Severe Anemia in Malawian Children: Risk Factors, Mortality and Malaria Chemoprevention

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2 Abstract

Children aged less than five years who are hospitalized with severe anemia have nine times higher risk of mortality compared to children in the community. The risk of dying and re-hospitalization remains high up to 6 months after discharge from the hospital. Causes of severe anaemia are multifactorial and vary in different settings. These include genetic factors and malignancies, nutritional deficiencies and infectious diseases such as malaria. Malaria remains a major contributor to slow hematological recovery, morbidity and mortality. New or recrudescent malaria infections after discharge negate the initial rise in hemoglobin due to on-going red cell destruction and red blood cell production failure. Studies have found that in addition to the protective effect of insecticide treated nets (ITNs), provision of post-discharge malaria chemoprevention (PMC) using monthly doses of antimalarial medication to children with severe anaemia prevented as much as 31% of deaths or hospital readmissions.

Using data from a prospective study that was investigating severe anaemia in children aged less than 5 years old in Malawi, we did a cohort analysis to compare the risk of death between severely anaemic children who had moderate to severe malnutrition and those who had severe anaemia alone (Paper I). A total of 382 severely anaemic children were screened and 331 enrolled of which a total of 53 children had moderate to severe malnutrition (exposed) and 275 did not (unexposed). During the 18-month follow period, 28.3% of children with moderate to severe malnutrition died, compared to 13.1% among children with severe anaemia alone, (IRR 2.1, CI 0.9-4.2, p=0.03). However, the number of hospitalizations and recurrence of severe anaemia was similar between the two groups [IRR 0.8 (0.4-1.4), p=0.6 and IRR 1.1 (0.3-2.8), p=0.8] respectively.

We conducted a 5-arm, cluster-randomized trial among 375 hospitalized to determine the optimum PMC delivery mechanism by comparing community- versus health facility-based strategies in order to inform policy. Children, aged <5 years with severe anemia received 3-day monthly treatment courses of dihydroartemisinin-piperaquine (DP) either through community-based methods compared to health facility-based

methods. We found that adherence was 24% higher among children when PMC was delivered in the community compared to when delivered at the health facilities. In addition, we found that when compared to the facility-based, non-SMS arm (control arm); community-based delivery utilizing community health workers (CHWs) resulted in higher adherence [39/76 (51·3%) vs. 54/79 (68·4%); IRR=1·32, 1·14-1·54, p<0·001].

With the objective of assessing the feasibility of involving community health workers (CHWs) in the scaling up of PMC into the Malawian health system, we conducted focus group discussions and in-depth interviews to explore perceptions, experiences and motivation of the CHWs who were involved in the PMC trial in Malawi. We found that CHWs were motivated to remind caregivers to administer PMC medication to their children mainly by altruism. However, professional, structural and community factors were barriers that prevented them from carrying out the assigned tasks.
In conclusion, it is crucial to investigate and manage acute malnutrition among severely anaemic children, as this might be another treatable factor associated with high mortality. If PMC is scaled up and made into policy of treatment for children with severe anemia, community delivery is effective for high adherence and access. However, community delivery anchored in CHWs may not be feasible.

3 List of original papers

This thesis is based on the following original research papers, which are referred to in the text by their Roman numerals.

Paper I: Nkosi-Gondwe T, Calis J, Boele van Hensbroek M, Bates I, Blomberg B, Phiri KS (2021) A cohort analysis of survival and outcomes in severely anaemic children with moderate to severe acute malnutrition in Malawi. PLoS ONE 16(2): e0246267. https://doi.org/10.1371/journal.pone.0246267

Paper II: Nkosi-Gondwe T, Robberstad B, Mukaka M, Idro R, Opoka RO, Banda S, Kuhl M, Ter Kuile FO, Blomberg B, Phiri KS. Adherence to community versus facility-based delivery of monthly malaria chemoprevention with dihydroartemesinin-piperaquine for the post-discharge management of severe anemia in Malawian children: a cluster randomized trial. Submitted

Paper III: Nkosi-Gondwe T, Robberstad B, Blomberg B, Phiri KS, Lange S. Introducing post-discharge malaria chemoprevention (PMC) for management of severe anemia in Malawian children: a qualitative study of community health workers' perceptions and motivation. BMC Health Services Research. 2018;18(1):984.

4 Abbreviations

AL - Artemether-Lumefantrine
ANC - Ante natal clinic
CHW - Community health worker
CRT - Cluster randomised trial
DHMT District health management team
DP - Dihydroartemesinin-piperaquine
FGD - Focus Group discussions
HB - Hemoglobin
HSA - Health surveillance assistant
ICC - Intra-cluster correlation coefficient
IDI - In-depth-interviews
IPTc - Intermittent preventive therapy in children
IPTi - Intermittent preventive therapy in infants
IPTp - Intermittent preventive therapy in pregnancy
IPTpd - Intermittent preventive therapy post-discharge
IQR - Inter-quartile range
LMIC - Low-medium income countries
MAM - Moderate acute malnutrition
PMC - Post-discharge malaria chemoprevention
QECH- Queen Elizabeth Central Hospital
SAM - Severe acute malnutrition
SAP - Statistical analysis plan
SCD - Sickle cell disease
SD - Standard Deviation
SDG - Sustainable development goal
SMC - Seasonal malaria chemoprevention
SMS - Short message service
SSA - Sub-Saharan Africa
WHO - World Health organization

ZCH - Zomba Central hospital

5 Introduction

Infant and child mortality rates are basic indicators of a country's socioeconomic situation and quality of life. Since 2000, the risk of a child dying before their fifth birthday has halved in the Sub-Saharan African (SSA) region due to gains made in vaccination coverage for specific diseases. [1] Although this is substantial, the current under-five mortality rates still remains too high to achieve the Sustainable Development Goals (SDG) target in reducing under-five mortality to at least as low as 25 per 1000 live births. [2]

Under-five mortality remains a significant concern in the developing world, with one in twelve children dying before they reach the age of five years. [1] In 2018, the under-five mortality rate in Africa was reportedly eight times higher than in Europe. [1] The Malawi health and demographic survey in 2015 reported the all cause under-five mortality rate was 63 deaths per 1000 live births with most childhood deaths being related to conditions such as HIV, diarrhea, pneumonia malaria and malnutrition.[3]

This PhD project builds on findings from studies in Malawi where severe anemia is a major cause of not only in-hospital mortality, but in the long-term among under-five children. Findings show that in malaria-endemic countries, the major etiological factor for severe anemia is malaria infection. [4, 5] Furthermore, it was found that provision of malaria chemoprevention to severely anemic under-five children for three months after discharge from hospital, significantly reduced the risk of all-cause death as well as re-hospitalization.[5]

Anemia, malnutrition and malaria are the commonest health problems affecting children.[6] It has also been established that malnutrition is one of the most important underlying factors for childhood mortality and a major etiological factor for severe anemia among children aged less than five years in developing countries.[7-9] Areas endemic for malaria often have a high prevalence of micronutrient malnutrition and anemia. [10]

With this background, the aim of this thesis is: 1). to investigate the mortality risk among children with severe anemia and moderate to severe acute malnutrition, 2). to identify the optimal delivery strategy for malaria chemoprevention among under-five children with severe anemia and 3). to determine if mobilization of community health workers to deliver malaria chemoprevention is feasible.

5.1 Malnutrition in children

Childhood malnutrition is a major global health problem that significantly contributes to under-five morbidity and mortality. [11, 12] Malnutrition is a complex and multifactorial condition that results from deficiencies, excesses, or imbalances in a person's intake of energy and/or nutrients. [13] Children's nutritional status influences their survival, cognitive development, and lifelong health. [14-20] Stunting, or low height-for-age, is an indicator of overall nutritional status and an important cause of morbidity and mortality in infants and children.[14, 18, 21]

5.1.1 Types of malnutrition

Although one child can have more than one form of malnutrition, the WHO released new growth standards for children aged 0– 59 months in 2006 which represent the standards on which all WHO definitions and estimates of all forms of malnutrition are based. [22] Undernutrition refers to deficiencies in nutritional intakes. [23] The four main forms of undernutrition in children are wasting, stunting, underweight and deficiencies in vitamins and minerals.

Micronutrient malnutrition refers to conditions caused by dietary deficiencies of vitamins or minerals and is often interlinked with all types of malnutrition. Stunting is an indicator of long-term and chronic intake of poor nutrition signified by a child being too short for his or her age. [24] Children are defined as stunted if their height-for-age is more than two standard deviations below the WHO Child Growth Standards median. [22] Stunted children often suffer severe physical and cognitive damage that is not reversible and lasts a life-time. [25] Under-weight children are those that have weight for age two standard deviations below the WHO child growth standards median. [22] Children who are under-weight have two times the risk of dying compared to those without nutritional deficits in developing countries. [14, 19]

Wasting, also referred to as acute malnutrition results from rapid drops in food consumption or food quality and frequently co-exists with pathological causes. [26] Children suffering from wasting have weakened immunity, are susceptible to long term developmental delays and face an increased risk of death. [14] These children require urgent feeding, treatment and care to survive. [27, 28]They are two forms of acute malnutrition; severe acute malnutrition (SAM) and moderate acute malnutrition (MAM). In children aged 6-59 months of age, SAM is defined as; weight-for-height below -3 z-scores of the median of the WHO growth standards, visible severe wasting, mid upper arm circumference (MUAC) less than 11.5cm or presence of bilateral pitting edema. [22, 23] On the other hand, MAM is defined as a weight for height between -3 and -2 scores below the median of the WHO growth standards, wasting and a MUAC between 11.5 and 12.5 cm. [22, 23]

5.1.2 Global burden of childhood malnutrition

Childhood malnutrition is the underlying cause of death in an estimated 45% of the 8 million deaths among children under the age of five years. [21] The burden of childhood malnutrition remains high globally, with one in 150 million children in 2017 having any form of malnutrition. [29] The trend of nutrition indicators between 2010 and 2019 clearly shows that the progress in reduction of childhood malnutrition is not sufficient to reach the World Assembly targets set for 2025 and the Sustainable Development Goals set for 2030. [21, 29]

Many countries, especially LMIC suffer the major severe brunt of malnutrition. While only half (46%) of all under five children live in LMIC, 75% of wasted children live there. [29] In 2019, it was estimated that 47 million children were affected by wasting of which 14.3 million were severely wasted. [26] The WHO global nutritional target for wasting is to keep the global prevalence to below 5% by 2025. [30] However, the trend shows that little progress has been made since 2012 when the prevalence was 7.9% compared to 7.3% in 2018. [31] In 2019, more than two thirds of all wasted children under 5 lived in Asia and more than one quarter lived in Africa. [31]

SAM or wasting is the most severe form of malnutrition which accounts for 4.4% of deaths among children aged less than five years. [30, 32, 33] The association between SAM and mortality has been well established. [34] Due to the ongoing metabolic imbalances in a child with SAM, there is a reduction in their capacity to regulate normal physiologic processes such as temperature and gastrointestinal absorption. As a result, children with SAM more are prone to dehydration, hypothermia, hypoglycemia and increased risk of infections and severe illness due to the preceding immunosuppression than a well-nourished child. [14, 18] Nearly one in ten children who are moderately and severely wasted are at risk of dying during the initial admission as well as after discharge from hospital. [33] Globally, over 3.6% (15.9 million) of under five children are both stunted and wasted which further increases the risk of dying. [31]

5.1.3 Burden of childhood malnutrition in Malawi

Just like in other countries, malnutrition remains a major challenge that contributes significantly to morbidity and mortality among under-five children in Malawi. Although it has been performing relatively well against other developing countries, [35] Malawi still experiences a significant malnutrition burden among its under-five population. The 2016 DHS showed that 37% of children under-five years of age are stunted while 12% are underweight and children younger than 18 months are most affected. [35]

Malawi is somewhat on the right course to meet the global targets for under-five overweight and under-five wasting rates. As of 2015, the estimated national prevalence of under-five wasting was 3 %, which has decreased slightly from 4 % in 2010 but it is much less than the developing country average of 8.9%. [35] Despite this positive trend towards reduction in wasting, mortality in children with severe acute malnutrition has remained high, with up 42% of children admitted with SAM dying in Malawi. [33]

5.1.4 Risk factors and causes of childhood malnutrition

The pathophysiology and causes of malnutrition are complex and often linked. the UNICEF conceptual framework for undernutrition was developed to generally demonstrate the determinants of undernutrition among specific individual, household and environmental factors. [36] These determinants were grouped into three: immediate, basic and underlying causes of undernutrition. Immediate factors are factors related to inadequate dietary intake and exposure to diseases which leads to poor appetite, poor absorption, increased metabolic requirements and nutrient losses. [37, 38] Underlying determinants are factors that are related to inadequate access to appropriate diet and health and cause poor nutrition and basic determinants are influenced by social, economic and political factors. [36, 37]

Diverse and safe foods in early childhood and a healthy environment; including access to basic health, water, hygiene and sanitation services are important for reduction of all forms of malnutrition. Similar to other developing countries, 69% of people in Malawi live on less than US$2 a day and therefore factors related to poverty are the main determinants of the burden of malnutrition. [39] These factors include poor diets and infectious diseases, lack of food, poverty, over-dependence on maize as a staple, high population density and population growth. [3]

5.1.5 Prevention of acute malnutrition

Strategies for reducing and preventing acute malnutrition should aim at optimizing provision of healthy diets, promotion of good health and growth in infants and children. In 2012, WHO adopted targets that aimed to reduce the burden of many forms of malnutrition. The “Comprehensive implementation plan on maternal, infant and young child nutrition’ includes targets on stunting and wasting among children under five years of age. [13] And in 2015, UN member states adopted the ambitious target to “end malnutrition and in all its forms” by 2030 as part of the target 2.2 of the SGDs in recognition of the importance of nutrition for development. [13, 31]

In 2007, the Government of Malawi developed the first edition of the National Nutrition Policy and Strategic Plan (NNPSP) to guide the implementation of a multisectoral nutrition response and facilitate the improvement of the nutrition status of all Malawians. Through the implementation of the NNPSP 2007–2011, significant progress was made in improving key nutritional indicators in the country. [40] The current Malawi National Multi-Sector Nutrition Policy 2018–2022 (MNSNP) is in line with the World Health Assembly targets for 2025 and SDGs; and serves to redirect focus on maternal, infant, young child and adolescent nutrition, acute malnutrition, interventions across sectors and nutritional governance. [41, 42]

5.1.5.1 Provision of adequate nutrition

Preventing the development of acute malnutrition includes improving feeding practices among children who are particularly susceptible to malnutrition. The WHO minimum acceptable diet (MAD) is one of the core indicators for assessing infant and young child feeding and is a combination of dietary diversity and minimum meal frequency among children aged between 6-23 months. [43, 44] Exclusive breastfeeding for the first six months is recommended for improved nutritional status and disease prevention. [45, 46]

However, only about 42% of babies are exclusively breastfed globally. [31] Introducing appropriate complementary foods with high nutrient density and bioavailability of micronutrients that are prepared hygienically to children is key in improving uptake of optimal nutrient and prevent malnutrition but only 18 % of children between 6 and 2 months received a MAD in 2019. [31] Similarly and sadly in Malawi, only 59% of children under six months were exclusively breast fed and only 8% met the minimum required diet for children between six and 23 months in 2015. [47]

5.1.5.2 Prevention of infections

The relationship between malnutrition and infection is described as a vicious cycle. Children with SAM are in a deranged metabolic and physiological state which makes

them more susceptible to infections and severe illness which in turn worsens the malnutrition. [28, 36, 48] Effective strategies for preventing malnutrition should aim at breaking the infection-malnutrition cycle especially those related to immunosuppression, diarrhea and respiratory tract infections. [49, 50]

5.1.5.3 Appropriate management of acute malnutrition

WHO developed the specific guidelines which are supported by available evidence and expertise for management of children with SAM in order to reduce malnutrition deaths, improve outcomes and prevent further cases of malnutrition. [51] Despite many countries adopting the 2013 WHO treatment guidelines for severe acute malnutrition into their management protocols, the post-discharge mortality has remained as high as 31 deaths per 1000-person years in developing countries. [33, 51, 52]

While SAM without complications is managed through the community-based therapeutic care centers or out-patient children with complicated SAM are admitted to hospital. [28, 51, 53] The standard in-patient management steps are split into three phases; the initial treatment phase, rehabilitation phase and the follow-up phase. The management steps also include stimulation of the child's emotional sensory and physical development. Inpatient care involves initial stabilization phase to treat any immediate medical complications and careful feeding with specially formulated low-calorie milk to allow the gut to repair.

