ASSESSMENT OF THE COST-UTILITY OF PRE-REFERRAL MALARIA TREATMENTS IN KENYAN CHILDREN USING DECISION ANALYTIC MODELING

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A Thesis submitted in partial fulfillment of requirements for award of Masters degree in Pharmacoepidemilogy and Pharmacovigilance

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DECLARATION

This is my original work and has not been presented for examination in this or any other University.

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DEDICATION

I dedicate this work to my wife Dr. Agatha Olago and my children Muhiri and Mbira for giving me the strength and hope of a better tomorrow.

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ABSTRACT

Background

Mortality due to malaria occurs mostly in children aged below five years in Sub-Saharan Africa region. This is because of high malaria endemicity and limited access to healthcare. Pre-referral antimalarial treatment is treatment initiated at a primary or low level health facility without the necessary specialized services to treat the patient. The aim of this treatment is to delay the progress of severe malaria, which could result in mortality, while the patient is transferred to a secondary or tertiary health facility with the necessary services and expertise. Though pre-referral rectal artesunate has been included in the Kenyan National Guidelines for the diagnosis, treatment and prevention of malaria, it has yet to be implemented in the public healthcare system. Therefore it is important to establish its cost-utility compared to current parenteral treatments in the Kenyan setting. Rectal artesunate can easily be administered by community health workers (CHWs) unlike the other parenteral pre-referral interventions.

Objective

The main objective of the study was to assess the cost-utility of pre-referral antimalarial treatments in children less than 5 years living in rural hard to reach areas of western Kenya with high malaria endemicity. The study evaluated the cost-utility of provision of pre-referral treatments provided by community health workers (CHWs) as opposed to similar services at a primary health facility. The secondary objective was to compare the cost-utility of rectal artesunate, intramuscular quinine and intramuscular artesunate against no treatment. In addition a qualitative study was carried out whose objective was to identify the malaria program costs and factors affecting implementation of changes in treatment guidelines

Methodology

The study design was a prospective decision model based cost-utility analysis. The study was conducted from the provider perspective with a time horizon of 5 years. The study population was a theoretical cohort of 1000 children less than 5 years of age living in highly endemic areas of western Kenya.

The comparator groups were pre-referral antimalarial treatments provided by CHWs or at primary health facility, direct access to a tertiary health facility and no treatment. Costs were obtained from key informant interviews as well as from literature, expert opinion and empirical estimates. The cost categories included acquisition costs of antimalarial drugs, inpatient costs, health worker costs and implementation costs.

The key outcome measure was Disability adjusted life years (DALYs) averted. Data on effectiveness was obtained from literature. Data was analysed using HyperResearch® and Treeplan® Excel software. One way sensitivity analysis was done to assess the impact of uncertainties in costs and effectiveness.

Results

From the qualitative study, the incremental costs associated with implementation of rectal artesunate were capital costs of training of health workers and community health workers. Other costs were drug acquisition costs and inventory management costs.

Provision of rectal pre-referral treatment by CHWs was estimated to avert 12,406 DALYs at a cost of $7.1 per DALY averted; primary health facility was estimated to avert 12,613 DALYs with a cost of $7.3 per DALY averted while going to a tertiary health facility was estimated to avert 18,152 DALYs with a cost of $7.0 per DALY averted. The incremental program costs ranged from $0.003 -0.32, and was highest with the CHWs and lowest at tertiary facility.

Findings of the comparative cost-utility of the different pre-referral treatments showed that i.m artesunate was estimated to avert 5,898 DALYs at a cost of $15.5 per DALY averted, i.m quinine was estimated to avert 5,686 DALYs at a cost of $16.2 per DALY averted and rectal artesunate was estimated to avert 5,757 DALYs at a cost of $16.0 per DALY averted.

Referral compliance as well as life expectancy significantly affected the cost effectiveness with high referral compliance and longer life expectancy being more cost effective.

Discussion

Implementation of new treatments is a slow and rigorous process characterized by availability of irrefutable evidence especially local and availability of funds to provide the new alternative. It requires consensus building, stakeholder involvement as well as adequate expertise.

Use of CHWs was as cost effective as primary health facility with regards to provision of pre-referral treatments especially if there is referral compliance. However, access to tertiary facility remains the most effective option for better health outcomes. The cost-utility of rectal artesunate indicates that it is comparable to that of parenteral interventions.

Conclusion

Pre-referral treatment using rectal artesunate is a cost effective intervention when compared to current parenteral treatments and its administration by CHWs is as cost effective as at a primary health facility.

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LIST OF ACRONYMS AND ABBREVIATIONS

ACER	Average cost-effectiveness ratio
ACT	Artemesinin Combined Therapy
AL	Artemether Lumefantrine
CHAI	Clinton Health Access Initiative
CHW	Community Health Worker
DALY	Disability Adjusted Life Years
EV	Expected value
GDP	Gross Domestic Product
ICER	Incremental cost-effectiveness Ratio
IEV	Incremental expected value
IM	Intramuscular route of drug administration
IMCI	Integrated management of childhood illness
IV	Intravenous route of drug administration
KEMSA	Kenya Medical Supply Agency
KNH	Kenyatta National Hospital
MOH	Ministry of Health
NMCP	National Malaria Control Program
QALY	Quality Adjusted Life Years
RDT	Rapid diagnostic test
UNICEF	United Nations Children's Fund
USAID	United States Agency for International Development
UoN	University of Nairobi
WHO	World Health Organization

WHO-CHOICE	World Health Organizations' Choosing Interventions that are Cost Effective Project
YLD	Years Lived with Disability
YLL	Years of Life Lost

OPERATIONAL DEFINITIONS

Average cost-utility ratio	This is the total cost of the program per treatment alternative divided by its clinical outcome to give a ratio representing the cost per specific clinical outcome of that alternative
Cost-utility analysis	An economic analysis that compares two or more interventions, measuring the inputs in monetary terms and outcomes in quality-adjusted life years (QAYLs) or similar outcome measure, disability adjusted life years (DALY) which combines morbidity and mortality data.
Disability adjusted life years	The disability-adjusted life year (DALY) is measure of overall disease burden, expressed as the number of years lost due to ill-health, disability or early death.
Expected value	This is the total cost of each option of the decision made in choice of health care intervention.
Incremental cost-utility ratio	This is the ratio of the change in costs of a therapeutic intervention (compared to the alternative) to the change in effects of the intervention.
Incremental expected value	The additional program cost due each of the different interventions.
Time horizon	This is the length of time over which costs and clinical outcomes are being evaluated.
WHO-CHOICE	The CHOICE (CHOosing Interventions that are Cost-Effective) project is a WHO initiative developed in 1998 with the objective of providing policy makers with evidence for deciding on interventions and programs which maximize

	health for the available resources.
Years lived with disability	This is a measure of the burden of living with a disability
Years of life lost	This is an indicator of premature death, compared to the average life expectancy.
Neurological sequelae	These are impairments of neurologic or cognitive function. The neurologic impairment consists of loss of function in motor, including coordination, speech, vision, and hearing domains.

CHAPTER ONE

1.0 INTRODUCTION

1.1 Background

Malaria is a vector borne infectious disease of the red blood cells caused by a parasitic protozoan of the Plasmodium genus. The causative agents under this genus include: *Plasmodium falciparum, Plasmodium malaria, Plasmodium ovale, Plasmodium vivax* and *Plasmodium knowlesi*. The disease is transmitted by the bite of an infected female anopheles mosquito which introduces the parasite into the person's blood (1). Malaria is classified into either uncomplicated malaria or severe malaria. Uncomplicated malaria is defined as presentation of, a history of fever and parasitemia, without vital organ dysfunction (2).

Severe malaria is defined by the presence of malaria symptoms with vital organ dysfunction. The clinical manifestations supported by laboratory findings include; prostration, cerebral malaria, altered consciousness, respiratory distress, shock, convulsions, pulmonary oedema, jaundice, acute renal failure, heamoglobinuria, aneamia, hypoglycemia and hyperlactatemia (2).

Severe malaria is a medical emergency that can result in death where there is no rapid response or immediate access to healthcare. Therefore, correct diagnosis and early initiation of treatment is very important in reducing mortality and malaria complications (3). However, clinical diagnosis is confounded by similarities in the symptomatic presentations between malaria and other diseases like pneumonia (4,5). This therefore poses a challenge in resource limited settings that do not have the necessary diagnostic equipment and expertise.

1.2 Epidemiology of malaria

Malaria has been a constant scourge in the world for a long time especially in Africa, and with majority of deaths due to malaria reported in children under the age of five years (6). In Kenya and Africa in general most of malaria infection is caused by *P. falciparum* which is endemic in the tropics and causes the most serious form of the disease especially if treatment is delayed (4,6,7).

It is estimated that globally 3.2 billion people are at risk of developing malaria. Of this number, 1.2 billion people are at a high risk, while the rest have a low risk of developing the disease. In the year 2013, there were 198 million cases of malaria with 584 000 deaths. The burden of malaria is greatest in the African region which accounts for almost 90% of malaria deaths; especially in children less than 5 years of age who account for 78% of all deaths (6). Sub-Saharan Africa is the most affected region with malaria accounting for most of the infections and people at risk are estimated to be about 840 million (6).

According to the 2014 WHO malaria report, there were 2 .34 million confirmed malaria cases in Kenya in 2013 with 360 deaths. However, this figure might be an underestimate due to under reporting since studies show that malaria is the leading cause of mortality in Kenya with about 70% of the population at risk of malaria (8). Majority of the population (40%) live in areas with a low transmission risk, with 36% of the population living in high transmission areas and others in seasonal transmission areas (6,7,9). In 2010, clinically diagnosed malaria accounted for 34 per cent of outpatient hospital visits in Kenya. The average prevalence of malaria in children aged below 14 years was estimated at 15%; however, there are differences in prevalence according to endemicity (7). This figure therefore, may be an underestimate.

There has been a decline in endemicity of malaria in Kenya from high to low transmission. There are four different epidemiological zones of endemicity. The coastal and lake endemic areas have high transmission throughout the year. The highland epidemic areas have seasonal transmission with high peaks during the rainfall period. There are also seasonal transmission areas and the low risk areas (7). This is presented in Figure 1 (6).

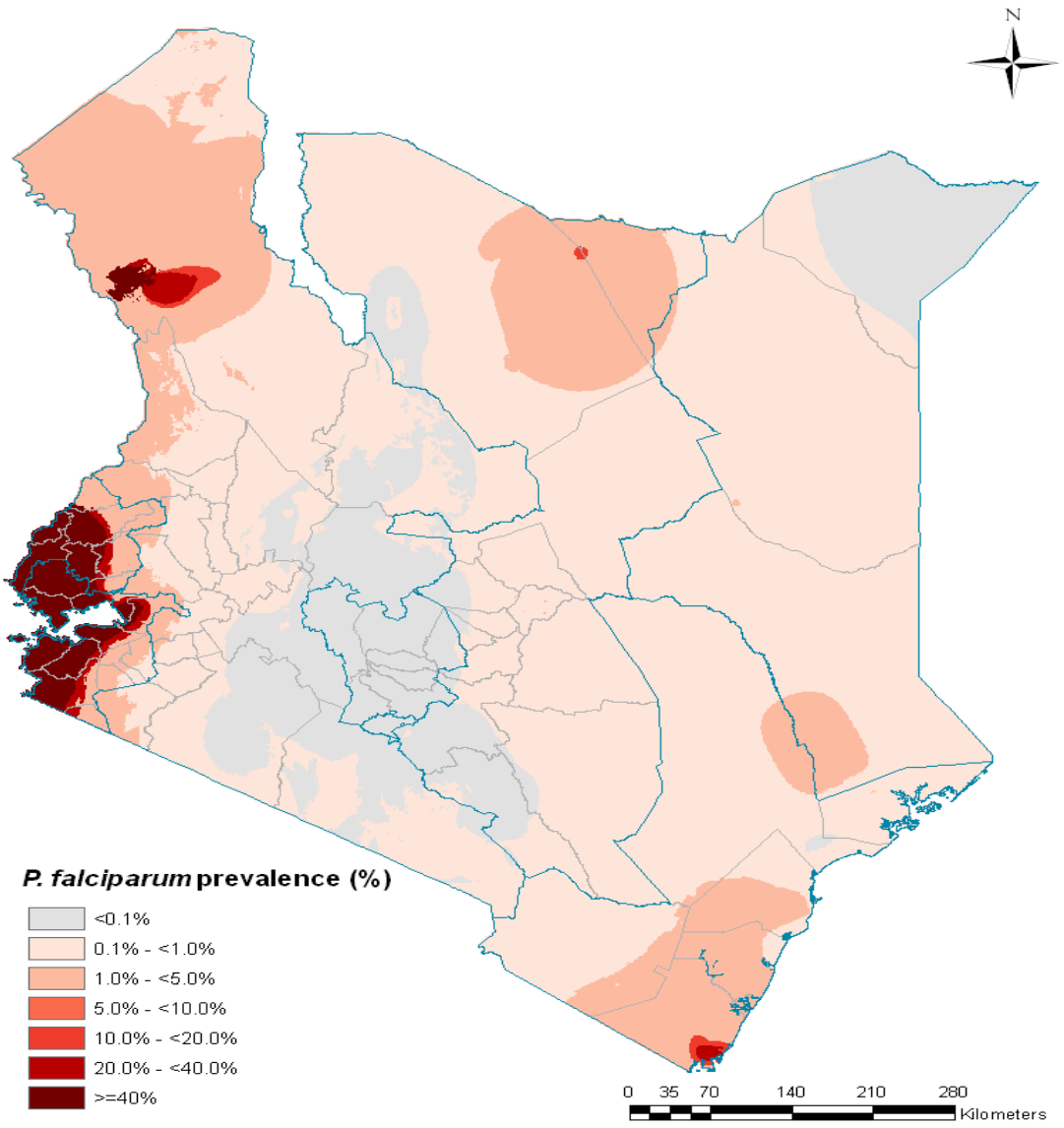

Figure 1 Malaria endemicity in Kenya (obtained from WHO World Malaria Report, 2014) **(6)**

1.3 Treatment of malaria

For uncomplicated malaria, the objective of treatment is to cure the infection as fast as possible so as to prevent progression to severe disease and to reduce morbidity. The World Health Organization (WHO) recommends use of combinations of two or more antimalarial drugs with different modes of action to avoid resistance and treatment failure. Therefore the treatment of choice is a combination of an artemesinin derivative with another drug (2).

