in a locked file cabinet. However, no system of protecting confidentiality can be secure so it is still possible that someone could find out your child was in this study and could find out information about your child. Also, answering questions in the interview may be uncomfortable for you. If there are any questions you do not want to answer, you can skip them. You have the right to refuse the interview or any questions asked during the interview. Furthermore, all study staff and interviewers are professionals with special training in these examinations/interviews.

In case of an injury, illness or complications related to this study, contact the study staff right away at the number provided at the end of this document. The study staff will treat your child for minor conditions or refer the child for treatment for conditions that require more extensive care.

ARE THERE ANY BENEFITS BEING IN THIS STUDY?

Your child may benefit by receiving quality information on how and when to use the medicine. Also, the information you provide will help us determine if Artemether Lumefantrine is safe and effective against malaria. This information is a major contribution to science and the healthcare system.

WILL BEING IN THIS STUDY COST YOU ANYTHING?

The study will not require you to spend any money other than the one required by the hospital.

IS THERE REIMBURSEMENT FOR PARTICIPATING IN THIS STUDY?

There will be no money given during the study as it is purely voluntary.

WHAT IF YOU HAVE QUESTIONS IN FUTURE?

If you have further questions or concerns about your child participating in this study, please call or send a text message to the study staff at the number provided at the bottom of this page. For more information about your child's rights as a research participant, you may contact;

the Secretary/Chairperson,

Kenyatta National Hospital-University of Nairobi Ethics and Research Committee,

Telephone No. 2726300 Ext. 44102

email uonknh_erc@uonbi.ac.ke.

The study staff will pay you back for your charges to these numbers if the call is for study-related communication.

WHAT ARE YOUR OTHER CHOICES?

Your decision to have your child participate in this research is voluntary. You are free to decline or withdraw participation of your child in the study at any time without injustice or loss of benefits. Just inform the study staff and the participation of your child in the study will be stopped. You do not have to give reasons for withdrawing your child if you do not wish to do so. Withdrawal of your child from the study will not affect the services your child is otherwise entitled to in this health facility or other health facilities.

For more information, contact **Wakoli Phidelis** at any time.

CONSENT FORM (STATEMENT OF CONSENT)

The person being considered for this study is unable to consent for him/herself because he or she is a minor (a person less than 18 years of age). You are being asked to give your permission to include your child in this study.

Parent/guardian statement

I have read this consent form or had the information read to me. I have had the chance to discuss this research study with the principal investigator. I have had my questions answered by him or her in a language that I understand. The risks and benefits have been explained to me. I understand that I will be given a copy of this consent form after signing it. I understand that my participation and that of my child in this study is voluntary and that I may choose to withdraw it any time. I understand that all efforts will be made to keep information regarding me and my child's personal identity confidential. By signing this consent form, I have not given up my child's legal rights as a participant in this research study. I voluntarily agree to my child's participation in this research study: **Yes** **No**

I agree to provide contact information for follow-up: **Yes** **No**

Parent/Guardian signature /Thumb stamp: _____Date _____

Parent/Guardian printed name: _____

Researcher's statement

I, the undersigned, have fully explained the relevant details of this research study to the participant named above and believe that the participant has understood and has knowingly given his/her consent.

Printed Name: _____ Date: _____

Signature: _____

Appendix 4 parent informed consent

(Swahili)

STUDY INVOVING CHILDREN

Jina la mtafiti mkuu: Dr Wakoli Phidelis Lutomia

Majina ya manaibu watafiti: Dr Sylvia Opanga **Dr Peter Karimi**

Chuo Kikuu cha Nairobi **Chuo Kikuu cha Nairobi**

Mhadhiri **Mhadhiri**

Utaratibu wa kukubali

Habari, Jina langu ni Dr Phidelis Wakoli. Ninasomea shahada ya pili katika chuo kikuu cha Nairobi. Nataka kudhibitisha kuwa dawa ya AL inaua Malaria na madhara yake kwa binadamu anayeugua malaria.