During the rehabilitation or transition phase, feeding with ready to eat therapeutic feeds (RUTF) or higher calorie milk is reintroduced to the child in preparation for outpatient supplementary feeding phase with dry feeds. A child is discharged from treatment when they have achieved a weight-for-height/length above –2 standard deviations of the WHO child growth standards median score or mid-upper-arm circumference above 125 mm and no edema for at least 2 weeks. [27]

5.1.6 Interaction between malnutrition and anemia

In addition to the high risk of dying, children with SAM also have significant comorbidities that further increase this risk. [54] The prevalence of these comorbidities

varies in different settings. The most significant comorbidities include infectious diseases such as pneumonia, acute respiratory tract infection, tuberculosis, HIV and micronutrient deficiencies such as anemia. [8, 9, 55, 56] Anemia and malnutrition are the commonest health problems that often co-exist among children aged less than five years old.

In Malawi, 15.8% children with severe anemia were found to be wasted, [33] while 67.3% of children aged between 6-59 months with severe malnutrition were found to be severely anemic. Another descriptive study investigating comorbidities in children with SAM found that the prevalence of severe anemia was 24%. [57] However, there is insufficient evidence of the long-term impact of having these two co-morbidities to guide appropriate follow up and micronutrient supplementation during rehabilitation. [27]

5.2 Malaria

Malaria is a life-threatening infection that is caused by parasites of the Plasmodium family and is transmitted to humans by infected female *Anopheles* mosquitoes. The five known human species of plasmodium are; *P. falciparum, P. vivax, P. malariae, P. ovale and P. knowlesi*. While *P. falciparum* and *P. vivax* are most prevalent, *P. falciparum* causes more severe disease and deaths. [58] The natural history of malaria involves cyclical infection where the parasites grow, invade and destroy red blood cells of humans and infected female *Anopheles* mosquitoes act as "vectors" that carry the disease from one human to another.

5.2.1 Global malaria burden

Despite being preventable and treatable, malaria continues to be a major cause of illness and death in the world. The 2019 World Malaria Report estimated that globally, there were 228,000,000 infected cases of malaria in 2018.[59] In the same year, the disease reportedly killed 405,000 people, [59] which a slight decline from the 429,000 malaria deaths that were reported in 2015. [60] Similarly, the number of malaria deaths among children was estimated to have decreased by 29% since 2010 but malaria remains a major cause of death among children. [61]

It is estimated that malaria takes the life of a child every 2 minutes. In 2015 alone, 303 000 malaria deaths occurred in children aged less than five years, which is equivalent to 70% of the total global estimates.[61] Despite encouraging progress made by many countries towards attaining target 3.3 of the sustainable development goals (SDGs) which aims to end epidemics including malaria, the African region still carries a disproportionately high share of the global malaria burden. [59] According to recent world health organization reports, 93% of all malaria cases and 94% of all malaria deaths occur in Africa alone. [59] [62]

5.2.2 Malaria epidemiology in Malawi

In Malawi, malaria is among the top five causes of deaths with around 4 million malaria cases reported annually and contributing to 39% of all outpatient visits. [63] Children under the age of five years bear the highest burden of malaria; with an estimated annual incidence rate as high as 1160 episodes per 1000 children and accounting for nearly 40% of all hospitalizations. . [64-66] attributing an estimated 7.84% of total deaths among this group. [6, 67, 68]

Malaria transmission patterns in Malawi show seasonal variation and is largely determined by the annual rainfall. [69] Vector capacity is high due to plentiful rainfall, raised temperatures and elevated humidity all year. [70] The highest transmission areas are along the hotter, wetter and humidly low-lying areas, while the lowest risk areas fall along the highland areas. [69, 71] *Anopheles funestus* is still considered to be the primary vector species but *An. gambiae* s.s. and *An. arabiensis* are also present. [72] *Plasmodium falciparum* is the most common species which accounts for 98% of all infections and cause of severe disease and deaths. [69]

5.2.3 Risk factors for malaria transmission

Factors that influence malaria transmission are complex and related to the human host, the vector, and the environment. In order to adopt feasible and targeted strategies and interventions for malaria control, we need to understand factors that drive malaria transmission. The main factors that are important for malaria transmission are: 1) environmental factors, 2) biological factors and 3) human related factors. [73]

5.2.3.1 Environmental factors

In many countries, malaria transmission is seasonal and varies at different times of the year particularly during or after the rainy season. Transmission is highly dependent on climatic factors such as temperature, humidity, altitude and amount and pattern of rainfall which determines the longevity and capacity of the *Anopheles* vector. [73] Rainfall provides aquatic breeding sites for mosquitoes; and high temperature, high humidity and low altitudes are favourable for mosquito survival and parasite maturation which leads to increased malaria transmission. By reducing the lifespan of the mosquito, the maturation of the parasite is also reduced thereby reducing proportion of infective bites. However, because environmental factors cannot easily be modified, targeted interventions that minimise contact between the mosquito and human and those that reduce mosquito longevity and density are important. [71]

5.2.3.2 Biological factors

Biological factors are factors that are related to the parasite, mosquito and the human host. The different types of the parasites influence the extent of impact of malaria. *P. falciparum* is the most common specie of plasmodium in SSA and also causes the most severe disease. In Malawi, where falciparum malaria accounts for 96% of malaria infections, the risk of severe disease is high. [72] Additionally, different *Anopheles* vectors have different behaviour and capacities which influence malaria transmission and insecticidal resistance of vector and parasites are major challenges on malaria control. [74]

5.2.3.3 Human factors

Human related factors include human activities such as access to health care, migration, gender, land use, socioeconomic status and use of interventions for malaria control. These factors influence the pattern and extent of malaria transmission. [75] Differences between human beings have influence on the patterns of transmission and the severity of malaria. Immunity to malaria develops after several exposures over

time and the ability to suppress the infection and survival will depend on an individual's immunity.

5.2.4 Malaria control strategies

Since the early 2000s, malaria interventions have been scaled up in sub-Saharan Africa with the goal to control and eliminate the disease. [58] The WHO global malaria programme recommends use of four prevention tools and strategies for malaria control. [76] These are: prevention through deployment of vector control interventions of 1) insecticide treated nets and 2) indoor residual spraying 3) use of antimalarial treatment for high risk populations including pregnant women and children and 4) malaria case management through early diagnosis and prompt, effective treatment.

Through the coordination of Roll Back Malaria (RBM) partners, malaria is one of the public health priorities within the Essential Health Package (EHP) in Malawi. With its vision to have all people in Malawi free from the burden of malaria and a mission to reduce the burden of malaria to a level of no public health significance in Malawi, The Ministry of Health (MoH), in collaboration with other partners, developed the National Malaria Strategic Plan (NMSP) with three core strategies for malaria elimination in Malawi : 1) vector control through ITN use and IRS, 2) improved malaria diagnosis and treatment, and 3) intermittent preventive treatment in pregnancy (IPTp). [77] The implementation of these policies has been associated with a 19 percent point drop in malaria prevalence in children aged less than five years from 43% in 2010 to 22% in 2017. [78, 79]

5.2.5 Current strategies and extent of coverage

5.2.5.1 Improved diagnosis and treatment

For effective management of malaria, early and accurate diagnosis with a parasitological test and prompt treatment with appropriate antimalarial agents within 24-48 hours of onset of malaria symptoms is key. [80, 81] Diagnosis of malaria should not be made by clinical symptoms alone as they cannot be reliably distinguished from other causes of fever. [80] Since 2010, WHO recommends parasitological confirmation of all suspected malaria with either light microscopy or rapid diagnostic tests (RDT) before treatment is administered. [80, 81] Although microscopy is the gold standard, it

requires competency and training to determine accurate results. [82] While RDTs do not offer the same high sensitivity as microscopy, they are important for prompt malaria diagnosis because they can be used at the bedside and do not require high skilled personnel. [83] Between 2010 and 2017, the percentage of children with a fever who received a malaria diagnostic test increased from 33% between 2010-2012 to 59% in 2015– 2017 in SSA. [59]

In 2011, the Malawi NMCP adopted the WHO recommendation that, parasitological malaria diagnostic should be done on all suspected cases. [78] [77] In the current MSP 2017-2022 in Malawi, priority has been placed on expanding and strengthening diagnostic capacity and increased procurement of malaria commodities to ensure that prompt and effective case management is provided and that there is reduction in the presumptive use of antimalarial medications. [84] In the 2017 Malaria Indicator Survey (MIS), 38% of children aged less 5 years with reported fever had blood collected from either the finger or heel for testing (used as proxy for diagnosis) compared to 32 % in 2014. [78]

Without effective treatment, severe malaria infection is always fatal. Due to evidence of growing malaria parasite resistance, the government of Malawi changed its malaria treatment drug policy for first line treatment for uncomplicated malaria from chloroquine monotherapy to sulfadoxine-pyrimethamine (SP) in 2003, and from SP to artemisinin combination therapy, [19] with artemether–lumefantrine (AL) in 2007. [84] The current second-line is oral artesunate- amodiaquine. Parenteral artesunate is used for complicated malaria while oral quinine is reserved for management of malaria in pregnancy in the first trimester. [77]

MoH continues to focus on improving and expanding availability of appropriate malaria management to health facilities and community through community mobilization, supportive supervision, HSAs using RDTs and pre-referral rectal artesunate and implementing the integrated community case management (iCCM) in areas where the health facility is more than five kilometers away. [85] Despite these efforts, there was not an improvement in the proportion children with fever that

sought advice or treatment in 2017 compared to in 2014 (54% compared to 59% respectively). [63, 79] However, 96% of children aged less than five with recent fever who received an antimalarial, took an ACT in 2017 compared to 92% in 2014; and 73% of these took it within 24 hours of being prescribed in the rural areas. [63, 79]

5.2.5.2 Malaria prevention using vector control

Vector control with either insecticide treated mosquito nets (ITN) or (IRS is effective for the prevention and reduction of malaria transmission. ITNs act as both a physical and a chemical barrier against mosquitoes therefore reducing the vector population, [86] [87] whereby IRS involves spraying interior surfaces of dwellings with a WHO pre-approved residual insecticide, to kill or repel mosquitoes. [87] Although evidence suggesting that one core vector control intervention is more superior to the other is conflicting, studies report that if coverage of either is high enough within a specific area, population wide protection will be conferred across the community. [87, 88] WHO recommends that the selection of vector control intervention should be based on factors specific to the local context. [87] Despite the emergence and spread of mosquito resistance to pyrethroids, ITNs continue to provide a substantial level of protection in most settings. [71, 89] In 2018, about half of all people at risk of malaria in Africa were protected by an ITN, compared to 29% in 2010. [60]

The government of Malawi prioritizes vector control and effective case management as an effective prevention intervention for malaria. According to the Malawi Vector Control Strategy 2015-2019, ITN use is the primary malaria vector control intervention in Malawi. [90] However, plans and targets for IRS implementation in the country have been included as an option. [77]

MoH adopted the subsidized ITN policy in 2001. ITNs are distributed free of charge through routine ANC and EPI clinics to expectant women and under-five children through mass distribution campaigns every two to three years. Between 2012 and 2016, NMCP with support from other partners has conducted four nationwide mass distribution of ITNs. [64, 90] The ITN ownership (ownership of at least one ITN per household) has increased from 55% in 2012 to 70% in 2014 and to 82% in 2017. [3]

The current 2017-2022 Malaria Strategic Plan (MSP), has targeted to cover 95% of all households with at least one ITN by the year 2022. [84] Currently, 42% of households have achieved universal coverage of ITNs (ownership of at least one ITN per 2 people in the household) from 30% in 2014. [78, 91]

In Malawi, IRS programmes were initially limited to private spraying in urban centers or sugar plantations since the 1990s. [71] In 2007, MoH launched a nationwide IRS programme in one high transmission district which was later scaled up to 5 additional districts. [71] In a 2010 survey, it was estimated that 83% of houses in the pilot district and less than 2% of the households in the whole country had been sprayed within the previous 12 months. [79] Due to growing pyrethroid resistance, logistical difficulties and financial constraints, funding was suspended in 2012 and the programme was scaled down. [92] In the 2014 MIS, 9% of households reported to have been treated with IRS in the previous year. [79] In its current 2017-2022 MSP, MoH is planning for IRS implementation in selected epidemiological areas, in line with international standards. [84]

5.2.5.3 Prevention through use of antimalarials in high risk populations

Implementation of preventive malaria control strategies, such as intermittent preventive treatment of malaria (IPT), have substantially reduced malaria transmission and burden among vulnerable groups such as pregnant women and children under five because they are at highest risk of repeated and severe infection and consequently death in Africa. IPT is the administration of full therapeutic doses of antimalarial medicine to pregnant women (IPTp), infants (IPTi), children (IPTc) under five years and seasonally to children (SMC). [93] IPT is effective for malaria prevention by clearing existing parasitemia, providing a prophylactic effect and preventing complications of malaria such as anemia and death. WHO currently recommends use of IPTp, IPti and SMC as context-specific preventive interventions against *falciparum* malaria. [61]

WHO's recommended package for prevention and treatment of malaria among pregnant women includes; promotion of ITNs, IPTp with SP (IPTp-SP) and prompt

and effective treatment of malaria infection. IPTp-SP has shown to significantly reduce adverse maternal and neonatal outcomes including maternal malaria episodes, maternal and fetal anemia, placental parasitemia, low birth weight, and neonatal mortality. [94, 95] For pregnant women living in moderate to high transmission areas in Africa, WHO recommends administration of up to three or more doses of SP during antenatal care (ANC) starting as early as possible after the first trimester, with at least 1 month between doses until the time of delivery. [96] Currently there are 36 countries that have adopted this IPTp-SP policy into their ANC package. [59]

It is estimated that in 2018, 31% of eligible pregnant women received at least three or more doses of SP. Although this is large increase than the 22% in 2017 and 18% in 2015, the proportion still remains below full coverage. [59] About 20% of pregnant women did not attend ANC and of those that did attend, 18% did not receive IPTp. This is worrying considering it is a missed opportunity to improve coverage. [59, 60] IPTp with at least two doses of SP has been recommended in Malawi as part of the three-pronged strategy for malaria prevention and treatment among pregnant women since 1993. [77, 97] In 2016, the MoH adopted the 2012 WHO IPTp-SP policy of administration of at least three-monthly doses of SP soon after the first trimester. [94, 96] It is estimated that in 2017, the proportion of pregnant women receiving at least one dose of SP increased to 92% from 90% in 2014 and 77% in 2012 and 41 % of pregnant women received three or more doses of SP in 2017 compared to 13 % in 2014. [63, 79] This is a commendable increase in uptake probably attributed to the adoption of the new IPTp-SP policy.