The recommended artemesinin combined therapies (ACTs) are, artemether plus lumefantrine, artesunate plus amodiaquine, artesunate plus mefloquine, artesunate plus sulfadoxine-pyrimethamine, and dihydrortemisinin plus piperaquine. These drugs should be administered for at least three days to ensure maximum effect (2).

The primary objective of treatment of severe malaria is to avert the possibility of death given that mortality due to severe malaria is almost 100% if not immediately treated. Fast and immediate treatment lessens the chances of death to about 15-20% (2). Prompt and effective parenteral antimalarials should be administered as soon as possible.

The recommended drugs in use are the artemesinin derivatives that include artemether, artesunate and artemotil and cinchona alkaloids class that includes quinine and quinidine (2). In Kenya the recommended treatment for severe malaria is parenteral artesunate or parenteral quinine (10).

Treatment of malaria is a challenge in Kenya since there is a problem of access to healthcare facilities and anti-malarial medicines especially in malaria endemic areas (11,12). Since severe malaria is an emergency, there may not be adequate time to carry out the diagnostic tests but rely on empirical treatment. Therefore the Ministry of Health through the National Malaria Control Program has included rectal artesunate in its formulary as a pre-referral treatment option in the primary health facility together with pre-existing parenteral options of i.m artesunate and i.m quinine (10). However, this has not been implemented.

1.4 Pre-referral treatment for malaria

Not all children who are febrile are taken to hospital and therefore they do not receive any treatment (6). This has led to concerted efforts to increase access to treatment including the adoption of rectal artesunate for pre-referral treatment in the current Kenyan malaria treatment guidelines.

The first line drug for severe malaria is intramuscular artesunate ; however, in areas where access to health facilities is difficult and delayed, then, pre-referral administration of rectal artesunate is recommended (2,4).

Rectal artesunate may offer advantages over parenteral artesunate and parenteral quinine that may include, greater population uptake as the treatment can be administered at home by untrained care-givers or CHWs. It may also be more effective in inducing rapid parasite clearance. It may reduce the risk of death from severe malaria especially if administered within 24 hours of malaria symptoms (13–17).

1.5 Economic impact of malaria

Malaria predominates in low and middle income countries especially among the poor and those who are marginalized and live in rural areas. There is need for sustained financial investment towards poverty eradication and health sector infrastructure improvement to combat the effects of malaria (6).

The global funding for malaria control and elimination in 2013 was approximately US $ 2.7 billion, with 82% (US $ 2.18 billion) of the funding coming from international investment while domestic funding accounted for 18% (US $ 527 million). The total amounts to a 3% increase from 2012 but still represents a 48% shortfall of the global annual estimates to achieve complete control and elimination of malaria. The African region takes up 72% of Global Funds since it has the highest disease burden. This means therefore that domestic funding has to grow to bridge the funding gap (6). However, the level of resources available domestically is usually less than the health needs (18).

There are various ways in which malaria impacts negatively on socioeconomic wellbeing of a population; these include reduced productivity, premature mortality, negative effects on population growth and increased medical costs. Malaria morbidity results in loss in productivity that affects the overall GDP of a country. The loss in productivity is highest in the rural areas as compared to the urban areas and more so among women than males (19–21).

The total household expenditure and other costs among families in most of Sub-Saharan countries due to malaria morbidity ranges between $0.23- $25 of income on prevention and treatment.

It is estimated that in Kenya, an admission in a district hospital for treatment of severe malaria costs US $47.19 to US $81.84, while the inpatient recurrent costs to hospitals of malaria wasUS $9 (22,23).

These costs are quite high given that most households are low income earners and that the burden of disease is more so in rural areas where there are limited economic activities. Therefore there is need to reduce the overall direct and indirect costs of malaria. In this regard there has been a concerted effort to ensure that the funds provided domestically as well as by donors are used cost effectively to achieve the targets of reduced mortality and morbidity due to malaria.

1.5 Study problem

Pre- referral antimalarial treatment was introduced as an important measure to combat the progress of severe malaria leading to death. The treatment options for pre-referral as recommended by the WHO are intramuscular artesunate, intramuscular quinine and rectal artesunate. Although rectal artesunate has been included into the Kenyan National Guidelines for the diagnosis, treatment and prevention of malaria, it is yet to be implemented. Given that malaria is a leading cause of morbidity and mortality in children less than 5 years, provision of rectal artesunate may lead to beneficial health outcomes. In Kenya, however, there are no formal studies that explore the impact of pre-referral rectal treatment in terms of effectiveness and costs compared with existing interventions. Policy makers may therefore, require local evidence of cost-utility of rectal pre-referral artesunate compared to current pre-referral treatments.

Given that funding for malaria does not meet the burden experienced, it is vital to assess whether pre-referral treatment option as currently practiced was cost effective and whether there are any advantages gained by the introduction of rectal artesunate as an alternative to pre-existing options. We therefore undertook to evaluate the cost-utility of pre-referral treatments against direct access to tertiary facility and no access to treatment.

Though there is extensive experience with use of parenteral pre-referral treatments, these can only be administered by skilled health workers, adding to the delay in obtaining prompt therapy. Rectal artesunate offers an avenue of ease of access as it can be used by CHWs. Only one study by Tozan et al, has evaluated the cost-utility of pre-rectal artesunate (24).

According to Tozan et al, pre-referral artesunate was administered by CHWs and was found to be cost effective in rural settings. However, this study had a number of gaps which included use of international prices as opposed to local country specific prices. It is likely that since costs are highly context specific, the demonstrated superiority of pre-rectal artesunate could not be replicated in the Kenyan context. It also did not contrast the cost-utility of rectal artesunate against parenteral options of i.m artesunate and i.m quinine. The study also considered neurological sequelae as the only complication resulting from severe malaria.

Given that there are regional variations in incidence of complications and types of malaria it is possible that the cost of managing the different complications varies. It is necessary to model how this may affect the overall cost-utility program. We therefore propose to evaluate the cost-utility of pre-referral malaria treatment in Kenya provided by CHWs versus primary health facility.

1.6 Research question

1. Is provision of pre-referral treatments by CHWs more cost effective than at primary health facilities?

2. Is pre-referral rectal artesunate more cost effective than pre-referral intramuscular quinine and intramuscular artesunate?

3. What is the incremental program costs associated with implementation of rectal artesunate?

1.7 Hypothesis

1.7.1 Null hypothesis

1) There is no difference in the cost-utility of CHWs and primary health facility in provision of pre-referral treatment.

2) There is no difference in the cost-utility of pre-referral rectal artesunate, i.m artesunate and i.m quinine.

1.7.2 Alternative hypothesis

1) There is a difference in the cost-utility of CHWs and primary health facility in provision of pre-referral treatments.

2) There is a difference in the cost-utility of pre-referral rectal artesunate, intramuscular artesunate and intramuscular quinine.

1.8 Objectives

1.8.1 Main objective

The main objective was to assess the cost-utility of pre-referral antimalarial treatments in children less than 5 years living in rural hard to reach areas of western Kenya with high malaria endemicity.

1.8.2 Specific objectives

The specific objectives were to:

1) Identify incremental program costs associated with procurement and implementation of rectal artesunate for the management of severe malaria in children less than five years of age living in rural hard to reach areas with high malaria endemicity.

2) Compare the cost-utility of pre-referral treatments provided by CHWs against those provided at Primary health facility.

3) Compare the cost-utility of pre-referral rectal artesunate, i.m artesunate and i.m quinine versus no treatment in children less than five years of age living in rural hard to reach areas with high malaria endemicity.

1.9 Study significance

Though rectal artesunate has been adopted as part of the pre-referral treatments for severe malaria in Kenya, its use has not been implemented. We therefore sought to establish and evaluate its cost-utility against existing pre-referral treatment options.

This study can be used to inform policy makers to implement the treatment guideline that recommends rectal artesunate for management of severe malaria particularly in areas where geographical access to both primary and tertiary health facilities may be limited.

In addition we sought to provide an argument for the supply of CHWs within existing programs in the country with rectal artesunate in order to increase coverage for severe malaria. Adoption of rectal artesunate would reduce the burden of illness and promote equitable access to healthcare.

CHAPTER TWO

2.0 LITERATURE REVIEW

2.1 Barriers to access to malaria treatments.

Malaria accounts for a lot of deaths in sub-Saharan Africa making it the leading infectious disease in this region and remains a challenge in other parts of the world, especially the developing countries. The challenge is compounded by the fact that access to treatment is usually curtailed and slow due to poor infrastructure and lack of adequate medical supplies in the health institutions (25).

Kenya has poor health infrastructure especially in the rural areas where malaria is highly concentrated. This delays prompt treatment which is necessary to save lives. Where health facilities are not easily accessible due to distance, patients tend to seek services in the informal sectors which may lead to adverse outcomes (26,27). Delays in reaching health facilities providing parenteral treatment for malaria leads to increased mortality (7,11,12).

Studies have shown that irregular supply of antimalarial drugs and commodities impact negatively on the health outcomes especially in rural areas which already have pre-existing challenges with access to most healthcare services and commodities (26). In many African countries, regular supply of antimalarial drugs is a problem with low rates of availability especially in public health facilities (28). In a study done in Senegal, drugs were unavailable for long periods of time which affected the health seeking habits of the communities (29). In Kenya it is reported that public health facilities experience stock-outs of antimalarial drugs leading to patients sourcing drugs from private pharmacies and chemists, thus increasing the cost of healthcare (26).

Some community health care workers have poor knowledge of the malaria referral algorithm despite receiving training (29). Health care workers perceptions and understanding influences the way in which they offer services and in some instances they do not provide the required medical interventions (30).

Transport costs to and from health facilities in places where the health facilities are far reduces the chances of seeking healthcare. This is compounded by the perception that in most instances drug supply is none existent in the facilities and seeking treatment may be futile.

User fee charges in most health facilities for services offered tend to increase the cost and thus limit access to medical care (26). Cultural beliefs as well as lack of education among the rural populations determine the choice of health interventions. The lack of ability to identify symptoms and link them to malaria or belief that a symptom is due to a cultural factor and hence can be treated traditionally means that formal health facilities are a last resort (26).

2.2 Pre-referral interventions in healthcare

Referral in the healthcare system is the scaling up of patient care from primary care facility to secondary care facility after exhaustion of therapeutic options at the lower level. It means that patients are referred to seek more specialized care and management which is expected at the secondary care facility in terms of infrastructure and expertise. The referral system is therefore essential in improving the patients' health outcomes by providing better services and facilities to manage more complicated cases (31).

Pre-referral interventions are those interventions that are initiated before referral to healthcare facilities. These are interventions that are aimed at stabilizing or improving the patient's condition, before they access a health facility. Pre-referral interventions are especially important in rural areas where there is limited access to healthcare facilities. They are a necessity for life-threatening illnesses such as malaria (3).

For effective referral, healthcare workers should be educated on the appropriate ways of referral and when to initiate referral procedures. To improve the referral process, guidelines for referral need to be developed and distributed and the consultant healthcare professionals involved in teaching and sensitization on referring (31).

2.3 Models for pre-referral treatment of malaria

Pre-referral management may be initiated either in the household or under a community health worker (CHW) program. In these programs there is often access to antimalarial and antimicrobial agents outside healthcare facilities.

Pre-referral treatment may also be initiated in primary healthcare facilities before referral to secondary healthcare facilities. The practice of pre-referral management can vary from limited interventions to more sophisticated interventions (32).

Pre -referral models vary from who initiates treatment, the assessment and diagnosis of the disease, and the modes of referral. The models described are community based and lay down the role of the family and community health care worker in the referral process (32). Table 1 presents the different models of pre-referral interventions.

Table 1 Pre-referral intervention models for malaria case management

Intervention model	Diagnostic approach	Initiation of treatment	Pneumonia co-management	Mode of referral
CHW basic management	Presumptive	None	None	Verbal
CHW basic management	Presumptive	Limited	Limited	Facilitated
CHW fever directed management	Use of algorithms	By CHW	None	Verbal
Family directed fever management	Presumptive	By family	None	Verbal
CHW malaria management and surveillance	Use of RDT	By CHW	None	Verbal
CHW pneumonia case management	Presumptive	By CHW	Yes	Verbal
CHW integrated multiple disease case management	Use of algorithms	By CHW	Yes	Verbal and facilitated

RDT- rapid diagnostic test (tests for presence of malaria parasites in blood), CHW- community health care worker

2.4 Role of community health workers in pre-referral treatment

In rural hard to reach areas far from a health facility, there is increased likelihood of patients seeking treatment from a CHW. CHWs are usually located in rural hard to reach communities and are the first contact in selected disease management strategies like malaria (33).

Studies have shown that the utilization of community based management teams of volunteers increased the possibility of accessing antimalarial drugs as well as positively impacting on treatment seeking habits and behaviors (34–36).

In Kenya CHWs are used in malaria case management. They provide services in hard to reach geographical areas such as the semi-arid regions in rural areas. Studies done on utilization in hard to reach areas found that on average about 38% of poor households used the services of CHWs, while only 17% of those who are not poor use these services (34).

Studies done in Zambia, Zaire and Asia have shown that CHWs can effectively diagnose and treat uncomplicated malaria. CHWs can also initiate correct referral procedure for further treatment for those with severe forms of malaria (37–41). Well trained CHWs under programs, if well supervised and supported, may lead to improved outcomes as they provide prompt access to antimalarials. However, presumptive treatment of fever with antimalarials may cause misuse of the drugs since many illnesses present with fever. Guidelines and treatment algorithms should therefore be developed for CHWs and support supervision strengthened to increase their effectiveness in malaria management (34,42,43).

For the successful utilization of CHWs they need to be trained on malaria case management with emphasis on the referral aspect in cases of severe malaria. This is because a big percentage of severely ill patients are not referred for further management as they view referral as unnecessary (30).

2.5 Effectiveness of pre-referral treatment for severe malaria in children

Pre-referral treatment has been shown to be effective especially in hard to reach rural areas with high incidence of malaria. However, most of these studies compare use of rectal artesunate against placebo (24,44). Studies comparing rectal artesunate versus i.m artesunate and or i.m quinine found no difference in fever clearance time, coma recovery, or length of hospital. The only difference was the rate of parasite clearance which was achieved much faster with the artemesinin based compounds than quinine. This may indicate that these options are generally as effective as each other (13–17). Studies that have evaluated the effectiveness of pre-referral treatments are summarized in Table 2. In all these studies pre-rectal artesunate caused more rapid reduction in parasitemia compared to the placebo, i.m quinine and i.m artesunate.