Maelzo haya ndiyo fomu yako ya kukubai mwana wako kushiriki katika uthabiti na yana maelezo kuhusu utafiti. Tafandhali yasome kwa makini na uombe kufafanuliwa hasa maneno, msamiati au taratibu ambazo huelewi. Ukielewa na kukubali kushirikisha mtoto wako katika utafiti huu, nakuomba uandike jina lako na sahii kwenye fomu hii. Unafaa kuelewa yafuatayo yatakayotumika na kuzingatiwa na kila mshiriki katika utafiti huu wa kimatibabu;

1. Kukubali kwako kushiriki ni kwa hiari au kujitolea.
2. Unaweza muondoa mwana wako wakati wowote hata bila ya kutoa sababu ya kumuondoa
3. Kukataa kushiriki katika utafiti huu hautaadhiri kwa vyovyote huduma mnazostahili kupokea katika kliniki hii.

Sababu ya utafiti

Malaria ni mingioni mwa magonjwa ya kawaida na hatari kwa sehemu hii ya nchi. AL ni dawa inayotumika kwa sasa kutibu malaria ambayo si ngumu kutibu. Tunaenda kudhibitisha kama ni salama nab ado inaweza kuua malaria.

Aina ya matibabu

Uchunguzi huu utahitaji umeze tembe nne baada ya chakula halafu utafwatiliwa kwa njia ya simu.

Muda

Utafiti huu utachukua siku 28. Utahitajika kuchua simu zetu katika huumuda kila masaa 12 kwa siku tatu za kwanza mtawalia kisha kila wiki kwa masaa moja. Hautatumia pesa zozote. Kwa jumla, utajibu simu10

Dhihirisho la usiri

Uangalifu wa dhati utachukuliwa kuhakikisha kushiriki kwa mwanao katika utafiti huu kumepewa usiri. Habari zote zitakazotolewa kwenye faili yake zitahifadhiwa vyema na kutumika kwa madhumuni ya utafiti pekee. Jina lake halitatumika katika kushughulikia data ama uchapishaji wowote bali nambari ya siri itatumika. Rekodi zake za matibabu zitafungiwa na ripoti itatumiwa tu na mtafiti aliyekusanya data na wakaguzi wa utafiti huu.

Mawasiliano

Kwa maelezo Zaidi kuhusu utafiti huu, unaweza kuwasiliana nami ama Hospitali kuu ya Bungoma au Kamati ya utafiti na Maadili ya Chuo Kikuu cha Nairobi kupitia

Wakoli Lutomia Wakoli

Kitengo cha famasia

Chuo kikuu cha Nairobi

SLP 19676, Nairobi

Simu- 0700479805

Dkt Sylvia Opanga-mkaguzi

Idara ya utendakazi wa famasia,

Chuo kikuu cha Nairobi

Simu-0721296448

Dkt Peter Karimi

Idara ya utendakazi wa famasia

Chuo Kikuu cha Nairobi

Simu-0722436019

Utaratibu wa kukbali

Mtu anayeshiriki kenye utafiti huu hana uwezo wa kukubali kushiliki kwenye utafiti huu mwenyewe kwa sababu ni mtoto aliye na miaka chini ya 18. Tunakusihi wewe kama mzazi/ mlinzi wa mwana huyu utupe ruhusaya kumhusisha mwana kwenye utafiti huu.

Thibitisho la kushiriki

Mgonjwa

Nimeelea ujumbe ulio katika fomu hii. Nimepata nafasi ya kujadiliana na mtafiti na maswali yangu yameshugulukiwa. Nimeelezwa hatari zilizoko na faida. Naelewa kuwa kushiriki kwa mwanangu katika utafiti huu ni kwa hiari na ninaweza kumwondoa wakati wowote. Nimekubali kumshirikisha kwa hiari katika utafiti huu. Kwa kutia sahihi katika fomu hii, sijapeana haki yoyote ya kisheria niliyo nayo kama mlinzi ama mzazi wa mshirika katika utafiti huu.

Sahihi ya mzazi/ mlinzi wa mshirika……. Tarehe……..

Jina la mzazi/mlinzi…… Tarehe…….

Nakubali kuwa nimeeleza hali na athari za utafiti kwa mzazi/mlinzi wa mshiriki aliyetajwa hapo juu na nimaamini kua mzazi/ mlinzi wa mshirika ameelewa na kwa hiari ametoa udhuru wake.