5.2.5.4 IPT among children

In addition to the four key interventions for malaria control; vector control using ITNs and IRS, prompt and effective treatment of malaria and IPTp, the WHO also recommends intermittent preventive treatment among infants IPTi and SMC among children under five years. [98]

Similar to IPTp, IPTi is the administration of full treatment courses of malaria medication to infants less than one year old at risk of malaria; delivered at pre-

specified times of routine vaccinations through the Expanded Programme of Immunization (EPI). [98] IPTi with SP provides protection against clinical malaria, anemia and hospital admissions in areas of moderate to high malaria transmission. [98] Not to detract from the key malaria control interventions, IPTi is considered as an additional strategy which can be delivered through an effective and existing system. Although infants (under 6 months of age) have been considered to be relatively protected against malaria, the burden of the disease in Malawian infants is substantial, with 10% of children under 5 years of age hospitalized with malaria being under 6 months of age. [64, 99] However, Malawi MoH does not include IPTi as part of their malaria strategic plan. [84]

5.3 Anemia

5.3.1 Anemia Burden and impact

Anemia is defined as a reduction in the amount of circulating red blood cells (RBCs) which causes insufficient oxygen carrying capacity to meet the body's physiological needs. [52] Although other hematological assessments can be made to diagnose anemia the most commonly used clinical indicator of anemia is a low hemoglobin concentration (Hb) of <11g/dl. [100] The WHO Hb cutoffs for children aged < 5 years categorize anemia as mild (Hb < 11g/dl), moderate (Hb < 9g/dl) and severe (Hb < 7g/dl). [101] Moderate and severe anemia are major public health problems associated with increased child morbidity and mortality, increased susceptibility to infection and have negative consequences on cognitive development and physical growth. [101-105]

WHO estimated that 1.6 billion people are affected by anemia with the global prevalence at 24.8% of which, sub-Saharan Africa suffers the highest prevalence (67.6%) with a slower decline over time than any other region. [106, 107] Children are at highest risk with over 293 million affected globally of which 47.4% are aged less than five years. [104, 106, 108] In Malawi the prevalence of anemia among children is 63% of which 6% have an Hb<8g/dl. [35] Similar to other reports, in 2015 anemia was to be more prevalent among children aged less than 24 months than among older children, with a peak prevalence of 91% observed among children age 9-11 months. [35, 109] Overall, more than 6 in 10 children (63%) suffered from some degree of anemia: 27 % were classified as mildly anemic, 34 percent were moderately anemic, and 2 percent were severely anemic, [35] and the prevalence of decreased with age from 87% among children age 6-11 months to 48% among children age 48-59 months. [35]

5.3.2 Pathophysiology of anemia

Anemia develops when there is an imbalance between loss and production of RBCs caused by ineffective or insufficient erythropoiesis such nutritional deficiencies, and/or excessive loss of erythrocytes due to hemolysis or blood loss or both. There are multiple causes of anemia and its classification is usually based on either the

biological mechanism of the cause such as iron deficiency (ID) and/or RBC morphology.

5.3.3 Determinant factors for anemia

Anemia is pathophysiologically diverse and often multifactorial. Figure 1 is a conceptual framework of factors for anemia depicting how distal factors such as socioeconomic status contributes to the proximal determinants of anemia such as infections. Although these determinants are interrelated, global analyses of anemia burden between 1990 and 2010 have reported that the most proximal risk factors for anemia are genetic Hb disorders, nutritional deficiencies and infections. [110, 111]

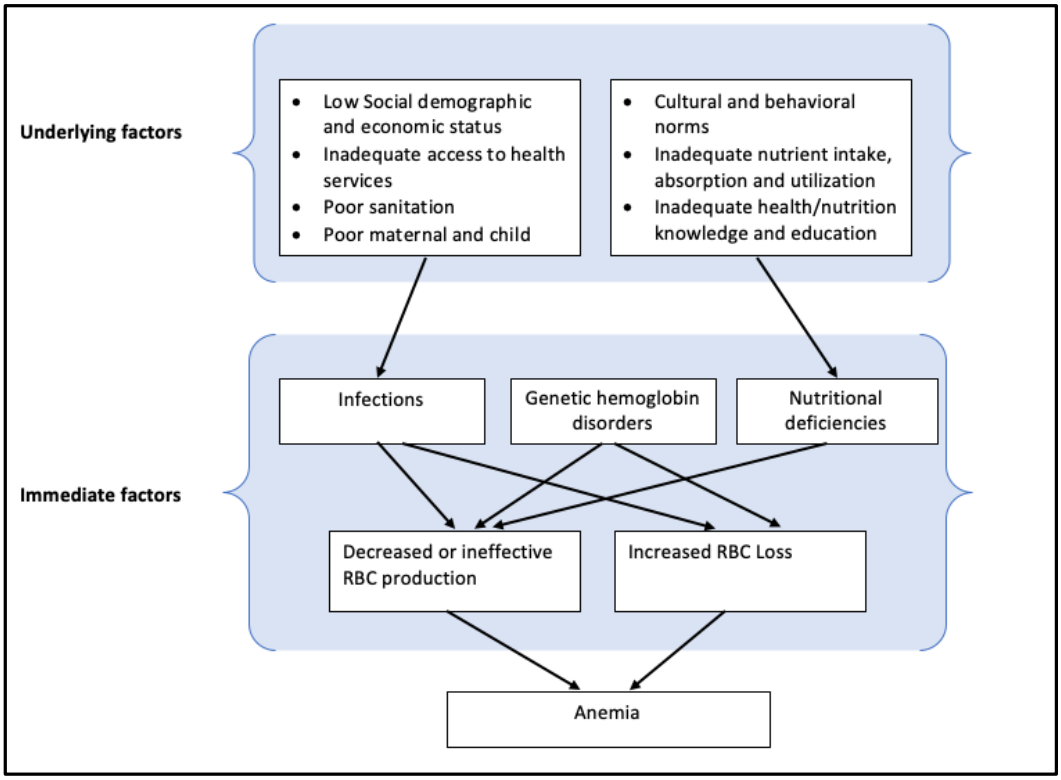

Figure 1. Conceptual framework model of the distal and proximal determinants of anemia among children (Adapted from refs. [110-112])

Figure 2 summarizes the major causes of anemia in SSA. Nutritional anemias result from insufficiencies in nutrients that favor adequate hematopoietic nutrient

concentrations for RBC production and maintenance. [104] Inadequate dietary intake, increased nutrient losses from blood loss, poor nutrient absorption and poor nutrient metabolism lead to reduced bioavailability of nutrients necessary for RBC production. [104] Although iron deficiency is the most important cause of anemia, nutritional deficiencies in vitamin A and vitamin B [Riboflavins, Pyridoxine (B6), Cobalamin (B12) and folate] also play a vital role in nutritional anemia. While vitamin A is important for erythropoiesis, immune function and have a role in iron metabolism, [113] B vitamins are also involved in Hb synthesis and iron metabolism. Their absence affects DNA synthesis and cell division in the bone marrow. [114] However, the extent to which deficiencies in these nutrients contribute to the global burden of anemia has varying epidemiologic characteristics and not very clear. [113]

Iron deficiency anemia occurs when dietary iron intakes are insufficient to meet iron needs particularly at the time of high demand such as in growing infants and during pregnancy. Iron deficiency is reported to affect 1.9 billion people and attributed to nearly half of all cases of anemia and the most common cause of anemia globally. [115] Iron deficiency has serious health consequences particularly in children's psychomotor development and cognitive function as well as increased risk of mortality. [116] The Malawi micronutrient survey (MNS) of 2015-2016 reported that 22% of children aged less than five years had iron deficiency but supplementation still remains low. [117] In many countries iron deficiency is aggravated by infectious diseases such as worm infestations and malaria.

Globally, many primary diseases such as hookworm, schistosomiasis and malaria are also associated with anemia by causing blood loss, increased hemolysis and reduced RBC production. [110] Chronic infections and diseases cause anemia by altering iron metabolism and increased cytokine proliferation which reduces the production and lifespan of RBCs. [118] An analysis of 16 population-based surveys reported that high infection countries with poor water, sanitation, and hygiene (WASH), high prevalence of malaria, diarrhea, and schistosomiasis; inflammation [measured by high C- reactive protein (CRP)] was associated with anemia prevalence. [112]

Soil transmitted helminths and schistosomiasis are parasitic infections that are very common in SSA. Although their association with anemia is dependent on parasite species, intensity of infection and co-infection with other parasites; they cause chronic anemia by attaching to the enteric and bladder mucosa, leading to blood and iron loss over a period of time. [109] Other infections such as Malaria and Human immunodeficiency virus (HIV) which are very common in SSA have a huge impact on anemia prevalence. [99, 102] Persons living with HIV have a persistent chronic and immune response phase that causes impaired iron metabolism as well as risk of opportunistic infections which significantly contribute to the risk of chronic anemia. [105]

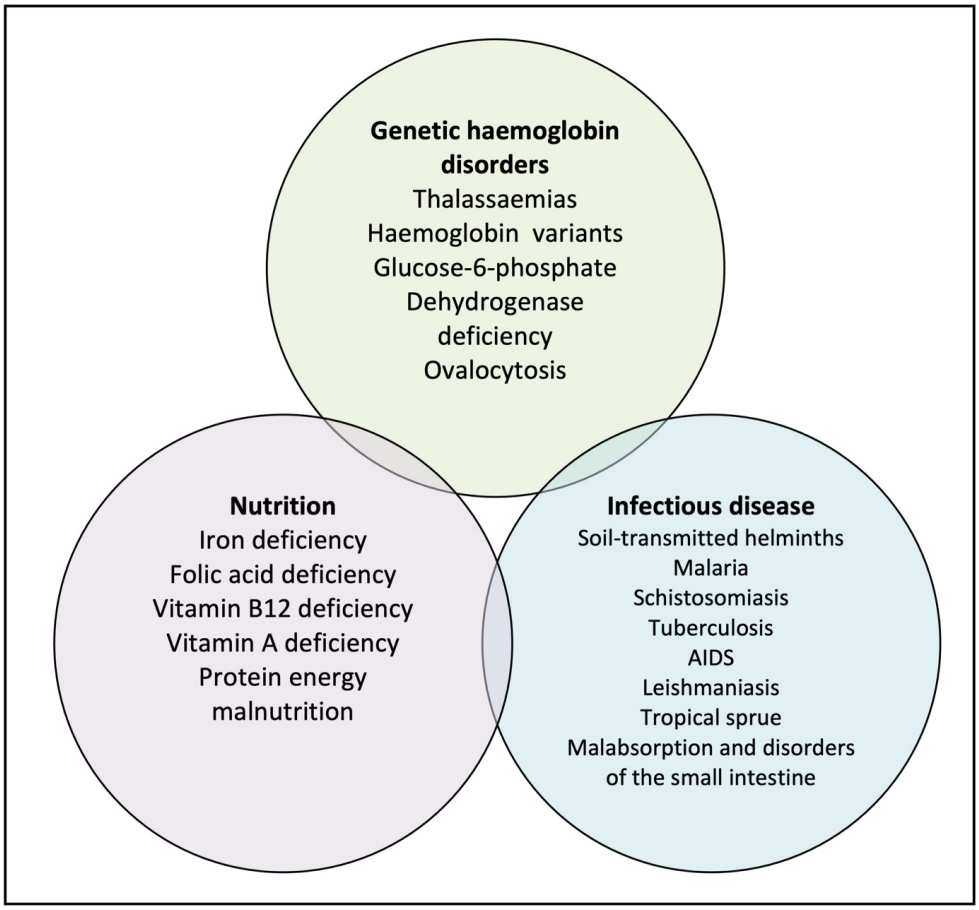

Figure 2. Causes of anemia in low-medium income countries (adapted from Boele van Hensbroek et al 2010)[119]

Malaria is a parasitic infection that often exists in settings with high ID prevalence. The malaria parasite requires iron for growth which in turn disturbs iron metabolism and distribution. [111] The pathophysiology of malarial anemia is complex but comprises of increased hemolysis of infected RBCs, impaired RBC production, reduced iron absorption and increased clearance by the spleen. [120] A single episode of malaria or repeated episodes due to reinfection or failure to clear parasitemia may result in life threatening anemia. [103]

5.3.4 Strategies for prevention and control of anemia

Causes of anemia are multifactorial and therefore strategies for prevention and control require a multi-dimensional and comprehensive approach in public health and nutrition. WHO developed comprehensive packages of public health measure to address different aspects of micronutrient deficiencies and anemia. The package can be implemented in countries with different levels of iron deficiency, anemia, malaria, helminth infections and schistosomiasis. [121, 122] The different interventions in this package aim to 1) increase iron intake, 2) control infectious and parasitic diseases .3) improve nutritional status.

5.3.4.1 Nutritional strategies

5.3.4.1.1 Iron supplementation

Increasing iron uptake and stores is important for preventing and treating iron deficiency. Iron supplementation is recommended by WHO as a public health intervention for children beginning at six months who are at risk of anemia or iron deficiency. [122] Although the safety of iron supplementation in malaria endemic countries has been put in question due the association with increased malaria morbidity and mortality, iron supplementation has been found to be beneficial for improving Hb when other malaria control interventions such as ITNs are utilized. [123, 124]

Under the Malawi National Nutrition Policy Strategic plan (NNPSP) 2007-2012, prevention and control of micronutrient disorders was one of the interventions prioritized to promote optimal infant and young child nutrition status in Malawi. [40]

Routine supplementation with vitamin A, iron and folic acid and deworming are provided through under five clinics or routine child health campaigns. [42] In Malawi, Iron supplements were given to 15.2% of children aged less than 59 months in 2015, [35] which is far less than the 22% of children who are reportedly iron deficient. [125]

5.3.4.1.2 Improvement of nutritional status

Provision of high nutrient diets to infants and young children is key for good nutritional status and prevention of nutritional deficiencies. Low cost interventions such as fortifying flour with iron and folic acid, diet diversification and supplementation of micronutrients such as vitamin A as well as have been recommended by WHO as steps to improve anemic status among children. [126]
In Malawi, routine supplementation with vitamin A is implemented through the expanded package of immunization (EPI) but programmes for ensuring a more adequate dietary requirements are lacking. [42, 127] In 2015, mothers reported that 79% of children aged 6- 59 months ate foods that were rich in vitamin A and 62.2% children had received vitamin A supplements. [35]

5.3.4.2 Infection control

Infectious and parasitic diseases are some of the contributing factors to anemia risk. These diseases are often preventable but still contribute significantly to childhood deaths globally. [18, 112] Interventions for preventable child deaths from infectious diseases include, but are not limited to; improving access to professional health care, improving access to nutrition and micronutrients and childhood immunizations. [128]
Infection prevention and treatment strategies such as immunization and control programmes for malaria, hookworm and schistosomiasis are key to prevent and control anemia among children. [121] Immunization protects children from common childhood diseases such as community acquired pneumonia and diarrhea therefore leading to improved nutrition, general health and reduced anemia. [21]

5.3.4.2.1 Deworming for helminth infestations

Poor sanitation practices including human waste disposal increases risk for intestinal infections such as hookworm and Trichuris in many developing countries. [129] In Malawi, antihelminth medication is distributed for free to young children by the government through deworming campaigns in the community to prevent anemia. In 2015, 53.4% of children aged less than five years received deworming medication. [35]

5.3.4.2.2 Malaria control

Findings from malaria intervention studies have shown compelling evidence that malaria contributes substantially to anemia in endemic regions. [120] A recent systematic review of 29 community-based studies of insecticide- treated nets (ITNs), antimalarial chemoprophylaxis, and insecticide residual spraying found that among children aged less than five years old exposed to between one and two years of any of the malaria control interventions, the mean Hb increase was by 0.76 g/dL compared to those who did not use any malaria control measures. [108] As part of malaria control strategies, WHO recommends provision of ITNs and IPTi to infants and children for malaria prevention which in turn reduces malaria incidence and prevalence. [87] In Malawi, ITNs are provided to under-five children at birth or at the first contact with the health facility. [90]

5.4 Severe anemia

5.4.1 Burden of severe anemia

Severe anemia is characterized by hemoglobin concentration level that is less than 7g/dL or hematocrit below 15% by WHO. [130] Severe anemia is a major public health problem that affects over 10 million children globally and significantly contributes to morbidity and mortality in Sub-Saharan Africa (SSA). [106, 131] In Malawi, the prevalence of severe anemia from a survey in 2015 was 3%. [35] However, scarcity and inconsistency of collecting routine in-patient data may underestimate the number of cases of severe anemia that present to hospital.