Table 2 Summary of studies on effectiveness of pre-referral treatment

Study	Comparator groups	Setting	Outcomes	Key findings
Gomes et al 2009 (14)	Rectal artesunate vs placebo	Ghana, Tanzania, Bangladesh	Mortality and disability	Artesunate effective for patients not in hospital after more than 6 hours following administration.
Gomes et al 2008 (15)	Rectal artesunate vs i.m quinine	A review of efficacy and safety.	Parasite clearance rate	Rectal artesunate cleared parasites more rapidly than quinine.
Karunajeewa et al 2006 (16)	Rectal artesunate vs i.m artemether	Papua New Guinea.	Parasite clearance time	Mean parasite clearance time higher with rectal artesunate than artemether.
Barnes et al 2004 (17)	Rectal artesunate vs i.m quinine	Malawi	Parasitemia	Rectal artesunate was more effective for children < 5 yrs
Cao et al 1997 (18)	Rectal artesunate vs i.m artesunate and i.v quinine	Vietnam	Parasite clearance, coma, hospital stay and adverse reactions	Parasite clearance achieved faster with artesunate and artemether. No significant difference in other endpoints

2.6 Care-taker adherence to referral advice following pre-referral treatment

One of the failings of pre-referral treatment is that care-givers may fail to adhere to advice given following initiation of treatment and instead take their children to traditional healers, home, or drug shops instead of seeking further care in health facilities. Compliance to advice following pre-referral treatment has been shown to be positively correlated to the severity or seriousness of the presenting illness (45).

Other factors including the health state of the child after pre-referral treatment as well as charges at the health facility affect adherence to referral advice. Studies have shown that where there is an improvement in the health condition of the children after pre-referral treatment, then there was a high likelihood that the referral advice was not followed as opposed to where the condition deteriorated or did not change (45,46). Hospital charges are also a deterrent to seeking of further treatment especially in the rural areas where there are many competing needs and very little resources.

Care-givers understanding of the need for the referral and therefore knowledge of the health care needs of the children increase the chances of adherence. It is therefore important for the referring authority to effectively communicate to the care givers the need to adhere and seek further treatment (45). Even after pre-rectal treatment have been administered, long distances to health facilities still remains a challenge and restrict access to secondary health care facilities (29).

2.7 Uptake of rectal pre-referral treatment

Rectal treatment is not a mainstay route of administration in many settings especially the rural areas in Kenya and most African countries. This is because there are perceptions that this route of administration is not effective by both the care givers as well as health care workers. In addition, rectal administration is culturally not well understood or accepted and may be frowned upon (47).

However, studies done in Nigeria and Papua New Guinea on perceptions and acceptability of rectal artesunate found that, a majority of parents were in favor of its use as they found it easier to administer.

With adequate public awareness and knowledge on the use of rectal artesunate, there is an increased likelihood of acceptance which will lead to a decrease in mortality rates experienced in rural hard to reach areas (48,49).

The uptake of rectal pre-referral treatment as with the other parenteral interventions depends also on the early identification of the symptoms and the ability of the caregivers to identify these symptoms and the availability of these interventions. The severity of the symptoms as perceived by the care giver may lead to higher uptake of pre-referral treatment in general (50,51).

CHAPTER THREE

3.0 METHODOLOGY

The first part of the study was a qualitative study that involved key informant interviews aimed at obtaining the incremental program costs associated with implementation of rectal artesunate for pre-referral treatment. It also sought to identify factors affecting implementation of changes in malaria guidelines. The second part of the study was a cost-utility analysis of pre-referral treatments.

3.1 QUALITATIVE STUDY TO ESTIMATE PROGRAM COSTS

This qualitative study entailed key informant interviews aimed at obtaining the incremental program costs that would be incurred by provision of pre-rectal artesunate for early management of severe malaria in children less than 5 years of age. In addition the key informant interview sought to obtain a deeper insight into the procurement of antimalarial drugs as well as implementation of new interventions.

3.1.1 Study design and population

This was a cross sectional qualitative study of implementation changes in malaria treatment guidelines. The study population was managerial personnel in charge of procurement of malaria drugs and implementation of changes in treatment guidelines.

3.1.2 Study site

The study was conducted in Nairobi, specifically in agencies involved in procurement and management of malaria program; the National Malaria Control Program (NMCP), Kenya Medical Supplies Authority (KEMSA), African Medical Research Foundation (AMREF) and Clinton Health Access Initiative (CHAI).

The National Malaria Control Program is a Government body tasked with curbing the spread and effects of malaria through policy development and implementation. It ensures coordinated activities country wide to minimize the impact of malaria by ensuring adequate drug supply, vector eradication, prevention through nets and also training of health care workers.

The Kenya Medical Supplies Authority is the Government agency tasked with procurement, inventory management, distribution and supply of medicines to public health facilities. Together with the National Malaria Control Program it carries out quantification and needs assessment for antimalarials in the country. The African Medical Research Foundation is a Non-Governmental organization that implements community strategy program for malaria on behalf of the National Malaria Control Program. The Clinton Health Access Initiative is a Non-Governmental donor funded program that procures and supplies i.m artesunate to the public facilities either directly or through Kenya Medical Supplies Authority.

3.1.3 Sample size considerations

Principles of sample size considerations for qualitative studies were used (52). According to this principle, for a key informant interview a sample size of one is adequate. Since the study was a key informant interview, a sample size of one persons per organization, was considered adequate.

The final sample size was determined by the principle of saturation. This principle states that a study will be terminated if no additional information is likely to be acquired by interviewing more subjects.

3.1.4 Sampling and eligibility criteria

Purposeful sampling was conducted for the key informant interviews. In purposeful sampling any subject who meets a given criteria is included. Participants were therefore included if they met the following criteria;

a) Worked in management or procurement sections of the agencies above.

b) Had been involved in the program for more than two years

c) They gave informed consent to participate in the study

Anyone who did not meet the above criteria was excluded from the study.

3.1.5 Participants recruitment

A letter of introduction obtained from the School of Pharmacy, University of Nairobi and a letter of ethical approval from the University of Nairobi/Kenyatta National Hospital Ethics Review Committee (UoN/KNH-ERC) were given to program heads for permission to interview relevant managers. Identified individuals were requested for an interview at their convenience through either a personal visit or a telephone call.

3.1.6 Data collection

An oral key informant interview was conducted with aid of the appended key informant guide in appendix 2. The interviews were conducted by two research assistants. One took notes as another conducted oral interview.

The interviews were designed to obtain information on the resources used in implementing new interventions in the past and the costs associated with each of these interventions. In addition the interview sought to obtain data on recurrent costs associated with the supply of i.m quinine and i.m artesunate as well as factors that cause variation in the recurrent expenditure on antimalarial drugs. The written information obtained from the interviews was transcribed into a Microsoft word document within 24hours of the interview. This information was stored for a period of five years in compliance with national regulations for archiving of documents.

3.1.7 Data analysis for the qualitative study

A ground theory approach was used to analyse data. This involved identification of key themes which were coded. Data was then analyzed using HyperResearch® software version 3.7.3. In addition quantitative data on costs was tabulated and summarized.

3.1.8 Ethical consideration

Ethical approval was sought and obtained from the KNH/UoN Ethics Review Committee. The letter of ethical approval is appended in appendix 5, reference number (KNH-ERC/A/162). Informed consent was obtained with aid of informed consent form in appendix 3, and the participants were provided with the objectives, methods, and expected benefits of the study.

Participant's identities were concealed by using codes and any identifier information was excluded in the data tool to ensure confidentiality. The study adhered to the principles of ethical research as outlined in the Declaration of Helsinki (53).

3.2 COST-UTILITY STUDY

The aim of this study was to compare the cost-utility of pre-referral malaria interventions used to manage severe malaria provided by a CHWs against similar service provided in a Primary health facility. The study also compared the cost-utility of pre-referral treatments against no pre-referral treatment. We used the WHO-CHOICE guidelines for generalized cost-utility studies (54).

3.2.1 Study design

This was a decision analytic model based cost-utility study. This design was selected as it synthesizes existing knowledge and evidence from literature and then predicts the cost-utility of one treatment versus another using a decision tree. We chose this approach because long term evidence on the cost-utility of rectal artesunate is necessary but not locally available (55–57).

3.2.2 Study population and Area

The study focused on a theoretical cohort of 1000 children under the age of 5 years residing in the Western and Lake endemic region of Nyanza in Kenya; specifically the rural areas with high malaria endemicity (7). Children aged less than five years comprise17.4% of the population in Western Kenya. This was equivalent to about 1687787 children. The proportion of males and females in this age-group is 50.6% and 49.4% respectively (58).

3.2.4 Study perspective

The study was carried out from the perspective of the Government of Kenya which is the largest provider of healthcare services in Kenya (59,60). The services for malaria prevention and treatment are provided through the Ministry of Health under the National Malaria Control Program (57). Patient related costs were therefore not considered.

3.2.5 Time horizon

The time frame for the intervention was 5 years. The timeframe included the health benefits of the intervention in terms of averted early mortality and persisting neurological disability as well as effects of severe malarial anemia in a cohort of 1000 newborn babies until 5 years of age, when the incidence of clinical malaria wanes in high-transmission areas.

3.2.6 Comparator interventions

There were four comparators groups which represented the type of healthcare facilities and options to which people in rural areas have access. The first option was utilization of CHWs who would provide care using rectal artesunate only and refer patients to a tertiary health facility. The second was the use of a primary healthcare facility without any inpatient services where one could be put on rectal artesunate, i.m artesunate or i.m quinine and referred to a tertiary health facility. The third was where a sick child could directly access a tertiary healthcare facility having inpatient facilities without need for pre-referral treatment. The other option was where the child could not access any form of treatment.

The second option of access to a primary healthcare facility was used to develop a sub model for comparison of the costs and effectiveness of the three interventions for pre-referral treatments; rectal artesunate, i.m artesunate, i.m quinine against no pre-referral treatment.

3.2.7 Definition of primary and tertiary health facility

In this study, a primary health facility was defined as a low level government or public health facility without any specialized services in a rural area and offering outpatient services only. We defined a tertiary facility as a government or public health facility with specialized services including inpatient services, capable of admitting severely ill children due to malaria. This includes district as well as regional referral hospitals.

3.2.8 Effectiveness of pre-referral treatments in childhood malaria

We synthesized information from existing studies to establish the effectiveness of each of the interventions. A list of studies that have been conducted on the effectiveness/efficacy of pre-referral treatment is presented in Table 2. The studies chosen were relevant to our setup and environment in regards to endemicity, and resource settings.

The key measure of effectiveness and health benefits were Disability Adjusted Life Years (DALYs) averted; persisting neurological disability and severe anemia. DALYs is a composite measure that incorporates mortality data, life expectancy and reduction in quality of life in patients who develop disability.

DALYs were computed as a sum of Years of Life Lost (YLL) due to premature mortality in a population of 1000 children and the number of Years Lived with Disability (YLD) due to neurological sequalae and anemia that follow a bout of severe malaria using equation 1.

Equation 1

$$DALY = YLD + YLL$$

Years of Life Lost were computed using equation 2.

Equation 2

$$YLL = n/r\ (1-e^{-rl})$$

Where: YLL is years of life lost due to premature death; n is number of deaths; l is the standard life expectancy at age of death in years; r is the discount factor.

The number of deaths due to inpatient malaria was estimated using a case fatality rate of 7.5% (3.5-9.3%) for inpatient severe malaria as obtained from a study conducted in Western Kenya (61–63). The case fatality rate for untreated malaria was estimated at 70% from a study that sought expert opinion on case fatality rate for untreated febrile illnesses (64). No clinical study has been done in this population to establish the case fatality rate of untreated malaria hence these estimates are usually subjective. The life expectancy for children aged 0-1 yrs was 63.1 yrs for males and 65.6 yrs for females; and for children aged 1-4 yrs was 65 for males and 67.5 for females as obtained from WHO life expectancy ranking for Kenya (65).

The Years Lost due to Disability [YLD] was computed using equation 3.

Equation 3

$$YLD = IDW\,(1-e^{-rl})/r$$

Where; YLD is years lost due to disability; I is a number of incident cases; DW is disability weight; l is the average duration of a case until remission or death; r is the discount factor.

The disability weights were obtained from WHO data for the sub Saharan region and the disability weight associated with a malaria episodes was 0.211, neurological sequalae 0.4710 and anemia was 0.013 (66).

The incidence of neurological sequalae and anemia were 3 and 18% respectively for those seeking treatment as obtained from literature (22,61). The length of hospitalization was a median [IQR] of 5 [3-8] days (22). The duration of neurological sequalae was estimated to be 2 years, while anemia complications were estimated to last for about a month (67–69). We used a discount factor of 3% as recommended in literature (68).

Administration of rectal artesunate followed by inpatient care has been shown to reduce by 49% (95% CI 19.31-67.76) mortality due to severe malaria (13). We assumed that effectiveness of i.m quinine as a pre-referral treatment was 90% that of rectal artesunate and that of i.m artesunate was 20% more that of rectal artesunate with regard to reduction in mortality. This assumption was made because our endpoint was mortality and there was no study comparing the three interventions with mortality as the endpoint. Information obtained from literature showed that rectal artesunate had a faster parasite clearance than the parenteral interventions within 24hours but was less effective than i.m artesunate after 24hours (14). It was also shown to be more effective than quinine when used for treatment of severe malaria (70).

It was assumed that patients sought treatment within 24hours of onset of illness. It was also assumed that those who received pre-referral treatment but did not seek inpatient care had the same risk of dying as those who did not seek any treatment.

We assumed that the incidence of anemia in the population not seeking treatment was twice that of those who sought inpatient care after pre-referral treatment (7). Table 3 summarizes the variables used to compute effectiveness.