Jina……. Tarehe……

Sahihi……. Tarehe……

Kwa maelezo Zaidi kuhusu utafiti huu, unaeza kuasiliana name ama Hospitali Kuu ya Bungoma ama Kamati ya Utafiti na Maadili ya Chuo kikuu cha Nairobi kupitia

Wakoli Phidelis Lutomia- 0700479805

Dr Sylvia Opanga- 0721296448

KNH/UON 2726300 EXT 44102

Appendix 5

Minor Assent Document

(8 to 17 years)

Project Title: Effectiveness and safety of artemether lumefantrine in participants with malaria in Bungoma County Referral Hospital

Principal Investigator and institutional affiliation: Wakoli Phidelis Lutomia

Investigator(s): Dr Sylvia Opanga, **Dr Peter Karimi**

lecturer, **lecturer,**

University of Nairobi. **University of Nairobi.**

We are doing a research study to determine if AL is causing any problems when used to treat uncomplicated malaria and if it is effective against it.

Permission has been granted to undertake this study by the Kenyatta National Hospital-University of Nairobi Ethics and Research Committee (KNH-UoN ERC Protocol No. _____)

This research study is a way to learn more about people. At least 20 children will be participating in this research study with you.

If you decide that you want to be part of this study, you will be asked to speak to me on the phone every 12 hours and follow instructions I will give you or provide information about how you will be feeling.

There are some things about this study you should know. These are being woken up at night if necessary and taking pills.

Not everyone who takes part in this study will benefit. A benefit means that something good happens to you. We think these benefits might be you recovering from malaria and being protected from malaria for 28 days.

If you do not want to be in this research study, we will give you the medicines and allow you to go home.

When we are finished with this study we will write a report about what was learned. This report will not include your name or that you were in the study.

You do not have to be in this study if you do not want to be. If you decide to stop after we begin, that's okay too. Your parents know about the study too.

If you decide you want to be in this study, please sign your name.

I, _____, want to be in this research study.

_____ _____

(Signature/Thumb stamp) (Date)

Appendix 6

Minor Assent Document

(8 to 17 years)

Jina la mtafiti mkuu: Dr Wakoli Phidelis Lutomia

Majina ya manaibu watafiti: Dr Sylvia Opanga Dr Peter Karimi

Chuo Kikuu cha Nairobi Chuo Kikuu cha Nairobi

Mhadhiri Mhadhiri

Tunafanya utafiti juu ya dawa ya AL inayotumika kutibu ugonjwa wa malaria kugundua kama bado ina uwezo wa kuangamiza malaria na kama inasababisha madhara yeyote kwa mwili ya binadamu. Tumepewa ruhusa na kamati ya utafiti na maadiliya chuo kikuu cha Nairobi. Utafiti huu utatuwezesha kujua mengi juu ya mwili wa binadamu. Watoo 20 na Zaidi wengine watashiriki katika utafiti huu.

Ukikubali kushiriki kwenye utafiti huu tutakuomba tuongee na wewe kwa simu kila baada ys masaa 12 na utafuata masharti nitakayokupa ama unipe habari juu ya hali yako.

Utahitajika kumeza tembe kwenye utafiti huu.

Si kila mwenye anashiriki kwenye hii utafiti anafaidhika. Baadhi ya faida ni kupona malaria na kukingwa malaria kwa muda wa siku 28.

Kama hutaki kushiriki katika utafiti huu utatibiwa tu malaria na kuruhusiwa kwenda nyumbani. Baada ya kumaliza utafiti huu, tutaandika ripoti juu ya matokeo. Ripoti hii haitakua na jina lako. Kama hutaki kuwa kwenye utafiti huu ni sawa. Kama utataka kutoka kwenye utafiti huu baada ya utafiti kuanza pia ni sawa.

Kama ungependa kushiriki kwenye utafiti huu tafadhali tia sahihi aua kidole;

Mimi,……. Ningependa kushiriki kwenye utafiti huu.

Sahihi/kidole…… Tarehe……

\Appendix 7: Eligibility checklist

The principal investigator will fill in the eligibility criteria from participant file.

All recruited participants must meet eligibility criteria based on inclusion/exclusion criteria detailed in the application for approval by the KNH/UON Research and Ethics Committee.

1. **Study information**

Study title		
Principal investigator's Name		Signature
Date of recruitment		

2. **Participant information**

Participant code		
Sex	Male	Female
Allergies		

3. **Inclusion/Exclusion criteria checklist (tick or cross where appropriate)**

Inclusion criteria	**Yes**	**No**
Diagnosed with malaria		
Do they have 5 kg and above?		
Exclusion criteria		
Do they have severe or complicated malaria?		
Do they otherwise require second line or other medication other than AL for treatment of the malaria		
Do they consent or guardian consent to be in the study?		
Do they have access to a working phone at all times?		
Can they speak and understand either English, Kiswahili or Bukusu?		