5.4.2 Impact of severe anemia

In addition to the negative consequences on cognitive development and physical growth that severe anemia has on children [132], the mortality risk persists for several months after the acute phase in the hospital. [131-134] While in-hospital mortality rate of 6% has been reported in Malawi and mortality rates as high as 53% have been reported in other settings, limited studies have examined the mortality risk that persists in the long term among under-five children with severe anemia. [5]

One longitudinal study in Malawi found that children admitted to hospital with severe anemia died within 6 months after discharge compared to 1.6% community controls without severe anemia. [4, 5] In addition, 5.9% severely anemic children were re-admitted with severe anemia compared to 0.5% of those without severe anemia. [4, 5] [5] Similar post-discharge morbidity and mortality has been reported in Kenya and in Uganda. [131, 135]

5.4.3 Etiological factors for severe anemia

There are limited studies on the etiology of severe anemia. Factors such as vitamin A and vitamin B12 deficiencies, bacterial infections, hookworm, and parasitic infections such as malaria; are common among children with severe anemia. [4, 136] However, unlike in mild or moderate anemia, deficiencies in iron and folic acid are

negatively associated. [4, 119] Hemolysis, blood loss and red cell production failure have been found to be the main mechanisms that lead to severe anemia and the above etiological factors contribute. [119]

5.4.4 Malaria and severe anemia

Malaria has been attributed as a major risk factor for severe anemia in high transmission areas. In severe falciparum malaria infection, there is a decline in hematocrit due to multiple of factors that cause severe anemia by two mechanisms; increased RBC destruction and reduced RBC production. [120, 137-139] Increased erythrocytes destruction results from several mechanisms including; 1) rupture of parasitized RBCs, 2) increased removal of parasitized and non-parasitized RBCs 3) increased RBC clearance by the spleen and 4) intra- and extravascular hemolysis. On the other hand, RBC production is affected by recurrent and frequent falciparum malaria which cause; 1) defective and underdevelopment of RBCs, 2) reduction in cell signaling proteins and RBC producing hormones, and 3) interactions with other ongoing infections. [139]

5.4.4.1 Treatment strategies for severe anemia

In most parts of SSA, treatment for severe anemia aims to prevent and treat the underlying malaria infection as well as to correct the decline in hemoglobin. [121] The standard treatment for severe anemia is hospital admission to hospital with a blood transfusion given at 20 mL per kilogram, combined with presumptive parenteral artesunate; and antibiotics if bacterial infections are suspected. [140] Once the child is stable and able to eat, treatment is completed with a short course of oral artemisinin-based combination therapy, [19] usually artemether-lumefantrine (AL) for three days. [140] Children are often discharged to go home with a short course of iron and folate and typically with no scheduled follow-up.

5.4.4.2 Malaria as a cause of post-discharge severe anemia and mortality

After an episode of malaria-related anemia, it takes about six weeks for hematological recovery to occur [119, 141] Observational studies in Kenya and Malawi

found that among other factors, malaria infection during the recovery period among under-five children hospitalized with severe anemia was a significant contributor to the slow hematological recovery in high malaria transmission settings. [5, 142] After the initial rise in hemoglobin achieved by a blood transfusion; these children experience new or recrudescent malaria infections combined with the delayed hemolysis that occurs due to artesunate treatment which may prolong hematological revival leading to recurrence of severe anemia and death. [131, 143-145]

5.4.4.3 Control strategies for malaria-associated severe anemia

In addition to vector control strategies; ITN use and IRS, WHO recommended strategies for malaria prevention and control include intermittent preventive therapy (IPT) among pregnant women (IPTp) or infants aged between 6-24 months (IPTi) in areas with high malaria transmission and seasonal malaria chemoprevention (SMC) among children in areas that experience seasonal transmission. [94, 98, 146] IPT is a malaria control strategy that calls for administration of full treatment courses of long acting antimalarials at pre-defined intervals irrespective of the individuals' malaria status. [96] Currently there are no control strategies for the high-risk recovery period for under-five children previously treated for severe anemia in malaria endemic countries.

In addition of IPT clearing existing malaria parasitemia or providing prolonged protection against new malaria infections, it has been shown to have a beneficial effect on anemia [96, 120] Antimalarials can be used to create a prophylactic window period after an episode of severe malarial anemia to allow time for the bone marrow to recover, resulting in a more sustained recovery. A recent randomized trial in Malawi found that provision of malaria chemoprevention with full treatment courses of artemether-lumefantrine (AL) to under-five children hospitalized with severe anemia, given in-hospital and at one and two months after discharge, prevented 31% of deaths and/or re-hospitalization due to severe anemia or severe malaria by six months and 41% by three months after discharge in addition to the standard treatment course and protective effect of ITNs. [147]

Similar protective effects were reported in The Gambia, where provision of monthly IPT with SP or weekly pyrimethamine-dapsone targeted during the malaria transmission season reduced the rate of clinical malaria by half and 78% reduction in all-cause hospital readmission in one setting and 78% reduction in severe anemia in another. [148, 149] These findings suggest that provision of complete, rather than intermittent post-discharge malaria chemoprevention (PMC) with long-acting ACTs during recovery is a promising strategy for managing under-five children who were hospitalized with severe anemia. [150]

5.4.4.4 Current delivery approaches of malaria interventions

An effective delivery system is described as one that is accessible to the target population, offered correctly by the provider and given in the right regimen. [151] PMC is an intervention that could offer substantial public health gains in managing under-five children who are at risk of dying. Although PMC is a relatively simple intervention, implementation will require appropriate delivery strategies so that it reaches the population that need it most. However, a major concern is how it can be delivered in an effective and sustainable way. With the aim of achieving a malaria free world, the World Health Organization aims to achieve "universal coverage" of malaria control interventions. [61] However, a major challenge in malaria control is delivery of malaria interventions to the community that need it most. [152-154]

In Malawi, IPTp with SP is delivered free of charge to pregnant women in early second trimester at antenatal clinics. [77] Despite IPTp being effective and affordable, the proportion of pregnant women who received three doses of SP remained at 31% in 2015. [35] On the other hand, ITNs are delivered through two main methods; 1) at the health facility to pregnant women and under five children and 2) through mass distribution in the communities. [78] Utilizing these two delivery approaches, the number of ITNs in each household significantly increased from 71% in 2014 to 82% in 2017, of which 72% of ITNs were obtained from mass distribution campaigns compared to 9% from ANC and only 4% obtained for newborns at birth. [63]

Whereas other IPT strategies such as IPTp have established delivery systems, PMC targets a specific group of children who have come in contact with the health system but there are no guidelines for follow up care. In the Sahel region, WHO recommends provision of seasonal malaria chemoprevention (SMC) previously known as IPT in children (IPTc), to children aged less than five years during the high malaria transmission season for malaria incidence reduction and improvement of anemia status. [146] However, WHO does not specify the programming aspects of SMC except that it should be given using existing community platforms. [146] Utilizing community-delivered models for malaria control and elimination are promising approaches to the management of this infection in areas where access to treatment is difficult [153, 155, 156] However, the first consideration for sustainability is whether it is possible to achieve effective delivery through routine delivery systems.

Multiple studies have shown that community delivery of malaria interventions is effective for increased coverage, adherence as well as more cost-effective that facility-based delivery. One cluster-randomized trial in 12,000 children in The Gambia, reported that village health workers (VHWs) achieved significantly higher coverage of IPTc than delivery through mobile nurse-led clinics and that this was also more cost-effective and equitable. [157] Another randomized clinical trial in Ghana found that both community delivery of SMC through village volunteers and delivery at clinics through health workers achieved high coverage for lower levels of adherence but coverage reduced for adherence to all four courses in both delivery arms. [151]

Whereas in Mali, door to door delivery of SMC achieved higher coverage compared to fixed- point delivery in the community. [158] Another trial in Ghana also found that VHWs achieve higher coverage and adherence at lower costs than facility-based nurses at health centers or outreach clinics. [159] In contrast, community delivery of IPTp was explored in 12 villages in southern Malawi and they found that community delivery achieved better coverage but consequentially antenatal clinic attendance lowered thus affected pregnancy outcomes compared to routine delivery at the health centers. [160] Given the different settings and nature of interventions, a combination of

methods may have to be utilized in each unique setting. In the case of PMC, which targets a specific group of children a tailored approach of delivery will need to be explored.

6 Context of the research

6.1 Malawi: the country

Malawi is a land locked country in Southern Africa. It shares borders with Tanzania in the north, Zambia in the northwest and Mozambique in the east, south and southeast. It has a land coverage area of about 118,500 square kilometers of which 94,276 square kilometers is land, and a quarter of the surface area is covered by Lake Malawi (Fig 2). The country is divided into three regions (North, Centre and South), with a total of 28 administrative districts; six in the Northern Region, nine in the Central Region and thirteen in the Southern Region.

Figure 3. Map of Malawi

With an estimated population of 18 million people Malawi is considered as one of the least developed countries in the world with very poor health and economic indices. [161] Although there has been a reduction in the proportion of Malawians living below the poverty line from 52% in 2004 to 39%, it is still ranked 172 out of 189 countries on the Human Development Index and has the world´s sixth lowest Gross Domestic Product (GDP) per capita. [39, 162]

6.2 Health service system in Malawi

The Malawi health service delivery system is pyramidal, consisting of tertiary, secondary and primary care levels. Secondary care health services account for 9.5% of all health care facilities and are provided at district and Christian Health Association of Malawi (CHAM) facilities. They provide outpatient and inpatient services for the community as well as referral services to health centers and community hospitals. The tertiary level of health services is intended for provision of specialist health care and they are provided at Central hospitals. However; in reality, up to 70% of the health care services they provide are either primary or secondary level services due to leniency in the control systems. [70, 163]

Primary care is delivered through clinics and health centers where curative, maternity, and preventive services are offered. Malawi adopted the integrated management of childhood illnesses (IMCI) approach for comprehensive and integrated management of common childhood illnesses. Nearly 70% of health facilities offer basic child health interventions using IMCI approach. At community level, childhood illnesses are managed through the integrated community case management (iCCM) approach in more than 3,500 village health clinics (VHCs). The iCCM strategy targets rural communities who have challenges with access to health care and is aimed at community health workers (CHWs) providing timely diagnosis, treatment and referral services for the three common childhood illnesses; malaria, pneumonia and diarrhea. [164]

A total of 30 countries have adopted iCCM as a strategy to increase access and coverage of treatment interventions for childhood illnesses. Despite the iCCM programme being rolled out in Malawi in 2007, several national-level evaluations between 2013 and 2017 have reported that iCCM has had minimal impact on under-five mortality. Malawi continues to experience a high burden of infectious disease, in particular HIV/AIDS, respiratory infections, malaria, diarrheal diseases and perinatal conditions. [165, 166] However, the coverage of most childhood interventions has always been high, with the national immunization coverage at 85%. [163]

6.3 Community health workers in Malawi

Use of community-based programs are effective at reducing mortality low- and medium-income countries (LMCI) such as SSA. [156] In Malawi access to quality health care is limited and this is a major challenge. It is estimated that only 54% of the Malawian population resides within 5 kilometres radius of a health facility and even patients who do reach a health facility, encounter a shortage of health care services. [164, 167] There are approximately 7 doctors/clinicians and 37 qualified nurses per 100,000 population; signifying the need for minimally trained health personnel like HSAs. [163), 168] They have greatly contributed to the delivery of preventive health services in rural areas. [156, 169-171] In Malawi where 17 % of the population are children, CHWs are crucial in achieving healthy communities. [78]

In Malawi, iCCM is provided by CHWs known as Health Surveillance Assistants (HSAs). HSAs were initially recruited and trained by the Ministry of Health (MoH) as CHWs for smallpox vaccinations in 1960s and they create a link between the health care system and the community. [70, 164] [172] It was in 2008 that the government of Malawi with support from United Nations children's fund (UNICEF) established a programme to train this existing cadre of CHWs to provide iCCM in hard-to-reach areas with limited access to health facilities. HSAs have at least 2 years of Malawi secondary school education with no formal medical training. They receive a 12-week training course enables them to diagnose and treat the most common childhood illnesses such as malaria, pneumonia and diarrhoea.

The job description of HSAs is broad and their roles and responsibilities HSA have evolved over time. In addition to iCCM, HSAs provide health promotion and prevention services, work as environmental health monitors, data collectors and researchers with the duties of nurses being increasingly imparted to them. [169] [173] Apart from this multitude of tasks, HSAs are also required to reside within the community which they serve. [167] The major strengths reported for the motivation as reported by HSAs in communities are team spirit and cooperation, knowledge of local culture, language and environment. [174]

There are many reported technical and social constraints that affect the motivation and job satisfaction of HSAs. They have limited opportunities, limited supervision, limited training, low remuneration, lack of transport and housing to name a few. [169] These have been cited as the major reasons that they are unable to conduct their assigned tasks effectively. [173] Additionally, HSAs are often overloaded with work. There are instances where one HSA oversees a catchment area of an estimated 2364 people instead of the prescribed 1000. [169] Additionally, HSAs have limited training and are often not oriented when new interventions are being introduced in the health system. [175]

7 Problem statement and rationale of thesis

Severe anemia is major global health problem that causes of morbidity and mortality among under-five children in low-medium income countries. Severe anemia has been reported to cause up to 12% mortality rates and 6 % readmission within 6 months after discharge from hospital in Africa. [5] However, after standard in-hospital treatment with a blood transfusion and antimalarials there is no further scheduled follow up. [140] Causes of severe anemia are multifactorial but the major causes in developing countries are infections, malaria and poor nutrition. Malaria, anemia and malnutrition contribute substantially to childhood morbidity in Sub-Saharan Africa, and their respective roles and interactions are complex. [137, 176]

Malnutrition on its own is the underlying cause of poor health in children with nearly 144 million children and nearly half of all deaths in under-five children attributable to undernutrition. [31] All children with severe anemia have some form of malnutrition. [177] On the other hand, *falciparum* malaria is the major cause of malaria complicated by severe anemia and provision of malaria chemoprevention has been found to reduce the risk of death by 31% among children hospitalized with severe anemia. [147]

With this background, it was important to investigate the added risk of death among severely anemic children who also have severe acute anemia as it may be a treatable factor associated with high mortality. Moreover, given that malaria chemoprevention may provide substantial protection to children recovering from severe anemia during the post-discharge period, it was important to identify a strategy that will deliver this intervention most effectively to the children that need it most. Furthermore, it was important to assess if community delivery of this intervention is acceptable and feasible from the provider point of view.