Table 3 Epidemiological parameters used in calculation of effectiveness

Epidemiological prevalence and effectiveness	Point estimate (%)
Inpatient case fatality rate of malaria (61)	7.5
Case fatality rate of untreated malaria (64))	70.0
Average length of in-hospital stay (22)	5.0
Effectiveness of rectal Artesunate (13)	49.0
Probability of neurological sequelae (22,71)	3.0
Probability of anemia (61)	18
Assumed effectiveness of im quinine vs rectal	90
Assumed effectiveness of im artesunate vs rectal	120
Life expectancy	
Males (0-1)	63.1
Females (0-1)	65.6
Males (1-4)	65
Females (1-4)	67.5
Disability weights	
Malaria episode	0.211
Neurological sequelae	0.471
Anemia	0.013

3.2.9 Costing methodology

The costs were obtained from literature and from key informant interviews. Inpatient costs were estimated from a previous study done in Kenya that calculated the inpatient costs of managing malaria in pediatrics (22). This study calculated costs from different levels of health care and regions including western Kenya. The costs obtained from the study were inpatient costs incurred by the health care system at a tertiary health care facility in western Kenya. These costs were estimated at US$ 75.13 [36.33-102.64] per patient (22). The costs of managing neurological sequelae was US$ 48.52 and malarial anemia was US$ 45.02 as obtained from a study by Sicuri et al (72). These studies are summarized in Table 4. All the costs were updated to 2015 rates using the consumer price index for Kenya using equation 4 (73).

Equation 4

$$P=R(1+r)^n$$

Where: P was the current cost; R was the cost at year of study; r =the average inflation rate (74); n was the time period.

Table 4 Studies on cost of managing malaria in Kenya

Authors and reference	Title of the publication
Sicuri et al, 2013 (72)	The economic costs of malaria in children in three Sub-saharan countries: Ghana, Tanzania and Kenya
Ayieko et al, 2009 (22)	The economic burden of inpatient paediatric care in Kenya: household and provider costs for treatment of pneumonia, malaria and meningitis

3.2.9.1 Estimation of personnel and drug costs

The cost of time of a CHW spends treating a child was calculated with the assumption of a 2-hr workday and that they work for 5 days a week. The CHWs in Kenya earn a monthly salary ranging from $41.41 to $165.63. This information was obtained from key informant interviews and from literature (75).

The cost of obtaining pre-referral treatment from a healthcare worker was calculated per child. The estimated working time of a healthcare worker was 40 hours per week with a salary range of $1242.23 to $ 2070.39. This was an estimated salary of a senior nurse working in a public health facility obtained from key informant interviews and from Kenyan data on salaries and allowances for public servants (76–78). We assumed that every patient needed 20 minutes of care.

The acquisition costs of 50mg of rectal artesunate was estimated at $0.105-0.350 (79). The cost of i.m artesunate was estimated at $1.4-1.62 and that of i.m quinine was estimated at $0.20-$0.205. This information was obtained from a key informant interview. All costs were converted to international dollars at a rate of 48.30 Kshs per US dollars, 2015 (80).

3.2.9.2 Incremental program costs for implementation of pre-referral rectal artesunate

From the key informant interviews, the capital costs incurred by the program during the implementation of changes in treatment guidelines, included training of healthcare workers, community healthcare workers, as well as costs for monitoring and evaluation of the implementation of malaria case management. These costs are summarized in Table 6.

The costs obtained were annuitized with a discount rate of 8% over a period of 3 years (81). Equation 5 was used for annutization of the capital costs.

Equation 5

$$AC = Capital\ Cost / AF$$

Where: AC annuitized capital cost; AF is the annutization factor, calculated using a discount rate of 8% and expected period of 3 years.

The capital costs were calculated per health care provider providing services to one case of severe malaria. From a key informant interview, the number of CHWs in western Kenya was estimated at 7,100 with a total yearly case load for malaria of 170,000. This represents about 24 cases per year.

From the National Human Resources for Health Strategic Plan 2008, we estimated the number of nurses working in a primary health facility in western Kenya (60). According to the strategic plan, in 2008, 22.7% of the entire health work force in Kenya was working in Western and Nyanza. Given that the number of healthcare workers trained annually is 6000 as obtained from key informant interviews, we estimated that 1800 are trained from this region.

Children under 5 years of age were estimated at a population of 1687787 in this region. The yearly prevalence for malaria was 38% in this population, and 67.3% utilized Government facilities (7,60,82) . We estimated severe malaria incidence of 10% among the population with malaria (83).We therefore multiplied these rates with the population and then divided with the total number of nurses in the region to get 24 cases treated per healthcare worker trained per year.

We estimated the health work force for tertiary facility from the staffing rate of Western and Nyanza regions of 22.7% with 6000 trained annually for malaria case management as obtained from key informant interview. We used the same rates as for primary facility to estimate 24 cases treated per healthcare worker trained at tertiary facility per year. We ignored shared capital costs like training of trainers of trainers and printing of materials.

3.2.9.3 Calculation of average cost-utility ratio (ACER) and incremental cost-effectiveness ratio (ICER).

From capital costs and effectiveness (DALYs) obtained, we calculated both the ACER and the ICER. The Average Cost- Effectiveness Ratio represents the total cost of the program per treatment alternative divided by its clinical outcome to give a ratio representing the cost per specific clinical outcome gained independent of comparators and was calculated using the following equation.

Equation 6

ACER= program cost per intervention/ clinical outcomes of intervention

The incremental cost-effectiveness ratio (ICER) was calculated to determine the additional cost and effectiveness gained comparative to alternative treatments.

Equation 7

ICER= costs of intervention A-costs of intervention B/ effect of A – Effect of B

3.2.10 Decision analytic modeling

A decision analytical tree was drawn using TreePlan® to reflect the treatment seeking options accessible to a care giver with a severely ill child in remote rural areas (Figure 2 to 5). The options were a visit to a community healthcare worker; a visit to a primary health facility defined as a dispensary or a health center (with no inpatient facilities); directly seeking care at a tertiary health facility defined as a district hospital or regional referral hospital; and seeking no treatment.

A child seeking treatment from a community healthcare worker would be given either rectal pre-referral treatment or no treatment according to availability of rectal artesunate and thereafter referred to a tertiary health care facility for inpatient services. We assumed equal probability of receiving or not getting rectal artesunate.

Those seeking treatment from a primary health care facility would get either pre-referral or no pre-referral treatment. Those who get per-referral would be put on rectal artesunate, or parenteral interventions of i.m quinine, i.m artesunate or get no treatment. We assumed equal probability of getting rectal artesunate or parenteral options, and also for getting either i.m quinine or i.m artesunate for those put on parenteral pre-referral treatment. These children would then be referred to a tertiary health care facility for inpatient services. We assumed that at the tertiary facility all severe malaria cases will be admitted and given inpatient treatment as per the national malaria treatment guidelines (10). The last option was no treatment due to lack of access to care or delay in seeking care. The probabilities used in the decision tree for pre-referral interventions are presented in appendix 7.

The following assumptions were made in the model; we assumed that treatment will be sought within 24hours of onset of severe illness for it has been shown that mortality for severe malaria is high after this period and therefore it would be difficult to model effectiveness for pre-referral beyond 24hours (13,84,85). We assumed a patient referred from primary level facility to a secondary facility will get appropriate treatment within 24hours of the referral as this period gives the highest bioavailability and therefore effectiveness of rectal artesunate (14,16).

We also assumed that pre-referral treatment would be given only once at point of contact and thereafter patients would be referred. Referral completion or compliance was assumed to be similar from either the community health care worker or primary health facility and was estimated at 67.1% (34). We made this assumption because studies have shown that those with severely ill children were most likely to adhere to referral advice irrespective of other factors (45,46). In the base model we made the following assumptions, the availability of pre-referral treatments will be 50% with the CHW and 80% at facility. The impact of these assumptions was evaluated in sensitivity analysis.

We also modeled the comparative cost-utility of the different pre-referral treatments as a sub tree of the main model at the primary health facility (Figure 5). We assumed equal probability of receiving rectal artesunate, i.m artesunate and i.m quinine. A summary of the assumptions is presented in Table 6.

Table 5 Parameters and probabilities used to model cost effectiveness of pre-referral treatments.

Model assumption	Point distribution
Referral compliance	67.1%
Availability of pre-referral treatment at primary facility	80%
Probability of getting any pre-referral treatment.	50%
Probability of getting either i.m artesunate or i.m quinine	50%

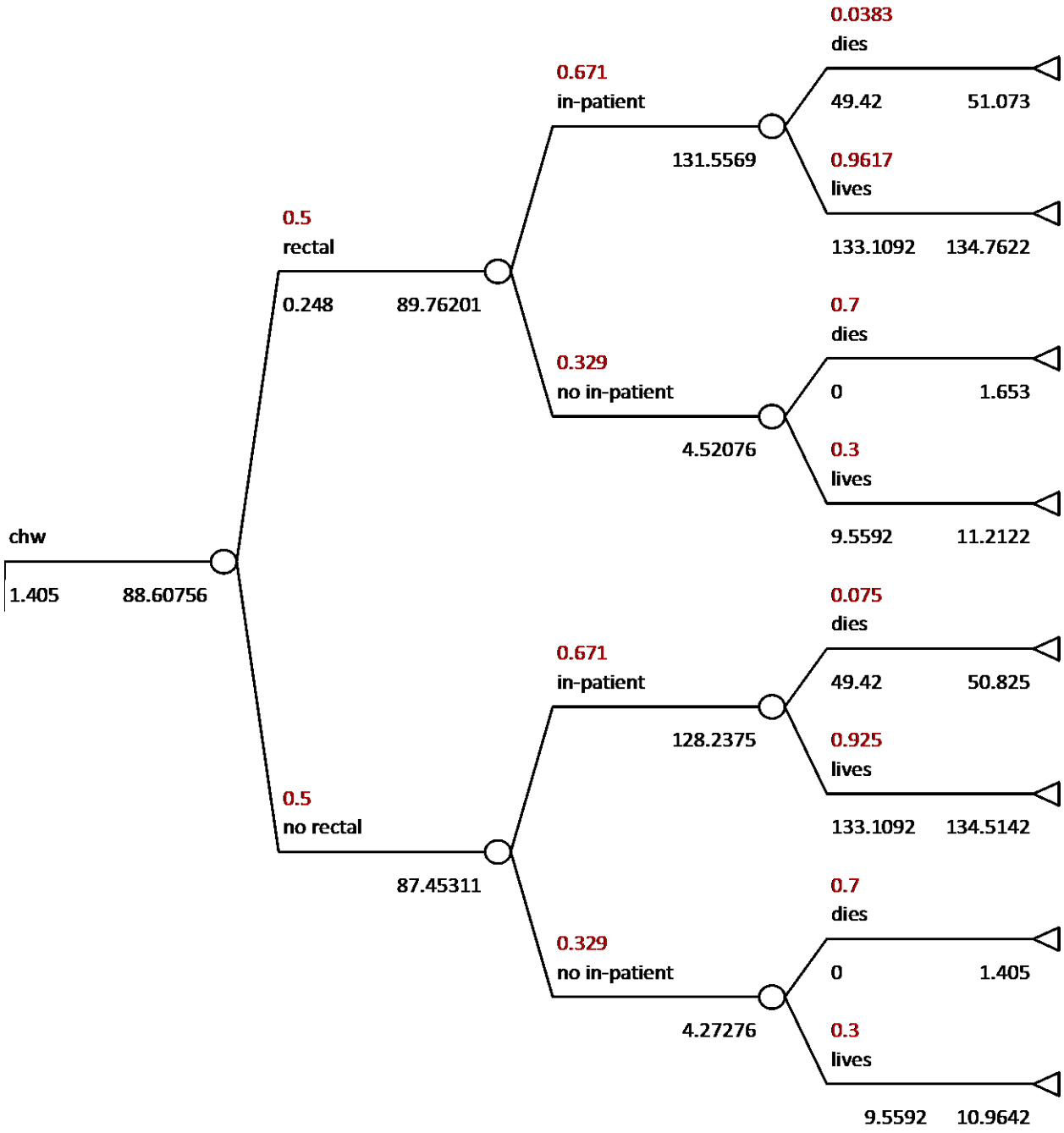

Figure 2 Decision tree to assess cost-utility of pre-referral rectal artesunate provided by Community healthworkers.