Appendix 8: Data collection form

Participant code:

Serial number: Date of collection: Version: 1

Name of data collector:

A.Biodata

1. What is your age (years):

2. Gender: 1.Male 2. Female:

3. Marital status: 1.Married: 2. Single: 3. I don't want to disclose:

4. Number of children:

5. (i) Do you have a reliable source of income? 1. Yes: 2.No:

   (ii) If yes, where is it from? 1. Formal Employement: 2.Self-employed
   3. Pension: 5 Other:

6. Level of education: 1.None: 2.Primary: 3.Secondary 4.Tertiary

B. Past medical History

8. (i) Have you been diagnosed with any condition in the past? Yes: No:

(ii) If yes, which one?

(iii) If yes, how long ago? (indicate in days)

C. Medication history

9. Medication (current) How long have you been taking (in days)

1.

2

3

4

5

D. Malaria Symptoms experienced before the drug was taken

10. Have you been having / is your child having the following signs and symptoms?

Sign/symptom	No	Yes	If yes, how long
(i) Fever			
(ii) Chills			
(iii) Profuse Sweating			
(iv) Muscle pain			
(v) Joint pain			
(vi) Abdominal pain			
(vii) Diarrhea			
(viii) Anorexia			
(ix) Nausea			
(x) Vomiting			
(xi) Loss of appetite/refusal to eat			
(xii) Cough			
(xiii) Lethargy			
(xiv) Malaise			
(xv) Headache			
(xvi) dizziness			
(xvii) Others (specify)…….			

E. Symptoms experienced after taking the AL.

FOLLOW UP SCHEDULE

11. Are you/ is your child experiencing the following symptoms?

Symptom	Day 1		Day 2		Day 3		Week 2		Week 3		Week 4	
	Yes	No	Yes	No	Yes	No	Yes (indicate as duration in days)	No	Yes (indicate as duration in days)	No	Yes (indicate as duration in days)	No
i. Headache												
ii. Loss of appetite/ refusal to eat												
iii. Dizziness												
iv. Body weakness												
v. Fever												
vi. Cough												
vii. Vomiting												
viii. Abdominal pain												
ix. Fast beating of the heart												
x. Disturbed sleep												
xi. Muscle pain												
xii. Joint pain												
xiii. Other (specify)….....												

F. Risk for treatment failure

Day 1 to day 3

	Day 1			**Day 2**			**Day 3**		
	Yes (indicate time)	**No**	**I don't know/ I don't mind**	**Yes (indicate time)**	**No**	**I don't know/ I don't mind**	**Yes (indicate time)**	**No**	**I don't know/ I**

									don't mind
12. Did you take your medication today?									
13. If no, why? (indicate reason in no box)									
14. Did you vomit after taking medication?									
15. Did you eat before taking medication?									
16. If yes, was it a fatty meal?									
17. Do you like the taste of medication									

18. (i) Have you ever been diagnosed with malaria before?

1.Yes 2. No

(ii) If yes, how long ago was it?

1.This month 2. Last month 3. Sometime this year 4. Less than five years ago 5. More than five years ago.

(iii) If yes, what medication did you use? 1. 2.

3. 4.

5.

19. What do you use to prevent mosquito bite?

1. Mosquito net and mosquito repellant: 2. Mosquito net only 3. Mosquito repellant only: 4. Others: 5. None

G. Risk factors for adverse drug reaction

	Day 1			**Day 2**			**Day 3**		
	Yes	**No**	**I don't know**	**Yes**	**No**	**I don't know**	**Yes**	**No**	**I don't know**
20. Did you eat before taking medication?									
21. If yes, was it a fatty meal?									
22. Did you take your medication today? (if yes indicate time)									
23. Have you ever had an ADR before?									
24. Have you taken any recreational drugs? (e.g									

alcohol, cigarette etc)									
25. Are you using other medication other than AL?									

H. Cure chart

	Week 1			**Week 2**			**Week 3**			**Week 4**		
	Yes	No	I don't know	Yes	No	I don't know	Yes	No	I don't know	Yes	No	I don't know
26. Have the symptoms resolved? (if yes, indicate day)												
27. If no, have you used any other medication for this condition?												
28. Have you developed new symptoms similar to those of malaria?												