8 Objectives

8.1 General objective

To investigate the mortality risk and the delivery of malaria chemoprevention among under-five children with severe anemia in Malawi.

8.2 Specific objectives

1. To investigate the risk of mortality among children with severe anemia and moderate to severe acute malnutrition.
2. To determine the optimum delivery method of post discharge malaria chemoprevention among children recovering from severe anemia.
3. To determine the feasibility of utilizing community health workers in delivery of post-discharge malaria chemoprevention among children recovering from severe anemia.

9 Methodology

9.1 Study setting, design and population

9.1.1 Study setting

All three studies were conducted in the Southern region of Malawi. Paper I was conducted at Queen Elizabeth Central Hospital (QECH) in the city of Blantyre and Chikhwawa district Hospital in rural Chikhwawa district. The 1000 bed, urban QECH is the largest tertiary hospital in the country. It is located in the southern region of the country and it is the main teaching and training hospital for the medical, clinical and nursing colleges. Chikhwawa district hospital on the other hand is in rural Chikhwawa district and caters for the 437,892 people who reside there.

The PMC trial for Papers II and III was conducted in Zomba District. Zomba District (former capital city of Malawi) is in the southern region of the Republic of Malawi and covers 3% of the total land area of Malawi. The District has a total population of 583,167. Health services are provided mainly at health posts in the community, 29 health centers and three tertiary hospitals. In addition, medical treatment is also provided by traditional practitioners and traditional birth attendants. The infant mortality rate in Zomba is 48 deaths/1,000 live births and child mortality is 14.4%, which is among the highest in the country. [161] There is a total of 630 HSAs, who report to the health facilities under the DHO. The PMC trial recruited children from the Zomba central hospital, which is the referral hospital for all health centers and neighboring districts.

9.1.2 Study design

For this thesis, the study designs, population and data collection for each paper have been summarized in Table 1. Paper I was a cohort analysis of data collected from the severe anemia (SEVANA) study in Malawi while Papers II and III were research studies that formed part of the major activities (MAs) of a GLOBVAC funded mixed-methods research project entitled " Post-discharge

Malaria Chemoprevention" (PMC).

Table 1. A summary of the study designs and participants for studies in this thesis.

Papers	Study design	Participants
A cohort analysis of survival and outcomes in severely anaemic children with moderate to severe acute malnutrition in Malawi (Paper I)	Cohort study	330 under-5 children with severe anemia from SEVANA study cohort
Adherence to community versus facility-based delivery of monthly malaria chemoprevention with dihydroartemesinin-piperaquine for the post-discharge management (PMC) of severe anemia in Malawian children: A cluster randomized trial (Paper II)	Cluster-Randomized trial	375 under-5 children with severe anemia at Zomba Central Hospital
Introducing post-discharge malaria chemoprevention (PMC) severe anemia in Malawian children: a qualitative study of community health workers' perceptions and motivation (Paper III)	Qualitative in-depth interviews and focus group discussions	39 Health Surveillance assistants (HSAs) in PMC trial

9.1.2.1 Summary of the PMC project

This PMC consortium was collaboration between University of Bergen, University of Malawi, University of Indiana, Liverpool School of Tropical Medicine, the Kenya Medical Research Institute (KEMRI), University of Amsterdam and Makerere University. Through five MAs, the project aimed to improve the health of under-five children suffering from severe anemia by providing malaria chemoprevention during the post-discharge period in areas with high prevalence of malaria. Papers II and III were under major activity 2. MA2 was a cluster randomized trial that was conducted in Zomba, Southern Malawi.

9.1.2.2 Summary of the SEVANA project

The SEVANA project that was a collaboration funded by the Wellcome Trust and University of Amsterdam. The aim of this project was to investigate the aetiologies, pathogenesis and long term outcomes among under-five children with severe anemia in Blantyre and Chikhwawa districts in Malawi. This was a long-term follow up study of severely anaemic children in rural and urban Malawi. Severely anaemic children aged less than five years old were enrolled after correction of their anemia at Queen Elizabeth Central Hospital and Chikhwawa district Hospital. For each child enrolled, one child admitted to hospital with another condition and another child from the community were also enrolled as controls.

The primary end-point for this study was the incidence of the first episode of severe anemia within the follow-up period. The 18 months follow-up period was both active and passive. During the active surveillance, follow up visits either at the study clinic or at the child's home were conducted at 1, 3, 6, 12, and 18 months after enrolment and the passive surveillance system entailed that guardians bring their child to the study clinic if any illness was suspected. [4, 5, 119]

9.1.2.3 Study Design and data for Paper I

Paper I, was a prospective study from the SEVANA study in Southern Malawi. We assessed the risk of death, re-hospitalization and recurrence of severe anemia among severely anemic children who also had moderate to severe acute malnutrition. Anonymized data of severely anemic children who had a recorded weight, height , age, hemoglobin concentration and outcome status during the 18-month follow up period was included. We collected baseline information on the socio-demographic characteristics , medical and dietary history and physical examination findings.

Anthropometric measurements were used to calculate z-scores from the median height for weight of the WHO child growth standards. Children who were equal to or below minus two standard deviations from median height for weight, met the WHO definition of moderate to severe malnutrition. Children with a weight for height above minus two were the comparison group. We collected clinical as well as laboratory information for all the scheduled and sick visits up until the last follow up date.

9.1.2.4 Study design and data for Paper II

In paper II, we conducted a five-arm, open label cluster-randomized trial among children aged less than five years with severe anemia (hemoglobin concentration less than 5g/dL) who were admitted to Zomba central hospital's pediatric ward. These children were screened and included if they were aged less than 59 months, weight above 5kg and were stable and discharged to go home after receiving the standard in-hospital care; which included blood transfusion, intravenous artesunate, and antibiotics for suspected bacterial infections. Children with other specific causes of anemia such as trauma, sickle cell disease, heart disease and those who residing out of the catchment area were excluded. Information on socio-demographic characteristics, medical history and physical examinations were collected on pre-tested and structured questionnaires.

We allocated children to each trial arm depending on which village they resided. All villages within Zomba district were randomized to each of the to receive monthly dihydroartemesinin-piperaquine as follows: 1) community-based delivery without an SMS reminder (Com-SMS); 2) community with an SMS reminder (Com+SMS); 3) community-based delivery with an HSA reminder instead of SMS reminder (Com+HSA); 4) facility-based delivery without SMS reminder (Fac-SMS); or 5) facility-based delivery with SMS reminder (Fac+SMS). Detailed descriptions of the methods have been provided in table 2 and in the published trial protocol (Appendix 3). [178]

Table 2. Detailed description of PMC trial delivery methods

Method	Arm	Description
Community-based	Com-SMS	**PMC drugs given at discharge without SMS reminders:** The guardian received all drugs for the first (PMC-1), the second (PMC-2) and the third (PMC-3) course. They were instructed on how and when to give these drugs to the child when being discharged from the hospital.
	Com+SMS	**PMC drugs given at discharge with SMS reminders:** The guardian received all drugs for PMC-1, PMC-2 and PMC-3 and was instructed on how and when to give the drugs to the child. Additionally, they were reminded via SMS to give the drugs to the child a day before each treatment course was due.
	Com+HSA	**PMC drugs given at discharge with HSA reminders:** The guardian receives all drugs for PMC-1, PMC-2 and PMC-3 and was instructed on how and when to give the drugs to the child. Additionally, HSAs who are officially government-supported community-based health workers were reminded via SMS to go and remind the guardian to give the drugs to the child a day before each treatment course was due.

Facility-based	Fac-SMS	**PMC drugs collected from the hospital:** At discharge, the guardian was requested to return to the outpatient department (OPD) of the hospital each month to collect drugs (a treatment course at each time) for PMC-1, PMC-2 and PMC-3. They did not receive any form of reminder other than what was documented in the child's health card.
	Fac+SMS	**PMC drugs collected from the hospital with SMS reminders:** At discharge, the guardian was requested to return to the OPD each month to collect drugs (a treatment course at each time) for PMC-1, PMC-2 and PMC-3. Additionally, they were reminded via SMS to come to the clinic to collect drugs a day before each treatment course was due.

All three monthly, co-formulated dispersible tablets containing 20 mg dihydro-artemisinin and 160 mg piperaquine was given in standard treatment doses according to weight over three days. Caregivers were given instructions to administer three full monthly treatment courses at two (PMC-1), six (PMC-2) and ten weeks (PMC-3). The maximum number of doses that could be administered was nine. Standardized verbal instructions about administration and frequency were given to the primary caregiver and specific dates of administration were documented in the child's health book. The drug blister pack also contained administration instructions in Chichewa. All the caregivers regardless of assigned arm were requested to come back to the study clinic for the end of study assessment at 14-15 weeks after enrolment. After enrolment, the study participants were traced to their home to collect GPRS positions for follow up and ascertain distance from the hospital.

To measure our primary outcome, full adherence; field workers made unannounced home visits to participants' homes collect blister packs and assess if study medication was indeed given to the child participating in the trial. If the caregiver was not at home, they were contacted and visits were made when they were at home. The number of tablets remaining in the blister packs was recorded and if none were remaining "0" was recorded. If the blister pack was missing, the field worker probed to assess if the medicine was given to the child or not. In addition, assessment for adverse events was made and children were referred to the nearest health facility if they were sick.

We collected a blood sample from a finger prick to check hemoglobin levels using the Hemocue 301 and peripheral slides for malaria microscopy after enrollment, at every sick visit and end of study visit at the study clinic.

9.1.2.5 Study design for paper III

For paper III, we used qualitative research methods to assess the acceptability and perceptions of health workers particularly health surveillance assistants

(HSAs) who were involved in the PMC trial. Children who were assigned to the community + HSA arm (COM+HSA) were given 3 months of PMC medication to take while at home and receive a monthly reminder from the HSA.

Prior to commencement of the main trial we conducted training workshops with all HSAs who were working within the catchment area of Zomba district health office. [179] The workshops covered topics about severe anemia, causes, diagnosis and complications. We also explained their role in the PMC trial and the activities that they were expected to carry out during the study. On the day when the child was discharged from the hospital, the mother was linked to the HSA in their catchment area. The HSA responsible for the catchment area had their contact details collected and were informed about the participant's participation in the trial, location and dates of medicine administration. When the HSA was not available the research staff contacted him/her through the phone or visited his/her home. One or two days prior to the scheduled date of drug administration, the HSA was expected go to the child's home to remind the caretaker to administer the study drug. The HSAs are not compensated for this work and it is expected that it is undertaken on "any other duties assigned" basis.

Utilizing interview guides, three independent research assistants conducted semi-structured in-depth interviews (IDIs) and focus group discussions (FGDs) in the local language of Chichewa . All interviews were digitally recorded, transcribed verbatim and translated into English by the research assistants. The information gathered was supplemented by ethnographic methodologies like observations and informal interviews from myself. Transcripts were loaded into NVIVO 11 for analysis. Each IDI and FGD was deductively and inductively coded and a coding system was developed based on the research objectives and the analytical framework of motivation. The coding system was

expanded during the coding process to capture emerging themes outside of the original study objectives.

9.1.2.5.1 In-depth interviews

The aim of IDIs is to uncover the perceptions and understandings of a topic as seen from the interviewees' point of view. [180] The semi-structured interview technique is based upon set topics, but has an open-ended approach which allow the informant to speak at length without interruption. This was best suited for this study because we aimed to uncover the perceptions and understandings of PMC from the interviewees' point of view. [181] In this study the interviewers used a list of guiding questions based on the pre-defined research questions. The interviewers probed when the responses were unclear and to seek clarity on the meanings.

9.1.2.5.2 Focus group discussions

An FGD involves a small group of participants (normally 6-12) with a moderator guiding the discussion with the use of a topic of discussion guide. [181] Although saturation was achieved with the initial IDIs that were conducted, the choice to conduct FGDs was made to further explore the different experiences and motivations between HSAs who made at least one hone visit and those who did not conduct any home visit and to explore further the findings from the analysis of the IDIs.

With additional information provided by the caregivers at their last study visit, we were able to determine whether HSAs made the visits to the children, the timing of the visit, the information given to the caregiver and any other activities. Thereafter we invited additional HSAs who were not involved in the IDIs. We grouped them into two, one group who made at least one visit and the other who did not conduct any visit. Utilizing a topic guide, a nurse and a research assistant conducted the FGDs separately in Chichewa. A description of the participants in FGDs has been provided in table 5.

9.2 Sample sizes

For Paper I, we used open EPI version 3 (www.openepi.com) to calculate the sample size. We calculated that we needed 201 children in each group to detect a two-fold risk of death among children with MAM/SAM compared to those without, with a 95% two-sided confidence interval and 80% power. However, due to the limited number of children among the MAM/SAM group and using the same assumptions as above with a sample size ratio of one to five (MAM/SAM/ no MAM/SAM); our study had a statistical power of 76.4%.

For Paper II, the sample size was determined on the primary outcome of full adherence, which was defined by as the administration of all nine doses of dihydroartemesinin-piperaquine. We estimated that, in order to detect 25% increase from medium adherence to full adherence and allowing 10% losses to follow up and intra-cluster correlation of 0.1; 25 clusters (villages) with three children each (75 each and 375 overall) were required to give our trial 80% power.

Given that Paper III was a qualitative study, no sample size was calculation was made. We purposely sampled the 39 HSAs because children under their care had completed the trial and this was important so as not to contaminate HSAs' behavior on the on-going trial. While we achieved saturation with the first 20 IDIs, we added the two FGDs to explore further the findings that had been identified in the initial analysis of the IDIs.

9.3 Statistical analysis

Data for Papers I and II were coded and analyzed using STATA 14 and 15 (StataCorp, College station, Texas, USA) respectively. We used appropriate descriptive statistics to summarize data, with mean or median (IQR) for continuous data, and frequencies and percentages for categorical data.
For Paper I, we calculated mortality rates among the severely anemic children with moderate to severe acute malnutrition and those without. We measured

time to death by survival analysis, using Kaplan-Meier curves to compare the probability of death between the two groups over the 18-month study period. Significance was calculated using a log-rank test statistic.

Incidence rates for other outcomes (re-hospitalization, malaria and severe anemia recurrence) were also calculated and compared between severely aneamic children with MAM/SAM and those with severe anemia alone. For the malaria incidence rate, 14 days was subtracted from the total time at risk for each episode from the child-years follow-up with each case of clinical malaria treated with AL.

For Paper II, the primary outcome was full adherence. Our analysis was by intention to treat at cluster and participant levels as per the agreed statistical analysis plan (SAP). A factorial design analysis approach was used to investigate interaction between the effect of community compared to facility delivery and the pooled effect of SMS and interaction terms were included in factorial models to assess the strength of interaction. We also did several subgroup analyses for the primary and secondary outcomes adjusted for clustering, socioeconomic and demographic variables stratified by each intervention arm with the Facility-SMS (Fac-SMS) group as the reference group.