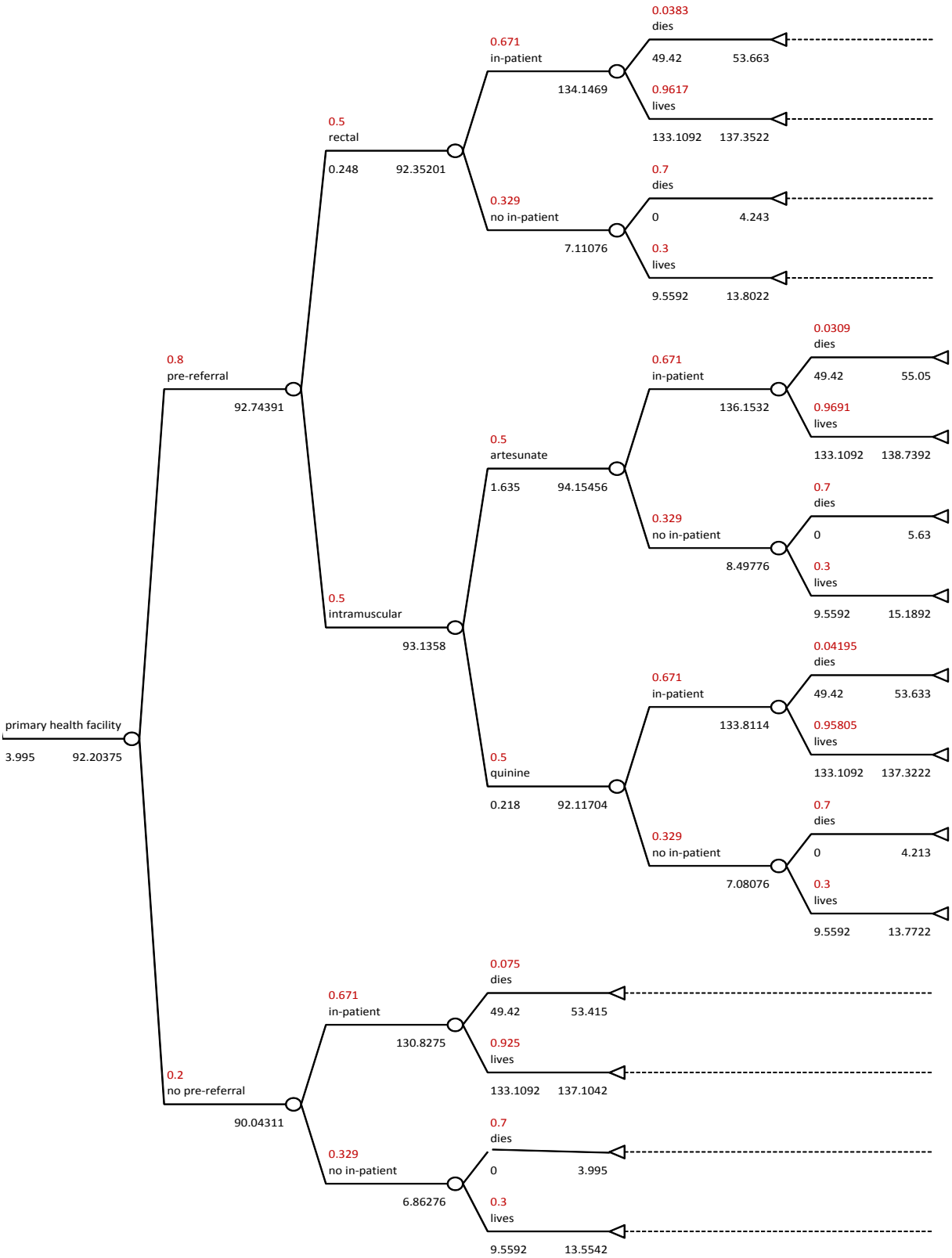

Figure 3 Decision tree for pre-referral treatments at primary facility

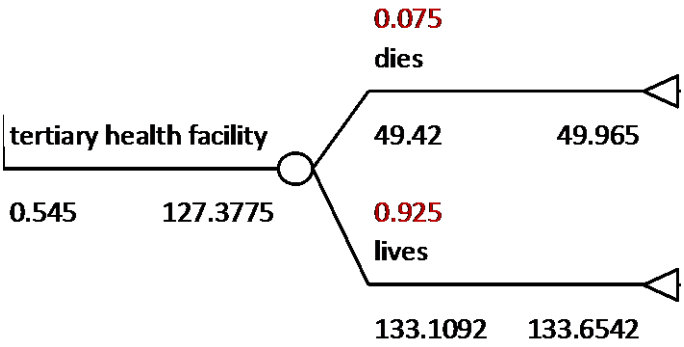

Figure 4 Decision tree for cost-utility of a tertiary facility

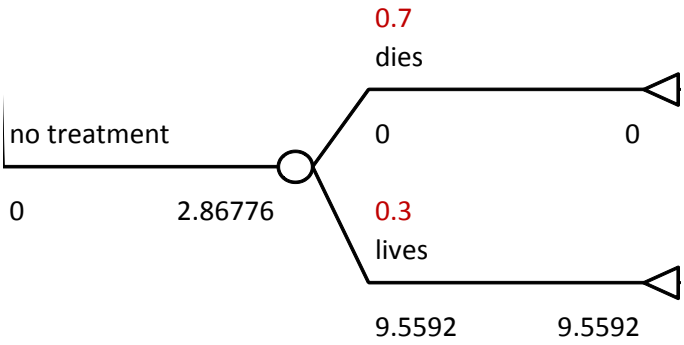

Figure 5 Decision tree for cost-utility of seeking no treatment.

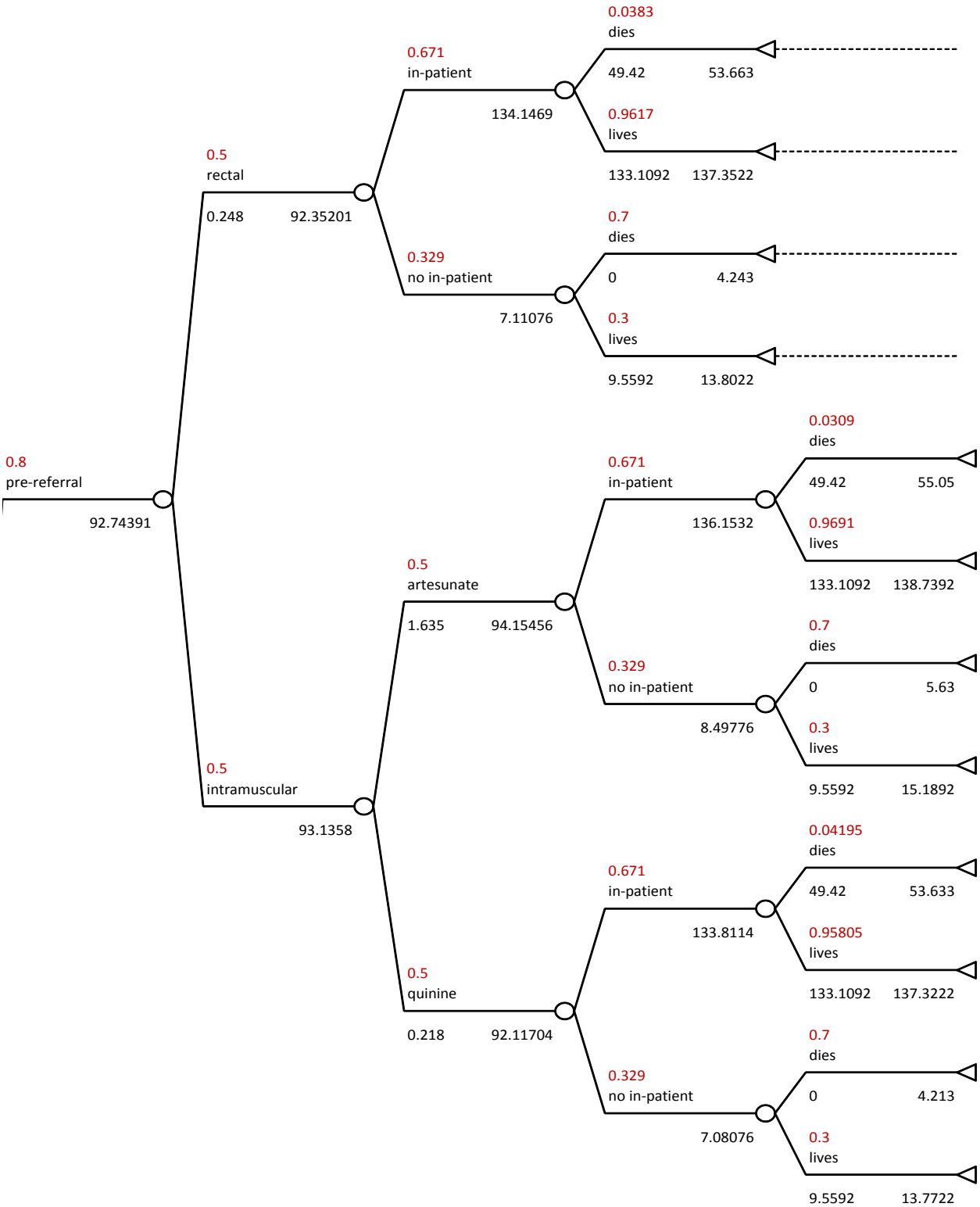

Figure 6 Decision tree to assess the comparative cost-utility of pre-referral rectal artesunate, i.m artesunate and i.m quinine

3.2.11 Sensitivity analysis

One way analysis using Microsoft excel was done to analyse the uncertainties in the model variables and to assess the robustness of the results. We varied those variables that were important with regards to health outcomes, including life expectancy, referral compliance and inpatient case fatality rate.

3.3 Data Management and Quality Assurance

3.3.1 Data Management

All data from the cost studies and the key informant interviews was entered into a MS-Excel Database and a MS Word document respectively. Data cleaning and validation was performed to achieve a clean dataset. Back up files were stored in a CD and flash disk and updated regularly to avoid loss or tampering.

3.3.2 Quality Assurance

The data collection tools and the interview guide were evaluated using a pilot study. The findings of the study were used to modify the data collection tools. Two research assistants were trained on research data collection methods, and the level of training considered sufficient if the degree of inter data collector agreement was 85%. The two research assistants were present during the key informant interview. One was writing the proceedings of the interview, while the other orally conducted the interview. Interviews were transcribed on the same day of the interview so as to capture all non-verbal and verbal interactions during the interview and to avoid loss of information. A codebook was used to guide the coding and identification of themes. The research progress was monitored daily by the study supervisors.

CHAPTER FOUR

4.0 RESULTS

4.1 Program costs obtained from the key informant interviews

We interviewed a total of ten managers from the identified organizations involved in procurement and implementation of malaria case management. Of the ten personnel interviewed, four were from Kenya Medical Supplies Agency, four from National Malaria Control Program, one from AMREF and one from CHAI. Those interviewed included 4 pharmacists, 1 medical doctor, 3 procurement managers, and 2 operations managers.

The costs obtained from key informant interviews were used in the cost-utility analysis and are presented in Table 6.

Table 6 Program level costs obtained from key informant interviews

Item	**Cost ($)**
Training of trainers for case management(per person)	552.2
Training of healthcare workers (per person)	496.9
Training of CHWs (per person)	25.1
Monitoring and evaluation	96625.4 (62633- 195890.8)
Printing of guidelines (each)	12.4
Printing of manuals (each)	25.9
Acquisition costs	
I.m artesunate (per vial)	1.49-1.62
I.m quinine (per vial)	0.20
Rectal artesunate(estimated)	0.105-0.350
Procurement (% of acquisition cost)	2%
Warehousing (% of acquisition cost)	3%
Distribution (% of acquisition cost)	5%
Personnel monthly salaries	
CHW	41.4
HCW (nurse)	1656.3

CHW=community healthcare worker, HCW= health care worker

From the key informant interviews we identified themes which included: selection, quantification, procurement, funding, implementation of guidelines inventory management and perceptions on rectal artesunate as shown in Table 7.

Table 7 Themes identified from key informant interviews

Codes	Themes
1	Selection
2	Quantification
3	Procurement
4	Funding
5	Implementation costs
6	Inventory management
7	Perceptions on rectal

4.1.1 Selection of drugs for the treatment formulary

From the interviews we identified that selection of new products and interventions is done through the Ministry of Health in conjunction with various donors.

"*For implementation of new interventions the Ministry of Health sets up a technical working group to look at the existing evidence versus the current epidemiological state in the country in regards to efficacy of current interventions, resistance as well as cost implications"*. The technical working group is made up of stakeholders from different organizations including funding organizations.

The recommendations of the working group are then forwarded to the Ministry for review by a Ministerial Committee. The process of selection however may be influenced by donor organizations even when country specific evidence and data on the new interventions are missing.

We identified quantification of medicines as a theme from the key informant interview. Quantification is important in that it ensures constant supply and provision of medicines but it also has a direct impact on cost. At the national level, quantification of antimalarial drugs is done by a committee involving the Ministry of Health, the National Malaria Control Program as well as KEMSA.

Any procurement of antimalarial drugs is hinged on the consumption data generated from the user facilities. The user facilities send consumption reports to KEMSA who aggregate the reports and then provide them with the required quantities.

'There is usually a challenge with quantification especially with new interventions and this sometimes leads to stock-outs and even expiries. Since consumption data is used for quantification, new interventions do not have this data and therefore it is difficult to quantify and project their use'.

After the quantification process at the national level, tenders are then sent out by KEMSA for procurement. The procurement is done from WHO approved manufacturers only. This was reported to causes long lead times and delays in supplies as there are very few pre-qualified manufactures. It was reported that this also leads to increased costs as the demand is usually higher than the supply. Antimalarials procured by the Government attracted a tendering charge of 2% of the total value procured to cover advertising costs. The acquisition price of these commodities usually includes the shipment costs incurred by the suppliers.

There are other agencies also involved in procurement of antimalarials apart from the Government of Kenya; these include donors like CHAI, the Global Fund and the United States Agency for International Development (USAID).

It was reported that the malaria sector is heavily funded by donors due to the global efforts to eradicate malaria. There are therefore different organizations meeting different activities and objectives that are involved in funding malaria activities. Some of these organizations include; WHO, UNICEF, Global Fund, CHAI, and USAID. The Government of Kenya through the national malaria control program engages the different donor organizations to ensure streamlined operations and coordinated activities. The funding organizations therefore play an important role in ensuring sustainability of the fight against malaria. Currently, CHAI is involved in provision of i.m artesunate to Government facilities and the Global Fund funds most of the program activities.

Program implementation costs identified from the key informant interviews included; training of health care workers, training of community healthcare worker through the community strategy managed by AMREF, monitoring and evaluation of the uptake and effectiveness of malaria interventions. It was noted that advertising costs are not usually incurred for severe malaria since the target group is health care workers and not the public. Another cost identified was the cost that may be associated with launching of a new product in this case that associated with introduction of rectal artesunate as a treatment alternative for pre-referral treatment. The implementation costs were a result of the required reach and target of number of healthcare workers and health facilities. The trainings carried out for updates on new malaria interventions target both private and public facilities with approximately 6000 health workers trained annually for malaria case management.

The CHW strategy is a country wide community based healthcare aimed at providing ease of access to healthcare to remote rural communities. This strategy is donor funded and implemented by AMREF. In this strategy, each sub-location acts as a community unit with an estimated number of 10-50 CHWs depending on population and expanse. This study found out that there are about 711community units in the country. Each CHW earns a maximum of $41.4 monthly working 2 hours a day for five days. The number of CHWs in western Kenya was estimated at 7,100 with a total yearly case load for malaria of 170,000 patients. The CHWs are supervised by community health extension workers (CHEWs) who are linked to the nearest facility to facilitate referrals.

One CHW is linked to approximately 100 households and they have to visit each household at least once a month. They offer basic healthcare interventions including but not limited to uncomplicated malaria, reproductive health, family planning and sanitation. The CHWs undergo periodic trainings on malaria case management updates.

This strategy was attributed to decrease 50% of case loads at the health facilities. However, it was difficult to estimate the referral compliance from the estimated cases by CHWs due to lack of records and feedback mechanisms from patients once referred. To address this issue the project aims to strengthen supervision and institute assisted referrals where the health facility provides feedback once a patient completes the referral process.

This study found out that inventory management for antimalarial is carried out by KEMSA who manage the procured stocks and also distribute and supply facilities. The procured drugs are warehoused at KEMSA at a rate of 3% of the value of the goods, and a rate of 5% for distribution.

The respondents were of the opinion that though rectal artesunate has been included in the treatment guidelines; there were barriers of perception against its use. These were due the mode and route of administration which is culturally frowned upon especially in the rural areas. It was therefore stated that it may require a lot of community education to create awareness and acceptability. It was also argued that local studies on its effectiveness should be undertaken to clear any contentions that may arise from its use

4.2 Comparison of the cost-utility of pre-referral treatment for severe malaria in children by healthcare providers.

From Table 8, provision of pre-referral treatment by CHWs has the potential to averting 12405.7 DALYs at a cost of $88.6 per child. The option of pre-referral treatment at primary health facility has the potential of averting 12613.2 DALYs at a cost of $92.2 per child while going straight to a tertiary facility without pre-referral treatment has the potential of averting 18152 DALYs at a cost of $127.0 per child.