29. If yes, was it malaria?												
30. If it was malaria, when was it diagnosed? (indicate in yes bracket date)												

Appendix 9: Dummy tables

A. Baseline characteristics of participants enrolled in the study

Table 1

Variable	**Mean**	**SD**	**Range**
Age			
Number of children			
Level of education			

Table 2

Variable	**n%**
Gender	
Marital status	
Children below 5 years	
Temperature	
Parasitaemia* (95% CI)	
Immune status	

B. Malaria Symptoms experienced before the drug was taken

Table 3

Sign/symptom	n%
(i) Fever	
(ii) Chills	
(iii) Profuse Sweating	
(iv) Muscle pain	
(v) Joint pain	
(vi) Abdominal pain	
(vii) Diarrhea	
(viii) Anorexia	
(ix) Nausea	
(x) Vomiting	

(xi)	Loss of appetite/refusal to eat	
(xii)	Cough	
(xiii)	Lethargy	
(xiv)	Malaise	
(xv)	Headache	
(xvi)	dizziness	
(xvii)	Others (specify)…….	

C. Cure rate

Table 4

	Week 1 cure rate (N = 117)		Week 2 cure rate (N = 98)		Week 3 cure rate (N = 98)		Week 3 cure rate (N = 98)	
	n (%)	95 % CI	n (%)	95 % CI	n (%)	95 % CI	n (%)	95 % CI
Overall								
By age (years)								
By BMI (kg/m2)								
By immune status								
By malaria species								
By parasitaemia								
By level of education								

D. Risk factors for adverse drug reaction

Table 5

Variable	Day 1 n%	Day 2 n%	Day 3 n%
1. Did you eat before taking medication?			
2. If yes, was it a fatty meal?			
3. Did you take your medication today? (if yes indicate time)			
4. Have you ever had an ADR before?			
5. Have you taken any recreational drugs? (e.g alcohol, cigarette etc)			
6. Are you using other medication other than AL?			

Appendix 10

UNIVERSITY OF NAIROBI
COLLEGE OF HEALTH SCIENCES
P O BOX 19676 Code 00202
Telegrams: varsity
Tel:(254-020) 2726300 Ext 44355

KNH-UON ERC
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Website: http://www.erc.uonbi.ac.ke
Facebook: https://www.facebook.com/uonknh.erc
Twitter: @UONKNH_ERC https://twitter.com/UONKNH_ERC

KENYATTA NATIONAL HOSPITAL
P O BOX 20723 Code 00202
Tel: 726300-9
Fax: 725272
Telegrams: MEDSUP, Nairobi

Ref: KNH-ERC/A/278

31st August 2020

Dr. Phidelis Wakoli Lutomia
Reg. No.U56/11792/2011
Dept. of Pharmaceutics and Pharmacy Practice
School of Pharmacy
College of Health Sciences
University of Nairobi

Dear Dr. Wakoli

RESEARCH PROPOSAL – EFFECTIVENESS AND SAFETY OF ARTEMETER LUMEFANTRINE IN PARTICIPANTS WITH MALARIA IN BUNGOMA COUNTY REFERRAL HOSPITAL (P172/03/2020)

This is to inform you that the KNH- UoN Ethics & Research Committee (KNH- UoN ERC) has reviewed and **approved** your above research proposal. The approval period is 31st August 2020 – 30th August 2021.

This approval is subject to compliance with the following requirements:

a. Only approved documents (informed consents, study instruments, advertising materials etc) will be used.
b. All changes (amendments, deviations, violations etc.) are submitted for review and approval by KNH-UoN ERC before implementation.
c. Death and life threatening problems and serious adverse events (SAEs) or unexpected adverse events whether related or unrelated to the study must be reported to the KNH-UoN ERC within 72 hours of notification.
d. Any changes, anticipated or otherwise that may increase the risks or affect safety or welfare of study participants and others or affect the integrity of the research must be reported to KNH- UoN ERC within 72 hours.
e. Clearance for export of biological specimens must be obtained from KNH- UoN ERC for each batch of shipment.
f. Submission of a request for renewal of approval at least 60 days prior to expiry of the approval period. (*Attach a comprehensive progress report to support the renewal*).
g. Submission of an *executive summary* report within 90 days upon completion of the study. This information will form part of the data base that will be consulted in future when processing related research studies so as to minimize chances of study duplication and/ or plagiarism.