For the secondary outcomes, the different levels of adherence were compared between the five groups. We used Poisson regression for the total number of doses administered. The unadjusted and adjusted incidence rate ratios (IRR) measuring the percentage of children receiving PMC according to schedule in each arm were obtained and compared between arms and the 95% CI for the IRR have been reported. The estimates of the IRR were adjusted for baseline characteristics using Poisson regression and clustering was accounted for. For all the measures of effect, 95% CIs were provided. The full statistical plan has been provided in the appendix.

No statistical methods or analyses were done for Paper III. However, inductive and deductive analysis and coding was done using NVIVO 11.

9.4 Ethical considerations

Paper I was submitted and approved by the ethics committees of the College of Medicine, University of Malawi and the Liverpool School of Tropical Medicine, United Kingdom. Papers II and III were submitted and approved by the research ethics committees of the College of Medicine in Malawi (COMREC, approval number P·02/15/1679 and the Regional Ethics Committee of Norway, approval number 2015/537 (REK Vest). The trial was registered at ClinicalTrials.gov (identifier: NCT02721420). For all studies, written informed consent explaining the aims and procedures of the studies was obtained from legal caregivers of the participating children in Papers I and II and from HSAs in Paper III prior to data collection. Completed data collection tools were kept in a secure place, only accessible to the research team.

10 Summary of results

10.1 Mortality among under-five children with severe anemia (Paper I)

Our primary objective for this study was to investigate if severely anemic children with moderate to severe acute malnutrition were at increased risk of dying compared to children with severe anemia alone. We also aimed to determine if these children were at higher risk for re-hospitalization, malaria incidence and recurrence of severe anemia during the 18-month follow-up period.

Data of a cohort of 382 under-five children with severe anemia was screened and 330 met the inclusion criteria. A total of 53 children had moderate to severe acute malnutrition (weight for height <-2 of Z-scores) and 27 did not. During the entire study period, a total of 51 children (15.5%) died, while 20 were lost to follow up (6.1%) and 259 (78.5%) completed the 18-month follow-up period. Of the 51 deaths, 17 (5.2%) children died within one month, 10 (3.0%) after three months and 10 (3.0%) after six months post-discharge.

Out of the 51 deaths, 15 (28.3%) were children with MAM/SAM and 36 (13.0%) children had severe anemia alone. The overall incidence of death among all the children was 3.0 (CI 2.2,4.0) children per 1000 child-days of observation. Among the children with MAM/SAM the incidence of death 5.4 (3.0,9.8)/1000 child-days and 2.6 (1.9,3.7)/1000 child-days among children without. This shows that children with MAM/SAM had a twofold risk of dying compared to children who has severe anemia without moderate to severe malnutrition) RR 2.1; CI 0.9,4.2, p=0.03).

In another analysis we found that severely anemic children who were underweight (defined as weight for age <-2 of Z scores) had 3-fold risk of dying compared to those with severe anemia alone (RR 2.8; CI 1.5-5.2, p=0.0006). This is further depicted in the Kaplan-Meier survival curves in

figure 3 which show that children with severe anemia alone had a higher probability of survival compared to those that also had moderate to severe acute malnutrition. However, this was not statistically significant (log rank=2.9, p=0.098).

We further found that more children who had severe anemia alone were readmitted to hospital during the follow up period compared to those with moderate to severe acute malnutrition (4.4% versus 3.5%), (IRR 0.8; CI 0.4-1.7, p=0.62); but this was not statistically significant. In addition, the proportion of children who had a recurring episode of severe anemia was similarly low (1.6% each) in both groups the two groups of severely anemic children (IRR 1.1, CI 0.3-2.8, p=0.8) over the entire study period. The main findings have been summarized in Table 3 below.

Table 3. Summary of findings of Paper I

Event	Moderate to severe malnutrition		Severe anaemia alone		Rate ratio (CI)	p-value
	Total events	Incidence rate (1000 person-days)	Total events	Incidence rate (1000 person-days)		
Deaths n (%)	15 (28.3)	5.4	36 (13.0)	2.6	2.1 (0.9, 4.2)	0.03
Hospitalisation n (%)	9 (3.5)	1.5	76 (4.4)	1.8	0.8 (0.4, 1.7)	0.62
Malaria incidence n (%)	106 (40.8)	17.3	573 (32.3)	13.0	1.3 (1.04, 1.6)	0.02[a]
Severe anaemia recurrence n (%)	5 (1.6)	0.8	32 (1.6)	0.7	1.1 (0.3, 2.8)	0.81

10.2 Delivery of malaria chemoprevention for post-discharge management of children with severe anemia (Paper II)

We conducted this 5-arm cluster randomized to evaluate the most effective method of delivering malaria chemoprevention with dihydroartemisinin-piperaquine for post-discharge management of under-five children recovering from severe anemia. The primary outcome was full adherence of DP (9 doses) during the 3 PMC courses. We screened 667 children who were admitted to Zomba Central Hospital with severe anemia between 24 March 2016 and 09 October 2018. A total of 375 children were eligible, enrolled and randomized as follows: (Com-SMS=69; Com+SMS=75; Com+HSA=79; Fac-SMS=77; Fac+SMS=75).

Overall, 93.6% were followed successfully until the end of the study; four children were withdrawn by their parents before the first home visit, four children died during the follow up period and twenty children were not brought for the end of study visit.Generally, the baseline characteristics of the children were similar across all the study arms. The median age and weight for all the participants were 29 months (IQR 19–39) and 11.3 kg (IQR 9.6–13.2), respectively. There were generally more males in each arm except in the Fac+SMS arm (48% male). A total of 99.7% of the children had malaria infection (confirmed by malaria rapid diagnostic test or malaria microscopy) and treated with intravenous or intramuscular artesunate during hospital admission.

All the children in the study received at least one blood transfusion. However, only 1.6 % of the children had a recent history of severe anemia (four weeks prior to hospitalization) that required a blood transfusion. Over 76.5% reported possession and use of an insecticide-treated nets (ITN) the previous night prior to admission. Fever was the most common presenting symptom (98%). Out of

the 150 participants who were expected to receive SMS reminders, only 25 (18.0%) reported to have received at least one SMS.

Overall, we found that adherence to all the 9 doses of DP was reported in 63.1% of the children. More children who received PMC in the community-based reported full adherence compared to those in the facility-based arms (70.6% versus 52.7%, respectively). Children who received PMC in the community with an SMS reminder reported the highest proportion of full adherence (79.7%) compared to those in the community without an SMS reminder (63.2%), or with an HSA reminder (68.4%), and also those from the facility-based arm without an SMS reminder (51.3%) and with an SMS reminder (52.0%). Generally, when PMC was delivered through the community-based methods, adherence was greater than facility-based methods (IRR=1.24; 95%CI 1.10, 1.44 p=0.006) and this was observed in both the SMS recipients (IRR=1.41; 95%CI 1.21, 1·64, p<0.001) and in the non-SMS recipients (IRR=1.37; 95%CI 1.18, 1.61, p<0.001).

10.3 Feasibility of utilizing HSAs for PMC delivery (Paper III)

In paper III we conducted individual IDIs with 20 HSAs in December 2016 and two focus groups in March 2018 with 19 HSAs who had children who participated in the PMC trial from their catchment areas. We found that most HSAs conducted at least one the home visit to give reminders to the caregivers, and only fourteen did not conduct a single visit. Appendices 2 and 3 provide characteristics of the HSAs who participated in the IDIs and FGDs.

All HSAs reported that that they were intrinsically motivated to take part in PMC because it is important and beneficial intervention that saves the lives of children who have malaria and anemia. The main source of motivation was a sense of obligation and altruism towards making sure the children in their community were healthy and recovering from this life-threatening

complication of malaria. They described that the assignment to visit children in their homes and provide reminders was relatively easy and did not require any additional effort. Many also reported gave them the opportunity to conduct other tasks that are part of their job description such as providing information on good hygiene. Most of the HSAs also said that this intervention helped them gain new knowledge that there is medication that can prevent children from malaria. Many HSAs reported that they appreciated being recognized for their importance in PMC. Knowing the participant's family, close distance and the need to maintain the trust of the community were also reported factors that enabled HSAs to adhere to the home visits.

Despite reporting high motivation to conduct home visits, many of the HSAs did not conduct all three home visits. They reported that they had faced challenges, which hindered them from doing so. Most of them reported that their workload was already too much to include home visits for PMC when it is not even on their job description. They also reported that the training they received at the beginning of the project was not adequate. A one-day training did not give them room to get enough understanding and they would have preferred at least three days of training and follow up refresher trainings to allow them to process the information. On the other hand, others reported that the initial training was adequate, but they were not supervised adequately by the research team during the project and they were unsure that what they were doing was correct. Another barrier that was reported by a few of the HSAs was that there was a negative reception from caregivers who were worried that the community questioned why they were visited on multiple occasions and speculated that there were problems in the household.

11 Discussion

11.1 Methodological issues

11.1.1 Study design and sample size

This thesis presents findings from studies among children aged less than five years old who were admitted to the hospital with severe anemia in Southern Malawi. Specifically, we explored the impact that moderate to severe acute malnutrition has among children with severe anemia, the different methods that can be employed to delivery DP for post discharge malaria chemoprevention during recovery and the feasibility of utilizing HSAs to provide home reminders to caregivers of children recovering from severe anemia.

In paper I, we used data from a prospective cohort study among severely anaemic children admitted to QECH in Blantyre and Chikwawa district hospital in Chikwawa. [4] A cohort study is a type of non-experimental or observational study design where by a cohort (a group of individuals), are followed up over a period of time from the time of exposure to the they experience the outcome of interest or not. This study design is useful for establishing temporal associations between the exposure and outcome, therefore directly measuring disease incidence. [182]

Although more expensive and time consuming compared to other observational designs such as case-control or cross-sectional studies, the main advantage of cohort studies is that it is less susceptible to bias. On the other hand, it is also not efficient for rare outcomes compared to case-control studies and provides less control for confounding factors as compared to randomized-controlled trails. [183] The cohort study design was appropriate for our study because we wanted to determine the incidence rates of death between severely anemic under-five children who had moderate to severe acute malnutrition compared to those who did not over an 18-month period.

In paper II, we conducted a five-arm cluster randomized trial that aimed to assess the most effective delivery method of DP for PMC by comparing

community-based s and facility-based methods among children recovering from severe anemia. [178] A cluster-randomized trial (CRT) is a trial in which individuals are randomized in groups (clusters) and not individually. [184] A cluster is defined as a unit comprising of a group of individuals such as a village, a school, geographic regions etc. [185]. In a CRT, all individuals within a given cluster are assigned to the same arm. [186] CRTs are used when; the nature of the intervention dictates its application at the community level, to minimize contamination when community allocation is more feasible, to measure and improve overall impact of the intervention on the population. [184] We utilized the CRT study design because blinding of participants or study staff would not have been possible, and we wanted to make sure that children coming from the same village were assigned the same intervention arm to minimize contamination. Contamination would occur if children from the same village were assigned different intervention arms, there will be too much shared knowledge and one individual's changing behavior can influence another individual assigned to a different arm. [187]

Other advantages of a CRT study design are that they offer cost and time efficiencies, it's appropriate for community interventions which are naturally applied to the cluster level and they enhance participant compliance to some degree. [184] Although CRTs are an efficient methodology for sampling, they also have a few disadvantages compared to individually randomized trials. They are more complex in design, they require more study participants to obtain the same statistical power and more complex analysis as they require inferences be made at the cluster level and not at the individual level. [184]

In paper III, we conducted a qualitative study aimed at exploring the feasibility of HSAs to conduct home visit reminders to caregivers for PMC. Qualitative research is a systematic scientific inquiry which seeks to build a holistic, largely narrative, description to inform the researcher's understanding of a social or cultural phenomenon. [181] Qualitative research is a broad term for

investigative methodologies. In comparison to quantitative research, qualitative research focuses on words rather than numbers, depth rather than breadth. [188] Qualitative methods are exploratory; they seek to unearth people's opinions, feelings, and experiences and understand behavior. This differs from quantitative research, which attempts to gather data by objective methods to provide information about associations, test a predefined hypothesis and predictions. [189] There are four different types of qualitative methods, phenomenology, ethnography, grounded theory and case studies. [181]

Our study was largely phenomenological in nature. A phenomenological study is one, which is used to study phenomena such as events, situations and experiences among others. [190, 191] For this we utilized three qualitative research techniques; in-depth interviews, focus group discussions and ethnographic techniques such as my observations and experiences during the field work in the main PMC trial.

In-depth interviews are a data collection method that involves direct one on one engagement with individual participants. [192] IDIs allow the researcher to gather more extensive and insightful information compared to other data collection techniques. Additionally, the researcher can establish a rapport, ask follow-up questions, explore emerging ideas and able to get real opinions without the effect of peer pressure dynamics that might exist in FGDs. On the other hand, they can be time consuming and require an expert interviewer. We conducted the IDIs in a semi-structured approach by using an interview guide with preset open-ended questions to explore our respondents more systematically and comprehensively while staying focused on our objectives. [192]

Focus group discussions involve gathering of about six to twelve people of similar backgrounds or experiences to discuss their knowledge, attitudes, experiences and perceptions of a specific topic. We conducted the two FDGs because they are useful for gathering in-depth information about the opinions

and thoughts of the community in relatively a short time and to "triangulate" with our findings from IDIs. While they are structured and led by an interviewer, the questions are set loosely to allow open and expressive discussions among the participants. [180] FGDs require a skilled moderator who does show judgement or bias based on his/her opinion or experiences.

The main disadvantages of FGDs are that respondents may be reluctant to share the true opinions on sensitive topics because of fear of judgement or the opinions shared are influenced by the dynamics and set-up of the group. [190] In our study, both FGDs were conducted by experienced research assistants and myself and given that the topic was not a sensitive one, we believe that the opinions and experiences expressed were accurate. In addition to the above methods, we integrated observations and experiences from the trial staff and from reports from caregivers of the children who participated in trial. [190]

11.1.1.1Sample size

A sample size is calculated to determine the number of participants that will be required to include in a clinical study to have enough power to adequately answer the research question. [193] For Paper I, we calculated the sample size using Open Epi (www.openepi.com) based on the findings from Malawi among children with severe acute malnutrition. [33] To give 80 % statistical power and 95 % confidence to detect a risk difference of 20% between severely anemic children with MAM/SAM compared to those with severe anemia alone , 63 children were required in each study group. However, there were only 56 severely anemic children with moderate to severe malnutrition in the study. We did a post-hoc calculation to find the power of our study and found that it gave us a power of 74.6%.

Paper II was a CRT, whereby villages (clusters) rather than individual children were randomized. For CRTs, the sample size is calculated based on the number and size of clusters that need to be sampled. [186] In the sample size calculation,

we adjusted the design effect using the coefficient of variation method that assumes that the clusters have variable sizes. [194, 195] We assumed an intra-cluster correlation coefficient (ICC) of 0.1 and allowing for 20% loss-to-follow-up or efficiency loss due to varying cluster sizes, a sample size of 125 clusters (villages) of an average of 3 children per village (i.e. 75 children per arm and 375 overall), had 80% power to detect a 25% absolute increase in coverage from an estimated 50% in the standard out-patient groups to 75% in the arms supported by mobile phone reminders (α=0.05).