Table 8 The cost-utility of pre-referral antimalarial treatments by healthcare provider.

	CHW	PHF	THF	NO TREATMENT
DALYs	7717.2	7509.8	2183.4	20123.0
DALYs averted	12405.7	12613.2	18152	-
cost ($)	88.6	92.2	127.0	2.9
CER ($)	7.1	7.3	7.0	-
ICER ($)	0.29	0.06	0.05	-
Probability of dying	0.268	0.261	0.07	0.75

CHW= Community healthworker,PHF=primary health facility,THF=tertiary health facility,ICER=incremental cost-utility ratio,CER=cost-utility ratio,

The most cost-effective option was a direct visit to a tertiary health facility with a CER of $7.0, though this was comparable to use of a CHW with a CER of $7.1 and primary health facility with a CER of $7.3. Receiving no form of treatment option was the cheapest option with a CER of $2.9, with just the attendant costs of malaria complications. It was however, associated with the largest disease burden of 20123 DALYs.

4.2.1 Sensitivity analysis

We conducted a one way sensitivity analysis to assess the effects of uncertainties of variables. The results are presented in Table 9. Compliance to referral advice and changes in the life expectancy had the greatest effect on cost-utility with full compliance being more cost effective than low referral uptake. High life expectancy was also more cost effective than a low life expectancy.

Table 9 Sensitivity analysis to assess the effects of uncertainties of input variables on cost-utility of pre-referral treatment at different levels of healthcare.

Compliance (1%-100%)			
	CHW	PHF	THF
DALYs	18274.3-7358.5	18243.8-7220.0	-
DALYs averted	1848.7-12764.5	1879.2-12902.9	-
Cost($)	15.9-129.9	19.9-133.8	-
CER($)	8.6-7.3	10.6-7.1	-
ICER($)	0.38-0.28	0.09-0.06	-
Inpatient case fatality rate (5%-10%)			
DALYs	7358.5-8076	7220.0-7799.6	1323-2617
DALYs averted	12764.5-12047	12902.9-12323	18657.2-17505
Cost($)	89.3-87.2	93.0-91.3	129.5-125.3
CER($)	6.9-7.2	7.0-7.4	6.9-7.3
ICER($)	0.28	0.06	0.06
Life expectancy(40-70yrs)			
DALYs	64162-7919.4	6243.8-7706	1643-2020.2
DALYS averted	10306.1-12732	10778.1-12945	15078.1-18631.3
Cost($)	88.3	92.2	127.3
CER($)	8.6-6.8	8.7-7.0	8.4-6.8
ICER($)	0.35-0.28	0.07-0.06	0.07-0.05
Neurological sequelae (0.022-0.24)			
DALY s	7711-7858.4	7505-7652.4	1963-2148.9
DALYS averted	12409-12322	12616-12528	18156.9-18031.9
Cost($)	88.3	92.2	127.0
CER($)	7.1	7.3	7.0
ICER($)	0.29	0.06	0.06

CER=Cost-utility ratio, ICER=incremental cost utiliy ratio,DALYS=Disability adjusted life years

4.3 Comparative cost-utility of rectal artesunate against i.m artesunate and i.m quinine.

The results of the base model (Fig 6), using the point estimates obtained, for the comparative cost-utility of pre-referral treatments are presented in Table 10. Intramuscular artesunate had the least number of deaths [20] and averted most DALYs [5898] as opposed to both i.m quinine [28], [5685) and rectal artesunate [25], [5756]. The cost effectiveness of i.m artesunate was $15.5 per DALY averted, i.m quinine was $16.2 per DALY averted while rectal artesunate was $16.0 per DALY averted.

This shows that in a primary health facility, i.m artesunate was the most cost effective. However, i.m artesunate was more costly at $ 94.2 per case treated. The incremental cost ranged from 0.06-0.03 and i.m artesunate had the highest incremental cost.

Table 10 Comparative cost-utility of pre-referral rectal artesunate, intramuscular artesunate and quinine.

	i.m artesunate	i.m quinine	rectal artesunate
Deaths	20.7	28.1	25.6
DALYs	625.9	838.3	767.5
DALYs averted	5898.3	5685.9	5756.763
Cost($)	94.2	92.1	92.4
CER($)	15.5	16.2	16.0
ICER($)	0.005	0.003	0.003

CER=cost-utility ratio, ICER= incremental cost-utility ratio. i.m=intramuscular

Sensitivity analysis of the effects of input variables on the cost-utility of the interventions is presented in Table 11. The cost-utility was quite sensitive to referral compliance and life expectancy.

Table 11 Sensitivity analysis to assess effects of uncertainties of variables on comparative cost-utility of pre-referral treatments

Personnel salaries (2.58-4.31)			
	i.m artesunate	**i.m quinine**	**rectal artesunate**
Deaths	20.7339	28.13168	25.66575
DALYs	625.9277	838.2697	767.4891
DALYs averted	5898.324	5685.982	5756.763
Cost($)	93.3-95.0	91.2-92.9	91.5-93.2
CER($)	15.4-15.6	16.0-16.4	15.9-16.2
ICER($)	0.005	0.003	0.003
Hospital length of stay(3-8 days)			
Deaths	20.7	28.1	25.7
DALYs	624.7	837.1	766.3
DALYS averted	5898.6	5686.2	5757
Cost($)	94.2	92.1	92.4
CER($)	15.5	16.2	16.04
ICER($)	0.005	0.003	0.003

Table 11 Continued.....Sensitivity analysis to assess effects of uncertainties of variables on comparative cost-utility of pre-referral treatments

Referral compliance (0.1-1%)			
	i.m artesunate	**i.m quinine**	**rectal artesunate**
Deaths	3.09-30.9	4.1925-41.9	3.825-38.2
DALYs	119.7-917.6	151.4-1234	140.9-1128.5
DALYs averted	17674.9-(-887.1)	17643.2-(-1204)	17653.8-(-1098)
Cost($)	21.3-136.2	19.8-133.8	19.8-134.2
CER($)	0.8-(-153.5)	1.1-(-111.2)	1.1-(-122.2)
ICER($)	0.0008-0.048	0.0002-0.021	0.0003-0.024
Efficacy of parenteral interventions against rectal artesunate (0.5-1.5)			
Deaths	37.9-13.3	37.9-13.3	25.6
DALYs	1121.3-413.5	1121.3-413.5	767.5
DALYs averted	5402.8-6110.6	5402.8-6110.6	5756.8
Cost($)	92.7-94.7	91.3-93.4	92.4
CER($)	16.6-15.1	16.9-15.3	16.04
ICER($)	0.0038-0.006	0.0018-0.004	0.003
Inpatient case fatality rate (0.05-0.10)			
Deaths	13.8-27.6	18.8-37.5	17.1-34.2
DALYs	427.5-824.3	569.1-1107.4	521.9-1013.1
DALYs averted	6096.7-5699.9	5955.1-5416.8	6002.3-5511.2
Cost($)	95.5-94.4	93.7-92.2	93.9-92.5
CER($)	15.2-16.0	15.7-17.0	15.6-16.8
ICER($)	0.0047-0.007	0.0018-0.004	0.002-0.004
Incidence of neurological sequelae (0.02-0.24)			
Deaths	20.7	28.1	25.7
DALYs	616.9-814.7	829.3-1025.7	758.5-955.4
DALYs averted	5900.2-5857.9	5687.8-5647	5758.6-5717.3
Cost($)	95.01	92.9	93.2
CER($)	15.58-15.69	16.34-16.46	16.18-16.30
ICER($)	0.005	0.003	0.003
Life expectancy (40-70 yrs)			
Deaths	20.7	28.1	25.7
DALYs	525.2-641.5	701.6-859.5	642.8-786.9
DALYs averted	4999.1-6175.5	4822.7-5957.6	4881.5-6030.2
Cost($)	94.2	92.1	92.4
CER($)	18.8-15.1	19.1-15.5	18.9-15.3
ICER($)	0.006-0.005	0.003-0.002	0.004-0.003

CER=cost-utility ratio, ICER=incremental cost-utility ratio,

CHAPTER FIVE

5.0 DISCUSSION

From the qualitative study we observed that the key determinants for implementation of new interventions are selection and availability of funds that will ensure sustainable supply. Selection is a process that entails choosing interventions to be used. This process is very rigorous and requires evidence based approach to choosing medical interventions to be provided by the Ministry of Health. Before adoption of new interventions, local research data is carried out to determine the applicability of the intervention in the population. This research centers on efficacy and effectiveness compared to already existing interventions. Where local data is lacking but the benefits of the new interventions are clearly demonstrated beyond doubt, then it could be adopted.

Perceptions of the rectal route of administration were identified as a potential challenge in the adoption of rectal artesunate. Most respondents were in agreement that it may be difficult to ensure its uptake in rural areas of high malaria endemicity due to cultural beliefs. However, studies done show that rectal artesunate could be successfully utilized by these communities depending on varying factors not least the severity of the illness. Also with healthcare education targeting these communities to create awareness and impress upon them the importance of rectal artesunate in combating progression of severe malaria there is a chance of increased uptake (48–51).

Another major finding was the large proportional contribution of donor funding to the malaria program viz a viz Government funding (6). Government allocation of funds for health care provision does not meet the health care needs of the population in most sub- Saharan countries of which Kenya is one of them. This more so in the National Malaria Control program where there are multiple organizations involved in program activities (6,18). Funding, therefore, remains one of the single most important factors with adoption of new interventions. With inadequate funding, it is difficult to adopt new interventions however effective they are if they cost more than existing interventions especially in resource limited settings (86–88).

The high dependence on external funding is not sustainable especially if the donor organizations in case these organizations withdraw from the program. Donor agencies therefore play a key role in adoption and implementation of new treatment interventions.

From the cost-utility analysis, the most cost effective treatment option was seeking treatment in a tertiary health facility. This option was however the most costly and this finding was in line with a costing study done in Kenya (22). Seeking treatment directly at a health facility with inpatient services within 24 hours decreases the duration to initiation of treatment and has better health outcomes (4,84,85). Therefore, a tertiary health facility, even though more costly, gives the best health outcomes and should ideally be the first point of contact for those with severe malaria. However, capital costs of putting up a tertiary facility in rural areas are very prohibitive.

The use of community health care workers was slightly more cost effective and less costly than seeking treatment at a primary health facility. It was however associated with more DALYs and less DALYs averted; overall, however, the differences are not that marked. A recent study in low income countries suggest that the use of CHWs could be as cost effective as primary care workers given there are tangible and non-tangible benefits offered by CHWs (89). Other studies have also shown that the use of CHWs is a cost effective option especially where there is a high uptake and utilization of community strategy as well as adherence to referral advice by care givers. A system whereby there is enhanced supervision and strengthening of community strategy will ensure that this option remains cost effective in rural remote areas with little access to healthcare facilities especially in relation to direct patient costs (29,38,42,75). The difference in cost-utility between CHWs and primary health facility could be explained by differences in the salaries, number of cases and hours of work of a CHWs and a health care worker. This is highlighted by incremental costs associated by CHWs which are twice those of a primary health care facility.

Referral compliance refers to patients seeking inpatient care after pre-referral intervention. Compliance had a high impact on the DALYS and DALYS averted. With increased referral compliance the DALYS averted increased significantly meaning that more cases survived.

The cost-utility analysis was sensitive to referral compliance with both CHWs and at primary healthcare facility.

The effect of compliance on cost-utility was similar to a study done on cost-utility of rectal pre-referral treatments (24). Strategies that may increase referral compliance include closer support supervision of CHWs, and CHW assisted referral whereby there is a linkage to a health facility with possible feedback mechanisms to confirm adherence to referral advice for follow up. Making access to healthcare facilities easier by providing transport and other measures like refunds for those with severely ill children may improve referral compliance.

Since the cost-utility of the pre-referral interventions is highly sensitive to compliance, there may also be need to empower CHWs to give repeated doses of rectal artesunate for those patients who are unlikely to seek inpatient services. A study done in Uganda showed that rectal artesunate was effective when used for treatment. It caused fewer mortalities than quinine in severely ill children (70). A drawback to this option however, may be the lack of specialized care options and risk associated with malaria complications when children are managed outside tertiary healthcare facility.

The comparison between pre-referral antimalarial interventions, administered at primary facility, indicated that i.m artesunate averted more DALYS. This finding is consistent with studies which show that both rectal and i.m artesunate have a higher efficacy and prevent more deaths than quinine with respect to parasite clearance time within 24hours and even mortality after 24hours of administration (14,16,70). Intramuscular artesunate, though most cost effective, was the most costly of the treatment options. Given the fact that it requires skilled administration and cannot be given by CHWs, i.m artesunate may be less cost effective than rectal artesunate. We also did not consider hidden costs associated with both of the two parenteral interventions. The cost-utility of i.m quinine and that of rectal artesunate were similar, and given the advantages of rectal artesunate with regards to efficacy as well as ease of use, by community health care workers, rectal artesunate would be more cost effective for pre-referral treatments.

5.1 Implications for policy

This study can be used to inform policy makers the need for rectal artesunate for management of severe malaria particularly in areas where geographical access to both primary and tertiary health facilities may be limited. Though there is no recent Kenyan study that provides clinical evidence of efficacy of rectal artesunate, it has been evaluated in Tanzania and Uganda (13,70). Though the Ugandan study looked at the curative effects of repeated rectal administration, the findings of these two studies may apply to the Kenyan situation because of similarities in socio-demographic, cultural and disease epidemiological profiles.

5.2 Study limitations

We were unable to obtain local prices for rectal artesunate since it is not yet locally available, specifically at program level. We therefore used prices as obtained from a price review by WHO and UNICEF done in 2009 (79). There was no information from the key informant interviews or any local study on the level of referral compliance specifically for severe malaria; we therefore used referral rates from literature (34). We were also unable to interview all the relevant organizations involved in malaria control program activities and therefore our incremental costs obtained may not represent the true picture of all costs especially those incurred by donors. In this study, we used the same case fatality rate for those who sought no treatment and those who had pre-referral treatment but did not seek inpatient treatment. It is probable that these two groups had different case fatality rates. We also did not consider scenarios where a patient may have used all the available options of health care services by first going to a CHW then primary and eventually tertiary facility.