The ICC is the ratio of the between cluster variance to the total variance and it is used to quantify how much more similar outcomes are for individuals within clusters than for those in different clusters. [184] It has a value between 0 and 1, (0 indicates that individuals within clusters are no more like each other than individuals from different clusters (there is no between-cluster variability), 1 indicates that individuals within the same cluster all have identical outcomes (there is no within-cluster variability). [196, 197] We used an ICC of 0.1 based on a delivery trial of SMC in the Gambia. [157]

Being a qualitative study, no sample size calculation was done for paper III. As opposed to quantitative research methods which employ probability and statistical sampling, qualitative sampling is purposive and based on their capacity to get rich information relevant to the focus of the topic and the extent at which saturation (no new information given) is achieved. [198, 199] We conducted the IDIs to get a deeper understanding of the motivation, perceptions and experiences which were different and might have been unique for each HSAs. Although we achieved saturation with the IDIs, we found it was important to conduct additional FGDs based on the initial coding of the IDIs.

11.2 Internal validity

Internal validity refers to the extent which a research study can credibly and confidently establish that the findings cannot be explained by any other factors.

[200] Internal validity of a research study can be affected by random and systematic errors (bias). [193]

Random error occurs due to chance and it can be minimized by having an adequate sample size or by reducing errors in measurement. Bias on the other hand arises from deviation in the collection, analysis, interpretation and publication of data leading to conclusions that systemically underestimate or overestimate the true relationship between an exposure and outcome under study. All epidemiological studies are susceptible to bias. [193] Internal validity of a study can be compromised by three factors; selection bias, information bias and confounding.

11.2.1 Selection bias

Selection bias results from any error in selecting study participants or those affecting participation. [200] This can occur when two groups are not similar in the response, non-response and attrition rates and therefore the group are not comparable. [193] The commonest source of selection bias in prospective cohort studies is errors in selecting study participants (recruitment bias) and loss-to-follow up, whereby study participants are no longer available or willing to continue participation. Distortion occurs when there is differential loss to follow up with respect to both the exposure and the outcome (more losses among those exposed with an outcome). [193]

11.2.1.1Sampling strategies

In Paper 1, we screened all the children who had severe anemia based on a clear entry criterion which also defined the exposure and outcome variables to avoid differential and non-differential misclassification. However, 13% of the children screened were excluded due to missing anthropometric data. This was a potential source of selection bias because the children who were excluded may have been significantly different in their exposure and outcome status from the children that were included (differential misclassification). [193] This could have led to underestimation or overestimation of the results. However,

our result was less likely to be affected because there was 94 % response rate of all the children who had all data points recorded. Another major potential for selection bias in paper I was our sampling technique. We conveniently sampled children from an existing study and therefore the exposed group (52) had a slightly low number of eligible children which would make our study underpowered. However, five times the required number of the unexposed group (277) was eligible and enrolled. This gave us a statistically relevant result with narrow confidence intervals.

Similar to individually randomized trials, cluster randomized trials are also at risk of bias. The comparability of study groups can be challenged because groups of trial participants rather than individual participants are randomized. [201] Recruitment/selection bias can occur when individuals are recruited to the trial after the clusters have been randomized, as the knowledge of whether each cluster is an 'intervention' or 'control' cluster could affect the types of participants recruited. [187, 202] To minimize this potential selection bias in paper II, the randomization was done by the trial statistician who was not aware of the villages and he was not part of the data collection team at any time during the trial. In addition, screening and enrolment of study participants was done by the clinical team while the allocation was done by the data officer.

Once a child was enrolled, the village from which they reside was given to the data officer. The data officer entered the name of the village and traditional authority into the pre-programmed randomization list which generated the intervention arm the child was assigned to. The data officer was not involved in screening or enrolment of trial participants. It is very unlikely that selection bias affected our results in paper II because the allocation was revealed and recorded at the same time to the clinical team and manipulation of the assignment was avoided. [203]

11.2.1.2 Loss to follow up

Loss to follow up (LTFU) refers to when research participants are no longer available or unwilling to continue participation in the study and it poses a threat to internal validity. [201] Bias results when there are different rates of losses between study groups and participants who are lost to follow are different from those that complete the study as this may reduce the statistical power of the study. [193]

In paper I, the overall proportion that was lost to follow up was only 6% during the entire the 18-month study period. Despite the differential loss to follow up (3.8% in the exposed group compared to 6.5% among the unexposed) that could have lowered the incidence of mortality among severely anemia children with moderate to severe acute malnutrition, we still observed a statistically significant difference in mortality between these two groups. We found that there was no significant difference in the age, location, severity of anemia and death rates among those that were lost to follow up compared to those that had a documented outcome.

In CRTs, differential loss of clusters is potential source of selection bias. [184] In paper II, we only had four children (1.1%) whose caregivers withdrew participation prior to the first follow up visit and 16 children (4.2%) who relocated and could not be traced. This was equally distributed across all five study arms. This represented a loss to follow up of 5.3%. This was considerably a small loss to follow up rate when compared to studies that have shown that a loss to follow up of up to 20% might not introduce bias provided it is similar between intervention groups and it is included when calculating the sample size to detect the given effect during the design stage of the trial. [182, 193, 204] In our sample size calculation, we allowed for a 10% loss to follow up and therefore this not likely to affect our results. To minimize losses to follow up in this trial, our research nurses were well trained and experienced. They provided comprehensive information that emphasized the importance of adhering to the

follow up schedule during the informed consent process. In addition to this, one of our eligibility criteria was to exclude children whose permanent residence was outside of the catchment area. Furthermore, field workers exhausted all necessary avenues to contact caregivers of children when children did not come for their end of study visit.

11.2.2 Information bias

Information bias occurs when there is an error in measurement or recording of the exposure or the outcome variables. [193] Like all other bias in research, information bias produces inaccurate results and conclusions. Information bias is also referred to as misclassification of which there are two types. Non-differential misclassification occurs when the degree of misclassification of exposure status among those with and those without the disease is the same and differential misclassification occurs when the degree of misclassification of exposure status among those with and those without the disease is different. Non- differential misclassification leads to bias towards the null, therefore diluting the true effect while differential misclassification can bias the effect in either direction depending on the number misclassified. [205]

In paper I, we minimized measurement bias by having a clear eligibility criterion to avoid misclassifying the exposed group (severely anemia children with MAM/SAM) and those who did not have MAM/SAM. We also minimized any type of misclassification of our health outcome status by using objective definitions and measurement of our key outcomes. Children were recorded as either died, alive or lost to follow up at the end of the study period. However, because we excluded children with missing outcome data and those that died on the same day they were recruited did not contribute time to our analysis, we might have underestimated the true effect. To minimize recall bias, all information in the main study was entered at the point of contact.

For paper II, the potential source of misclassification was how our outcome (adherence) was measured. Field workers conducted home visits to do a pill

count and confirm if the DP was given to the child participating in the trial. The number of tablets remaining in the blister pack was recorded. If there was no evidence that the medication was given it was assumed that none of the tablets were administered to the child as self-reported adherence is not objective. [206] Although pill count is not the gold standard of measuring adherence to medication and is a source of potential measurement error; it is an objective, noninvasive and suitable alternative to therapeutic drug monitoring and self-reported adherence. [207]

There are two main problems with this approach, firstly the absence of the tablets does not necessarily mean that the medication was given to the child in the trial and such this method might have overestimated the levels of adherence. Secondly, absence of a blister pack did not mean that the study medication was not given to the child. However, since these approaches were both applied across all trial arms, it is unlikely that there would have been differential misclassification that would affect our results. To further minimize information bias, home visits were conducted a day or two after administration of the last dose of DP to minimize recall bias.

Although cluster-randomized trials are more pragmatic and the best suited design for our study objectives, they have challenges during analysis. [208] Many CRTs use incorrect methods of analysis, whereby they are analyzed as if individuals had been randomized and clustering is ignored when the unit of analysis is different from the unit of allocation (unit-of-analysis error). [209] This leads to artificially small p-values and this can result in false positive conclusions that the intervention had an effect. [184, 208] To avoid this bias, we included a mixed effects model taking clustering into consideration. We found that village did not have a significant random effect, (likelihood ratio 2.9^{-05}, p=0.498) and the ICC was very small (7.56^{-06}), indicating that there were no correlations between individuals coming from the same village relative to those form different villages. Therefore, the data was as good as individual data and give the same results as analysis at the individual level..

11.2.3 Confounding

Confounding is a distortion of the association between an exposure that occurs when the study groups differ with respect to other factors that is associated with the outcome. Different from selection or information bias which are introduced by the investigator or study participants, confounding can be adjusted for. [193]

A confounding factor must be associated with the exposure and the outcome, must be distributed unequally among the comparison groups and must not be on the causal pathway between an exposure and an outcome. [193] Controlling for confounding can be done during the design or the analysis stage. Methods for controlling for confounding during the design stage include randomization, restriction and matching and during analysis; standardization, stratification and multivariate analysis.

We controlled for confounding during analysis in paper I. We used the Cochran Mantel-Haenszel method to calculate risk of death between severely anemia children with moderate to severe acute malnutrition compared to those with severe anemia alone. The Cochran Mantel-Haenszel is a technique that generates an estimate of an association between an exposure and an outcome after adjusting or considering confounding by stratifying data into two or more levels of the confounder. [210]

In paper II, our study design was randomized by clusters (CRT). Randomization is a process where study participants are randomly allocated to intervention arms and it is a powerful method of control and prevent confounding. [182] This gives each participant an equal chance of being assigned to any intervention group and therefore likely that groups will have similar distribution of possible confounding factors such as age, gender and residence and therefore making them comparable. [193]

During analysis of paper II, confounding was controlled for by using multivariable analysis statistics. [210] Our main strategy for analysis was applied

univariate and multivariate Poisson regression models. After univariate analysis, we found that common risk factors such as age and gender were similarly distributed across all the trial arms, and therefore we only included distance from the hospital and literacy in our final multivariate model as this was associated with adherence.

11.3 Discussion on External validity

External validity is the extent to which the results of a research study can be generalized to other populations and contexts. [182] External validity is influenced by internal validity. [211]

For paper I, we conveniently sampled children who participated in a cohort study and followed them up for 18 months. Although our simple size was limited, the dropout rate was low and the follow up period was long. Therefore, we were able to detect statistically significant findings. On the other hand, children who were in the study were likely to have had more access and contact with health care than those outside research contexts, but this would mean that we might have underestimated the results. Based on this, our findings can be generalized to the population of under-five children with severe anemia.

In our cluster randomized study for paper II, we randomized all the villages in Zomba district so that all children from that village would be assigned to the same intervention arm and that all villages had an equal chance of participating. In addition, our sample size was large enough to ensure adequate power with clustering considered and a low dropout rate. The major threat to generalizing our study findings to “real life” is that adherence might have been overestimated because caregivers would be influenced to administer medication because they were under study and received a home visit each month.

However, considering that all participants in all the intervention arms received a home visit each month, the difference in levels of adherent would still be detected and can be generalized to other ecological settings which have a

similar health system like Malawi.

On the other hand, the use of SMS to increase adherence was not effective but then only a few caregivers received at least one reminder. Therefore, this should be taken into consideration when interpreting our findings.

11.4 Bias in qualitative research

Paper III used qualitative research methods. Qualitative research is often criticized for lacking transparency in relation to the analytical processes employed, which hinders the ability of the reader to critically appraise study findings. [212]

Although "internal validity" of quantitative research is crucial for interpreting its' finding, the opposite is true for qualitative research. [213] Qualitative studies focus on explorations of phenomena to contribute to the understanding of the topic in question and do not make any causal inferences and each one is unique. [181] Despite this, it is equally important to promote rigor and ensure that the quality or "authenticity" of the data and the quality or "trustworthiness" of the analysis are valid in qualitative research. [214] This can be achieved by employing at least two out of the eight methods to verify qualitative research findings. The recommended procedures are: Prolonged engagement and persistent observation, triangulation, peer review or debriefing, negative case analysis, clarification of researcher bias (reflexivity), member checking, rich, thick descriptions and external audits. [213]

For paper III, we utilized triangulation, reflexivity and prolonged engagement. Triangulation refers to making use of multiple and different sources of information to provide corroborating evidence. [214] In addition to the IDIs and FGDs, we used information from caregivers and research field team to corroborate information that the HSAs provided.

Clarifying researcher bias also known as reflexivity; is a process in which the researcher is open about his or her position and assumptions from the onset of the study that would explain the approach and interpretation of the inquiry. [213]

In this paper, only one FGD was moderated by the researcher and the remaining FGD and 20 IDIs were moderated by research assistants who were not part of the research team.

Prolonged engagement and persistent observation refer to validating research by working with people for long periods of time. [198, 215] Given that the researchers are health workers who have regular interactions with HSAs and also during the PMC study, experiences and observations of the researchers provided the opportunity to have more insight into the different aspects of HSAs and their lives.

In qualitative research, external validity can be likened to the concept of "transferability", which refers to the ability of findings from one study to be transferred to contexts, settings and communities that are similar. [216] Given that our study populations' motivation and experiences with this intervention was influenced by their unique culture, setting and resources among other things, we only interpreted our findings within the context of our study population.

11.5 Discussion of main findings

11.5.1 Mortality among severely anemic children with moderate to severe acute malnutrition (Paper I)

The aim of the study for paper I was to assess the risk of mortality among children who have the co-morbidity of moderate-to-severe malnutrition and severe anaemia compared to severe anaemia alone. In this study we found that over a period of 18 months, severely anemic children who had moderate to severe acute malnutrition had a two-fold risk of dying compared to those that had severe anemia alone (IRR 2.2). Similar high mortality rates have been reported in previous studies among under-five children hospitalized with severe malnutrition children and anaemic children separately in other African countries.[55, 56, 131, 217]

Prior to our study we did not find any prospective study that investigated mortality among children who had both morbidities. High mortality rates have been reported among hospitalized children with severe anaemia and MAM/SAM separately in many African countries. One retrospective study in Kenya reported that among severely anemic children aged less than five years old, the risk of dying was higher when they also had some form of malnutrition. (T. Kwambai, unpublished) Our findings show a much higher mortality rate than that reported in studies in children with severe anaemia alone in Ethiopia and Nigeria. [218, 219] This higher mortality could be attributed to the fact that children in our study had both conditions, which independently are major causes of mortality in children under five years. [5, 28]

There are many observational studies that have reported the prevalence of these two co-morbidities together in young children but there is limited data on the long-term the impact on survival. Our findings from this study are important because in the context where up to 67% of severely malnourished children also had severe anaemia in other African countries and East Asia, screening for malnutrition in this patient population is not routinely done. [103, 220-225] In our study alone, we excluded 28% of the 382 children who were admitted with severe anemia because they weight or height was not recorded and of those that had it recorded, 16% were found to be moderately to severely malnourished. Although this is lower than findings from other countries, our findings suggest that there is a strong association between these two co-morbidities.

Although, evidence shows that the risk of mortality among children with either severe anemia alone or malnutrition alone is attributed to many risk factors, these comorbidities together have an additional burden that makes them more susceptible to a lowered immunity and infections. [226, 227] This suggests that children with these co-morbidities are likely to have more severe disease and more likely to experience poor outcomes.

The major limitation in our study was that the number of severely anemic children with moderate to severe malnutrition, was lower than the minimum required, thus lowered the statistical power of the study. However, our findings were statistically significant with narrow confidence interval. This suggests that there is an association between the risk of death and children having severe anaemia and MAM/SAM. This has the implication that malnutrition may be a treatable factor associated with high mortality among severely anaemia children.