6.0 CONCLUSIONS AND RECOMMENDATIONS

6.1 Conclusion

The use of CHWs in provision of rectal pre-referral treatment is a cost effective option when compared to the provision in a primary health facility. The benefits and advantages of CHWs would only be realized however where there is a clear strategy to enhance uptake of CHWs services and also those that ensure full compliance to referral advice. The ideal situation however remains access to tertiary health facilities. This, though, remains a long term options given low resource availability.

6.2 Recommendations for future research and policy

We recommend the strengthening of community strategy in regards to uptake and compliance to referral advice, for pre-referral treatment. This should also be accompanied by strict supervision and adherence to treatment guidelines requiring testing using RDTs before administration of any antimalarials to avoid irrational use. A pilot study on the use of CHWs to provide pre-referral treatment for severe malaria in children less than 5 years in hard to reach rural areas should be undertaken. This would provide evidence of effectiveness and identify potential challenges in scaling up the program.

A platform for information and data sharing by organizations involved in malaria policy making and implementation that would facilitate policy analysis and monitoring and evaluation should be created.

Given that malaria infections can occur more than once in a child less than 5 years, a cost-utility study based on a Markov model could be done to determine effects of both pre-referral treatment and curative applications of rectal artesunate.

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APPENDICES

Appendix 1: Summary of thematic codes generated per interviewee from key informant interviews

	Thematic Code 1	Thematic Code 2	Thematic Code 3	Thematic Code 4	Thematic Code 5	Thematic Code 6	Thematic Code 7
Interview number	Selection	Quantification	Procurement	Funding	Implementation cost	Invention management	Perceptions
1		✓	✓	✓		✓	✓
2		✓	✓			✓	
3			✓			✓	
4		✓	✓	✓		✓	
5			✓	✓		✓	
6	✓	✓	✓	✓	✓	✓	
7	✓	✓	✓	✓	✓	✓	✓
8	✓	✓	✓	✓	✓	✓	✓
9	✓	✓	✓	✓	✓	✓	✓
10			✓	✓	✓	✓	✓
%	40	70	100	80	50	100	50

Appendix 2: Key informant interview guide

Introduction

My name is Vivian Masiga Rakuomi, a pharmacist undertaking a Masters course in Pharmacoepidemiology and Pharmacovigilance at the University of Nairobi.

Purpose of the interview

I am carrying out a study on the cost-utility of pre-referral malaria treatment, at program level and would wish to know details pertaining to procurement and implementation costs of antimalarial interventions.

General background

Would you please tell me your position in the organization and how long you have worked at this organization?

Part A: Respondent's characteristics

Age_____Position in Organization_____

Number of years worked in organization_____

Years worked in current position_____

Part B: Interview topics

a) Assessing cost of antimalarial drugs

1) The malaria program has previously implemented new therapeutic agents for the management of malaria (artemesinin based drugs).

   Do you have any documents on past expenditure in the program with regards to implementing changes in the guidelines, contracting people to train health workers and expenditure on antimalarials over the past 5 years? (Ask to peruse documents)

2) Where can this information be obtained?

3) Do you have any idea on how much was spent on the following cost categories in introducing these interventions?

Item	**Unit**	**Each**	**Cost**
Tender for consultancy			
Training - trainers & trainees -printing of materials			
Monitoring & Evaluation of uptake -how was it done(in-house/contracted)			
Advertising -No. of adverts(on radio/TV) - printing of materials (no. & cost)			
Printing of guidelines			

4) Apart from these cost categories used in implementation, what other cost categories were incurred?

5) If you were to implement a new intervention such as introduction of rectal artesunate; what type of cost will be incurred (as per the above categories)?

6) What criteria were used to arrive at the total costs of the implementation program?

7) Where do you procure antimalarial commodities and what are the costs incurred from the tendering, shipment and final delivery to the end user?

Item description	**Im quinine**		**Im artesunate**	
	Unit	**cost**	**unit**	**cost**
Acquisition price				
Price variation (discounting)				
Warehousing				
Shipment				
Inventory management				
Inventory losses				
Taxation and tariffs				
Distribution				

8) What percentage constitutes wastage costs?

Are there any other factors associated with the cost of antimalarial drugs apart from above questions? If yes, explain.

9) Who bears non-drug related costs?

10) Do you have any more information concerning procurement that we have not covered that may help in the study?

b) Challenges

What are the challenges faced in procuring these drugs?

Probe on;

- Finances
- Infrastructure
- International treaties and patent

What would be the challenges if a new agent like pre-rectal artesunate is added to the guidelines?

c) Solutions

What would you do to address these challenges, given the opportunity?

Conclusion

Thank you for your time and willingness to participate in the study.

Appendix 3: Informed consent for key informant interview

TITLE OF THE STUDY

ASSESSMENT OF THE COST-UTILITY OF PRE-REFERRAL MALARIA TREATMENT USING DECISION ANALYTIC MODELING

Institution: Department of Pharmacology and Pharmacognosy, School of Pharmacy,

University of Nairobi, P.O BOX 30197-00400, Nairobi

Investigator: Dr Rakuomi Masiga Vivian, P.O BOX, 30197-00400, Nairobi .

Supervisors:

Dr F.A Okalebo,
Department of Pharmacology and Pharmacognosy

Dr. S. N Ndwigah
Department of Pharmaceutical Chemistry

Ethical Approval

Kenyatta National Hospital/ University of Nairobi Ethical and Research Committee, P.O BOX 20723-00100, Nairobi. Tel 2726300/2716450 Ext 44102

INTRODUCTION

In this study, am evaluating the costs and effecitiveness of pre-referral antimalarial drugs. Pre-referral antimalarial treatment seeks to combat the delay in access and the progress of severe malaria that contributes to mortality. Though pre-referral rectal artesunate has been included in the Kenyan treatment guidelines for malaria, its cost-utility has not been compared to current parenteral treatments in the Kenyan setting.

PURPOSE OF THE STUDY

The purpose of the study is to assess and evaluate the acquisition costs of the alternative pre-referral antimalarial drugs and model their cost-utility from the provider perspective.

Permission is requested from you to participate in this study. You should understand the following general principles which apply to all participants in a medical research:

i. Your agreement to participate in this study is voluntary.

ii. You may withdraw from the study at any time without necessarily giving a reason for your withdrawal.

iii. After you have read the explanation, please feel free to ask any questions that will enable you to understand clearly the nature of the study.

PROCEDURE TO BE FOLLOWED

With your permission, I will engage in a discussion procurement processes and costs involved in acquisition of the antimalarial drugs. I will take some notes using a pen and paper. All the information given will be handled with confidentiality and will only be used for the purpose of this study.

RISKS

There will be no risks involved in this study.

BENEFITS

There will be no direct benefits to you but the findings will be useful in informing policy on pre-referral treatment implementation in Kenya.

ASSURANCE OF CONFIDENTIALITY

All information obtained from you will be kept in confidence. At no point will your name be mentioned or used during data handling or in any resulting publications. Codes will be used instead.

CONTACTS

In case you need to contact me, my academic department or the Kenyatta National Hospital/ University of Nairobi Ethics and Research Committee concerning this study please feel free to use the contacts provided above.

I request you to sign the consent form attached.

Appendix 4: Consent form

ASSESSMENT OF THE COST-UTILITY OF PRE-REFERRAL MALARIA TREATMENTS USING DECISION ANALYTIC MODELING

I, the undersigned, willingly agree to participate in this study, the nature and purpose of which have been fully explained to me by the investigator. I understand that the information gathered will be used for the purposes of this study only and maximum confidentiality will be maintained**.**

Respondent …….

Sign…… Date…….

Witness (Research assistant)……

Sign…… Date…….

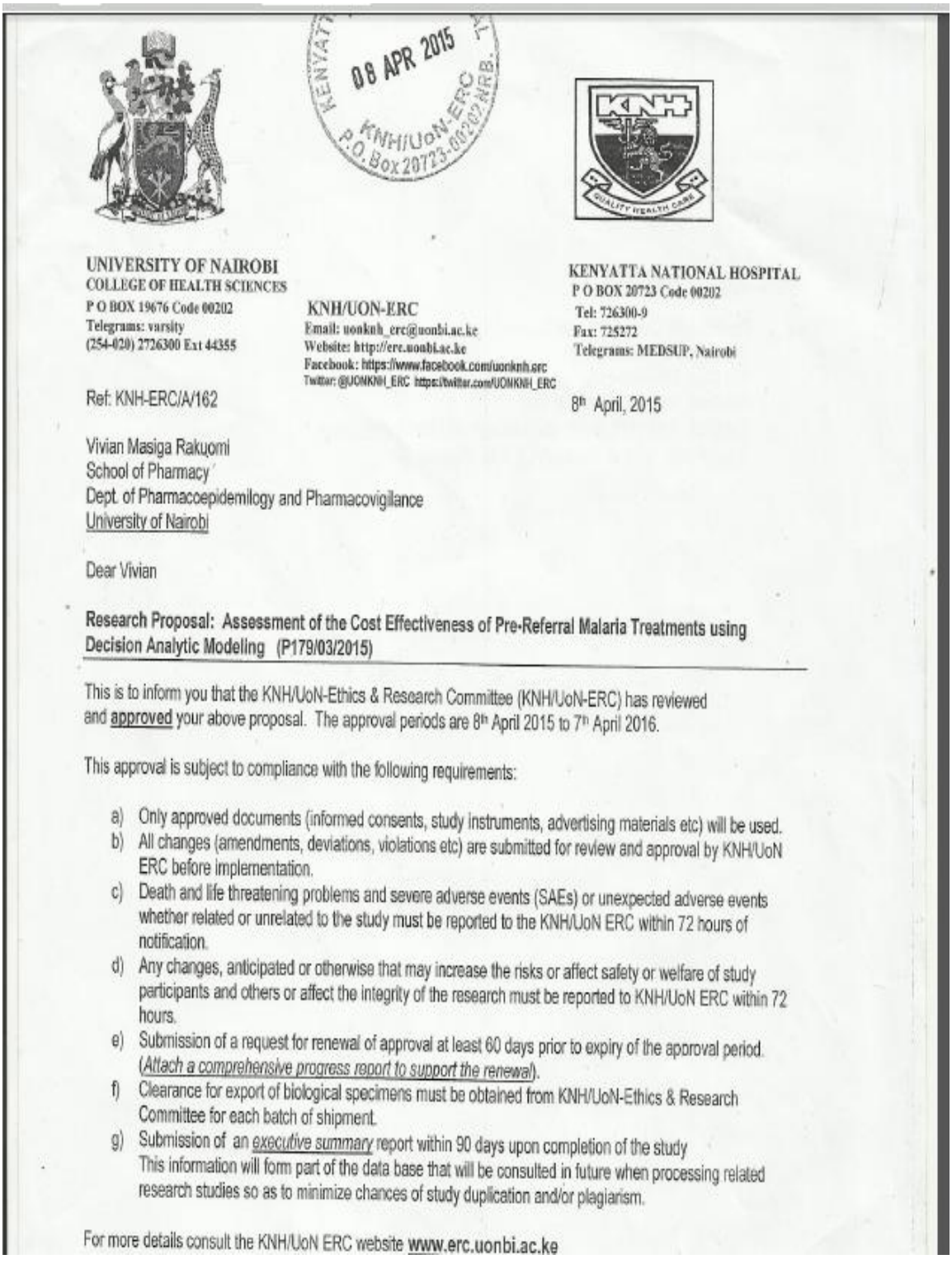
Investigators statement

I, the undersigned, have explained to the participant in a language he/she understands the procedures to be followed in the study and the risks and benefits involved.

Investigator……..

Sign……. ……...Date…….

Appendix 5: KNH/UoN-ERC Approval letter



08 APR 2015
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Ref: KNH-ERC/A/162

8th April, 2015

Vivian Masiga Rakuomi
School of Pharmacy
Dept. of Pharmacoepidemiology and Pharmacovigilance
University of Nairobi

Dear Vivian

Research Proposal: Assessment of the Cost Effectiveness of Pre-Referral Malaria Treatments using Decision Analytic Modeling (P179/03/2015)

This is to inform you that the KNH/UoN-Ethics & Research Committee (KNH/UoN-ERC) has reviewed and **approved** your above proposal. The approval periods are 8th April 2015 to 7th April 2016.

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 severe 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) 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*).
f) Clearance for export of biological specimens must be obtained from KNH/UoN-Ethics & Research Committee for each batch of shipment.
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.

For more details consult the KNH/UoN ERC website **www.erc.uonbi.ac.ke**

Yours sincerely,

PROF. M.L. CHINDIA
SECRETARY, KNH/UON-ERC

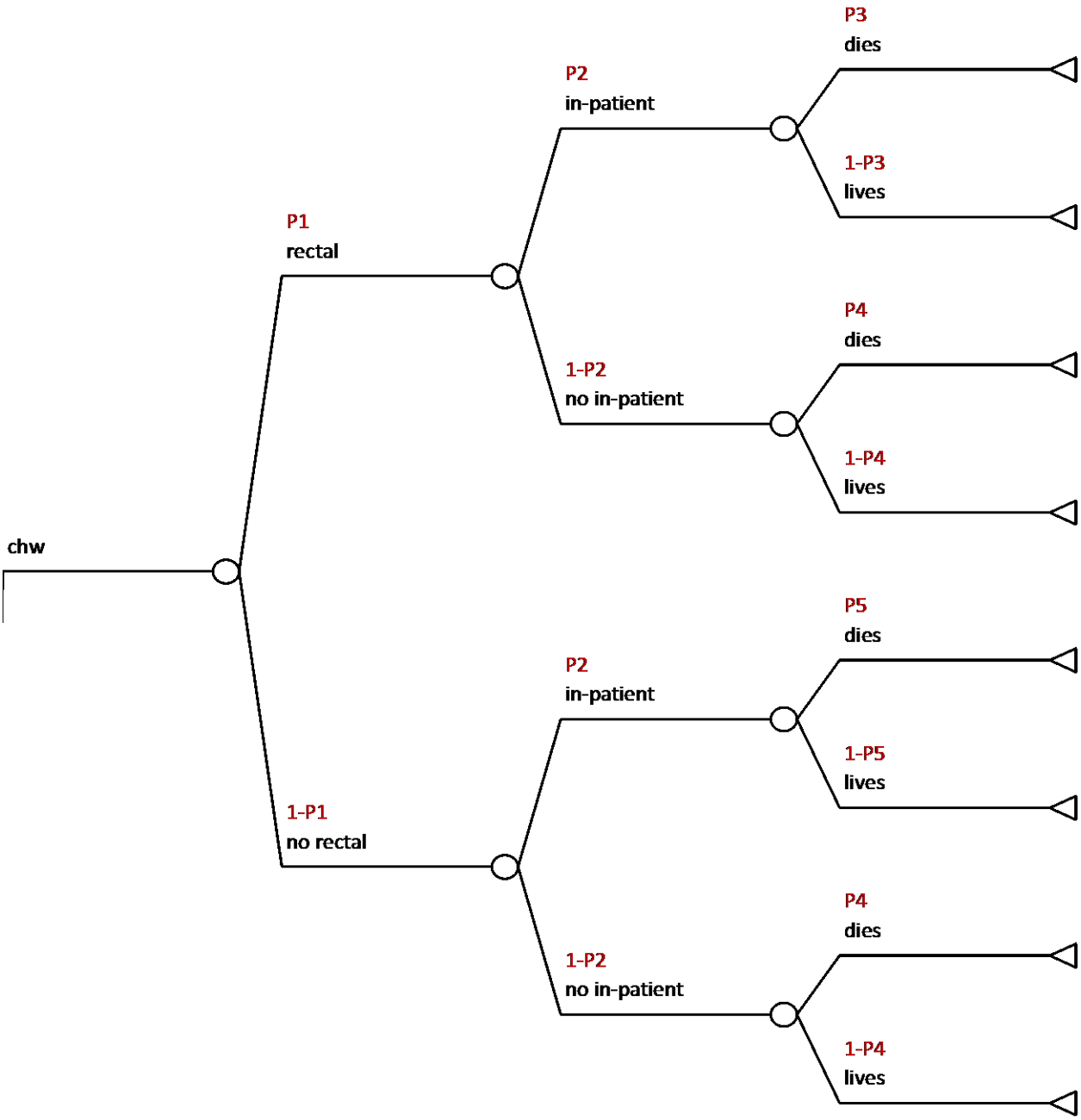
c.c. The Principal, College of Health Sciences, UoN
The Deputy Director CS, KNH
The Chair, KNH/UoN-ERC
The Dean, School of Pharmacy, UoN
The Chair, Dept. of Pharmacoepidemilogy and Pharmacovigilance
Supervisors: Dr. F.A. Okalebo, Dr. S.N. Ndwigah

Appendix 6: Cost categories for program costs

Recurrent expenditure	
Personnel	Personnel time allocated to each intervention is netted out from time spent by those personnel in other interventions. Personnel time used in the start-up and post start-up periods is expressed in person-months.
Materials & Supplies	Materials and supplies in terms of the quantities used for the programme. Examples are office supplies that are used by the programme.
Media operating costs	Media inputs such as radio or television time, leaflets or posters are provided in terms of their unit of measurement (e.g. minutes for radio, or quarter page ads in newspapers)
Transport operating costs	Transport is measured in terms of total kilometers traveled per means of transport.
Equipment operating cost	In cases where equipment is rented, the number of equipment and the duration of rental (in months) are reported
Maintenance	Maintenance costs are listed as a percentage of annual costs.
Utilities	The amounts of utility items allocated to the programme are listed . Examples of utility items are electricity, gas, and water. The allocation of the quantities used by the programme is based on the square meter surface area used by the programme, after applying any further allocation needed if the space is shared with other programmes
Others	
Rented buildings	In case buildings are rented, both the total square meter surface area of the buildings and the duration of rental (in months) are used.
Per diems and travel allowances	The types of personnel who are entitled for per diems and travel are listed. The types reflect the activity they are involved in, e.g. trainers, trainees, support staff in meetings, participants of meetings, supervisors visiting health facilities etc. Reported by the number of days per type of personnel
Miscellaneous items	Any other category of recurrent resources used that is not provided in the list are reported here by identifying the item and the quantities used.
Capital costs	
Building	Space used by the programme are reported in terms of the total square meter surface area allocated to that programme, i.e., if the space used by the programme is shared with other activities, the share of the space used for the programme under study are estimated and the value are entered here.

Transport	The number of means of transport used by the programme is listed here. If they are only partly used, the estimated share of their use are entered.
Equipment and implements	The number of office equipment, storage and distribution, maintenance, cleaning and other capital equipment are reported here. If they are only partly used, appropriate allocation is made, using the same allocation factors used for building space
Other capital costs	This section is used to report any other capital resources used by the programme.

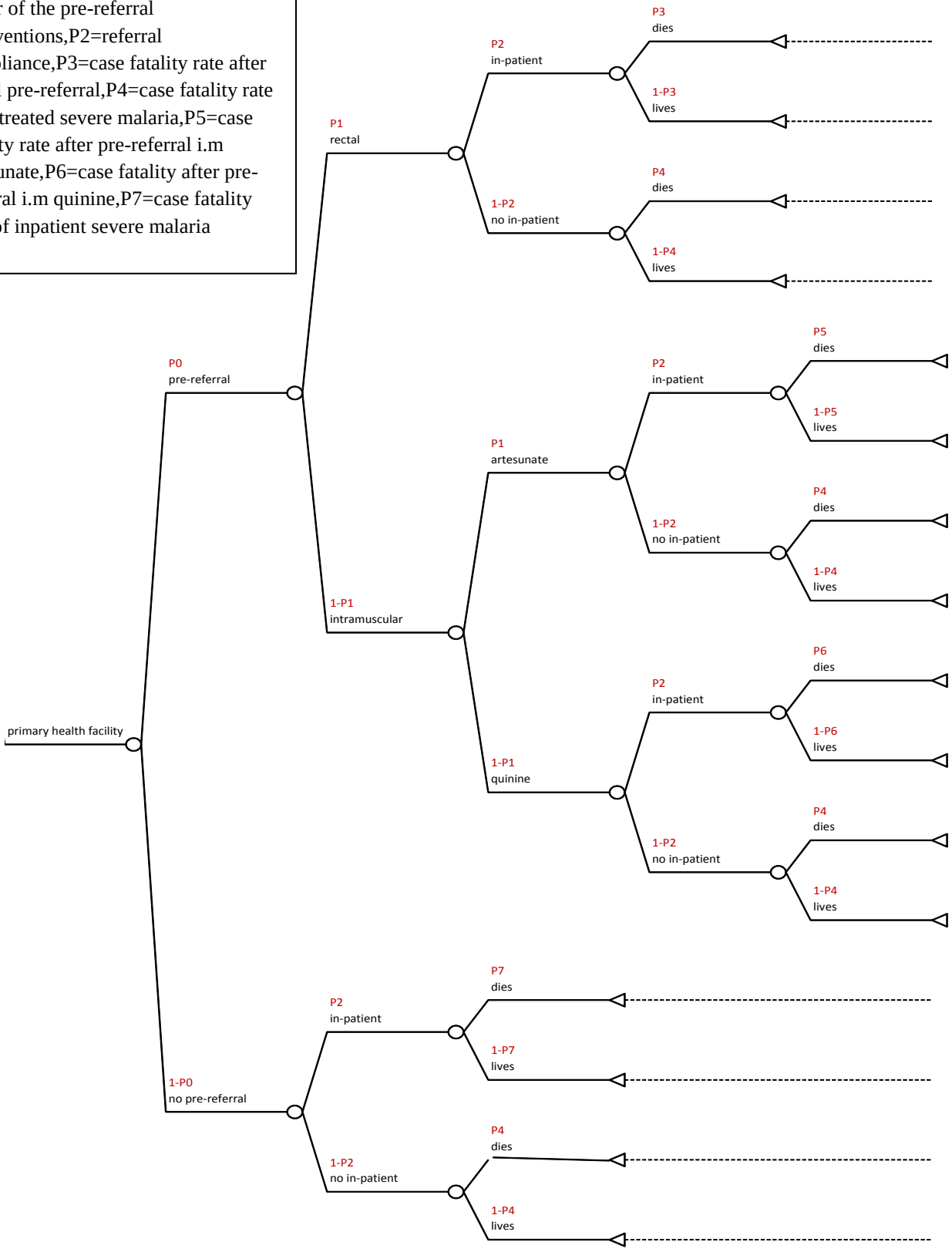
Appendix 7: Decision trees to Model the cost-utility of pre-referral antimalarial treatments.



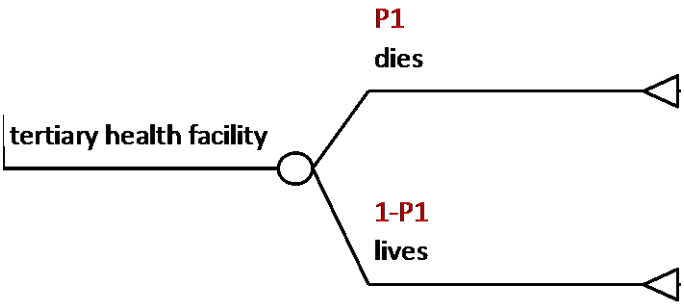
Decision tree of the cost-utility of rectal artesunate using community health workers

P1= probability of getting rectal artesunate,P2=referral compliance,P3=case fatality rate following pre-referral treatment,P4=case fatality rate of untreated severe malaria,P5=case fatality rate of inpatient severe malaria

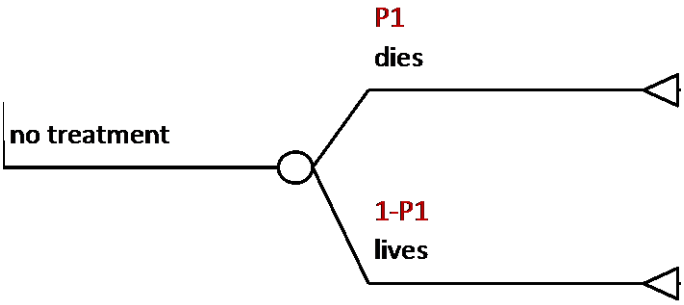
P0=probability of getting pre-referral treatment,P1=probability of getting either of the pre-referral interventions,P2=referral compliance,P3=case fatality rate after rectal pre-referral,P4=case fatality rate of untreated severe malaria,P5=case fatality rate after pre-referral i.m artesunate,P6=case fatality after pre-referral i.m quinine,P7=case fatality rate of inpatient severe malaria



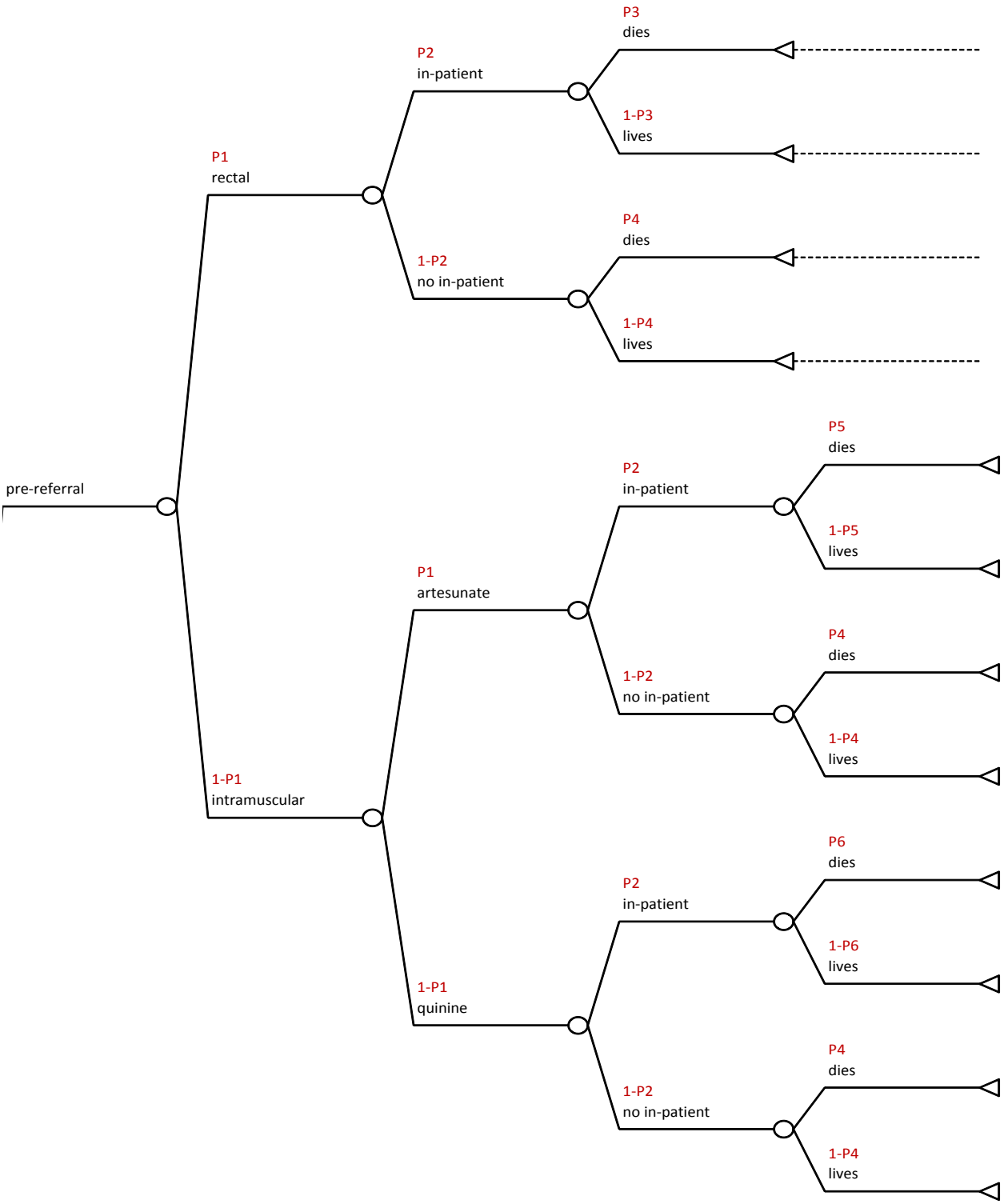
Decision tree of the cost-utility of pre-referral treatments at a primary health facility



Decision tree of the cost-utility of a tertiary facility
P1=case fatality rate of inpatient severe malaria



Decision tree of the cost-utility of not seeking treatment
P1=case fatality rate of untreated severe malaria



Decision tree to assess the comparative cost-utility of rectal artesunate, i.m artesunate and i.m quinine
P1=probability of getting either of the pre-referral treatments, P2=referral ompliance,P3=case fatality rate after rectal artesunate,P4=case fatality rate of untreated severe malaria,P5=case fatality rate after i.m artesunate,P6=case fatality rate after i.m quinine