11.5.2 Adherence to DP for PMC (Paper II)

In the 5-arm, cluster randomized trial for paper II, we aimed to identify the optimal delivery strategy that would result in high adherence to DP for PMC among children recovering from severe anemia. We found that children who had their monthly DP delivered in the community either by caregivers or HSAs reminders, resulted in 24% higher adherence compared to when caregivers collected DP from the health facilities.

Our findings are consistent with results from studies in Kenya, Uganda and Ghana that have found that community delivery by CHW of malaria control interventions such as malaria treatment, ITN ownership, IPTp, IPTi and IPTc or SMC result in higher coverage, access, adherence and reduced malaria incidence. [155, 159, 228] Similarly, in Malawi, community delivery of SP for IPTp by CHW improved coverage from 41.5% to 82.9%. [160] In Gambia, CHWs delivery of IPTc also achieved higher coverage, cost effective and reduced symptomatic malaria cases. [157]

Although utilizing CHWs for malaria treatment and interventions has proven to be effective for high adherence and reduced incidence of malaria and is supported by WHO , the effectiveness has shown to decline for subsequent doses or courses. In Mali, SMC delivered through routine programmes utilizing

existing CHWs reduced malaria prevalence, but 84% of the targeted children received the first course and only 54% received four complete SMC courses. [229] Our findings are also similar to this. Another study in Ghana reported that completion of all the three doses of IPTc was similar when delivered within the community by community village volunteers (91.6%) compared to delivery at health centers (91.7%). [151] This finding is important and will pose a challenge for the scale up of PMC, which is supposed to be delivered at specific time points.

Utilizing CHWs has its own challenges and requires additional resources for training, supervision and incentives which may be challenging for PMC delivery. [230] In addition, children receiving PMC would need to be scheduled in CHWs work plans. In our setting, it has been reported that CHWs are motivated to provide reminders for PMC.[231] However, even with this motivation, our study found that less than 50% of the HSAs conducted the required home visit reminders. Many of the reported challenges included, inability to locate the child, high existing workload, limited training, limited supervision and poor community acceptance. [232]

Another study reported that caregivers are capable of administering the first dose of an anti-malarial medication to the children with basic instructions and supervision from the CHW. [206] However, here are no studies that examined adherence to medication when utilizing caregivers to administer longer-term interventions at home. In our study we found that community delivery utilizing caregivers resulted to even higher adherence without requiring CHW reminders. Caregivers can administer monthly doses without additional reminders (SMS or CHWs reminder visits) and this is important because it will not require resources.

A qualitative study examining acceptance of PMC among caregivers in Malawi reported that caregivers' preference of delivery was to be given all the medication to administer to their children without any additional reminder because HSAs and phones were unreliable and collecting medication from the hospital was very challenging. [233] However, the concern with this method is the poor storage conditions and ensuring that medication will be administered to the sick child and not all children considered to be at risk in a household.

Use of digital technology such as mobile phones have been hailed as important tools to improve adherence to medication, treatment response, and outcomes in resource poor settings such as SSA. [234, 235] In our trial we were not able to establish that provision of SMS reminders had an effect on adherence. Despite all of the caregivers having access to a mobile phone, only 18% reported to have received at least one SMS. Reported factors included lack of ability to charge them due to electricity, loss of network and not personally owning the phone. These and other factors such as mobile coverage and literacy levels have been reported as determinants of the feasibility of utilizing mhealth interventions in other settings such as Kenya, Zambia and Nigeria. [236] [237] [78]

Our findings show that the feasibility of utilizing SMS reminders in the administration of PMC may be a challenge in settings like Malawi, where the literacy level (ability to read or write) is less than 70%, and only 11 % of households having reliable electricity. [125] Similar results have been reported in other studies conducted in southern Malawi, where SMS reminders showed to have a low impact on retention of HIV positive mother in HIV clinics in one study [238, 239] and health worker adherence and management of common childhood diseases in another trial. [240, 241] In this study only 43% intended SMS were received compared to a similar trial in Kenya where SMS receipt was reported at 91%. [241, 242]

The timing of PMC medication administration is sensitive. It would be a challenge for a caregiver to rely on receiving timely reminders on a personal phone or rely on others to receive the reminder and pass on the message. However, a study in Tanzania has shown that unsupervised malaria treatment given at home by caregivers has shown to be highly effective in malaria treatment in children aged less than five years without the utilization of any reminders. [230] Contrasting to this, a qualitative study in Malawi showed that caregivers have a higher preference and confidence to be given all PMC medication to administer at home without SMS reminders because the majority reported that they did not receive the SMS reminder. [233]

What our study adds is that there no studies that have assessed adherence to PMC, which is a new intervention for managing sick children during the post-discharge period. In addition, we investigated the effectiveness of utilizing caregivers who routinely administer medication and we have demonstrated that caregivers are effective for higher adherence among children receiving DHP for PMC. In this case community delivery by giving the medication to the caregivers may be the most successful strategy for this promising intervention.

11.5.3 Feasibility of utilizing HSAs to remind caregivers to administer DP for PMC (Paper III)

In this study we aimed to explore whether utilizing HSAs can be a feasible, practical and acceptable delivery strategy for PMC. We found that only one in four HSAs who were trained to incorporate PMC reminders into their normal duties were completely adherent. However, despite this poor level of adherence, the great majority of the HSAs reported that they are intrinsically motivated to do this work of reminding caregivers to administer DP to children in their community.

The main reported motivation for HSAs in PMC came from their altruism, the recognition that they play a major role in health service provision to the community and the appreciation they get from the caregivers. The HSAs' need to attain and maintain the trust of the community gives them a sense of duty and responsibility because they have developed lasting bonds with the people within the community. [232, 243, 244] In our study, they wanted to maintain the level of power by insisting that they need to be an integral part of this intervention.

However, when it came to conducting the duties assigned for this intervention this motivation was not demonstrated. Similar to other findings reported from other studies, they reported that the positive impact of their work and benefits of the intervention played a major role on motivation. [170, 179]
Some studies have also found that financial incentives may provide a source of motivation, while others have observed that this can negatively influence motivation. [174, 194] We found that most of the HSAs do not want additional financial interventions to conduct home visits since they made similar visits to community members as part of their normal duties, but they wanted financial incentives in the form of lunch allowances during trainings. This suggests that some form of reward either financial or non-financial for the extra work is needed to drive their extrinsic motivation, as they genuinely want to do well in their communities. On the other hand, some of the HSAs stressed that lack of refresher training with allowances reduced their motivation to make PMC visits which is also consistent with findings from studies of other community-based interventions. [194, 243]

The success of any programme is indicated by knowledge gained and adherence. Although awareness of the burden and impact of malaria and severe anemia was high among the HSAs, the question is why there was poor adherence to an intervention that could potentially minimize morbidity and mortality in the communities? In line with other studies, our study found that

the factors that influence HSAs motivation to carry out the PMC intervention activities are multilayered. [245] Professional factors allow for good intentions to carry out the duties but structural and community factors are a hindrance to them. Some of the non-adherent and partly adherent participants in this study referred to a high workload as one reason why they had not conducted the visits which has been previously reported. [169, 175] However most said the task was simple so perhaps in the event of a scale up there would not be this amount of resistance as demonstrated here. Structural barriers that existed such difficulty with the text messages, inability to locate the child and transportation challenges, mainly attributed to poor adherence. In the existing health system, the same is true.

All HSAs received similar training but there are other factors that come into play because with the same training some HSAs were adherent to all the required visits. Limited information and knowledge about the intervention reported meant that the HSAs did not have a proper understanding of their role and expectations. In order to minimize influencing the normal behavior of the HSAs, the study team did not make follow up supervision visits . As such no additional visits were made to the HSAs. With that said, many studies have shown similar findings, that training improves outcomes as acquired skills and knowledge are lost over time. [246-249] Since the majority of the HSAs felt that they needed more training with follow up refresher trainings then perhaps in the event of an upscale, resources should be placed into conducting more frequent training as a way of providing additional knowledge and feedback. [250]

Strengthening supportive supervision has also been shown to improve effectiveness of utilizing CHWs in similar contexts. Good supervision has been shown to be an effective way to boost team spirit and improve the work environment through a continuing dialogue in similar contexts. [251] Clarity of chains of command and accountability are some of the few reported sources of

extrinsic motivation where one fears rebuke and loss of professional respect. When establishing PMC reminders by HSAs, it would be important to ensure that the chains of commands are made clear. One of the major challenges during the study was that HSAs were not sure who to report to, the research team or the line managers. Their preference was that this intervention should be carried out in the existing supervision structure.

Reminding caregivers to give PMC medication is reportedly simple and requires minimal resources in the cases when the child lives nearby, but most of the challenges were related to identifying the child and incorporating that into their routine scheduled work plans. Firstly, locating the child was a challenge for some and in other instances when the HSA was available; they were driven to the child's home by the research team. HSAs who knew the child's home did not have this challenge. However, in the event of a scale-up, HSAs will not be driven to the child's home. Therefore, to address this, establishing and strengthening existing supportive supervision is important in the event of an upscale.

While HSAs in this study reported having strong relationships with their community who depend on them for guidance and community health needs. Caregivers in the trial preferred to use reminders documented in the child's health book rather than the HSAs reminding them. They reported that their HSAs were unreliable and often unavailable. [233] However, other reports have shown this to be opposite in that HSAs have close ties with the community and is an important driver for carrying out their duties. [245] Interestingly, the HSAs themselves report that most of the times the caregivers were capable of administering the medicine to their children without reminders from them. However, the main concern with this was that there might be misuse of the medication such as administering it to another child as well as poor storage conditions would render the medicine ineffective. They therefore believe that they should be an integral part of this and work hand in hand with the

caregiver. This is important because PMC delivered in the community has shown to be more effective than facility-based delivery.

12 Conclusions

The conclusions of this thesis have been reported in line with main objectives as follows:

Objective 1: We aimed to determine if moderate to severe malnutrition increases the risk of dying among hospitalized children with severe anemia.

- Among children who were hospitalized with severe anemia, those with moderate to severe malnutrition were two times more at risk of dying compared to children with severe anemia alone.
- Rates of hospital readmissions and recurrence of severe anemia were similar among severely anemic children with moderate to severe malnutrition and those with severe anemia alone

Objective 2: We aimed to evaluate the most effective delivery method of dihydroartemesinin-piperaquine to under-five children with severe anemia for post-discharge malaria chemoprevention.

- Adherence to DP was generally higher among children who received all treatment doses to take in the community compared to collect them from the health facility.
- Poor adherence to DP administration was generally low among all the children
- Utilizing SMS reminders to improve adherence did not have an effect on administration of all treatment doses of DP.

Objective 3: We aimed to explore the feasibility of utilizing HSAs in the scale up of PMC for post-discharge management of children recovering from severe anemia.

- More than half of the HSAs participating in the PMC trial conducted at least one home visits to the children
- All the HSAs were intrinsically motivated to conduct home reminders for PMC.

- The main motivating and enabling factors for conducting home visits for PMC were altruism, genuine love for the job, positive benefits of PMC, gaining new knowledge and knowing about the sick child.
- The reported barriers and challenges from conducting home visits were; a high workload, lack of provision of transport and additional incentives, limited supervision and lack of information regarding the study medication which is not known to the HSAs.

13 Recommendations

13.1 Policy implications

1. We aimed to determine if moderate to severe malnutrition increases the risk of dying among hospitalized children with severe anemia.
    - Children admitted to hospital with severe anemia should be adequately screened for malnutrition as this might be an attributable and treatable cause that might improve recovery and reduce poor health outcome.
    - Children diagnosed with moderate to severe malnutrition should be routinely screened for anemia in order to improve health outcomes.
2. We aimed to evaluate the most effective delivery method of dihydroartemesinin-piperaquine to under-five children with severe anemia for post-discharge malaria chemoprevention.
    - Community delivery of DP for PMC should be incorporated as policy for management of under-five children recovering from severe anemia.
    - Text message reminders may be an effective means to improve patient adherence, however more studies should be conducted to ascertain their effectiveness in a low resource health system such as Malawi
3. We aimed to explore the feasibility of utilizing HSAs in the scale up of PMC for post-discharge management of children recovering from severe anemia.

- The Ministry of Health should improve working conditions, continued professional development trainings and empowerment HSAs because they provide essential health services at the community level.

13.2 Further research

- A statistically well-powered, prospective study to investigate the high risk of death among severely anemic children with moderate to severe malnutrition.
- To investigate the effect of text message reminders on adherence to medication, an effectiveness trial that ensures that all participants in text reminder arms receive them should be conducted.
- Another statistically well-powered trial should be conducted to evaluate effectiveness of community delivery of PMC on clinical outcomes

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15 Original papers (I-III)

PLOS ONE

RESEARCH ARTICLE

A cohort analysis of survival and outcomes in severely anaemic children with moderate to severe acute malnutrition in Malawi

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Abstract

Introduction

Moderate to severe acute malnutrition (SAM/MAM) and severe anaemia are important and associated co-morbidities in children aged less than five years. Independently, these two morbidities are responsible for high risk of in-hospital and post-discharge deaths and hospital readmissions. The primary objective of this study is to investigate the risk of death among severely anaemic children with moderate to severe acute malnutrition compared to children with severe anaemia alone.

Methods

This was a retrospective analysis of data collected from a large prospective study that was investigating severe anaemia in children aged less than 5 years old. The study was conducted at Queen Elizabeth Central Hospital in Blantyre and Chikhwawa district hospital in southern Malawi. Children aged less than five years old; with severe anaemia were screened and enrolled. Each child was followed up for eighteen months at one, three, six, twelve and eighteen months after enrolment. Data were analysed using STATA 15.

Results

Between July 2002 and July 2004, 382 severely anaemic children were enrolled in the main study. A total of 52 children were excluded due to missing anthropometric data. Out of the 330 included, 53 children were moderately to severely malnourished and 277 were not. At the end of the 18-month follow period, 28.3% of children with MAM/SAM died compared to 13% of children without MAM/SAM (RR 2.1, CI 0.9–4.2, p = 0.03). Similarly, children with moderate to severe malnutrition reported a significantly higher number of malaria infection cases (33.9%) compared to children with severe anaemia alone (27.9%, p = 0.02).

Moderate_to_severe_malnutrition_in_severe_anemia_study_/13061447.

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However, the number of hospitalizations and recurrence of severe anaemia was similar and not statistically significant between the two groups (RR 0.8 (0.4–1.4), p = 0.6 and RR 1.1 (0.3–2.8), p = 0.8).

Conclusion

Among children with severe anaemia, those who also had moderate to severe malnutrition had a twofold higher risk of dying compared to those who did not. It is therefore crucial to investigate acute malnutrition among severely anaemic children, as this might be treatable factor associated with high mortality.

Introduction

Malnutrition is a complex and multifactorial condition that results from deficiencies, excesses, or imbalances in a person's intake of energy and/or nutrients and presents in two broad forms; undernutrition which includes wasting, stunting and underweight; and micronutrient deficiencies and obesity [1]. Globally, it is estimated that 52 million children under five are wasted, 75% of which are in low- and middle-income countries (LMIC) [2]. The 2016 Malawi demographic and health survey (DHS) reported that 37% of children under five years of age are stunted while 12% are underweight [3], and mortality of up to 42% has been reported among children hospitalised with severe acute malnutrition (SAM) [4, 5]. Such high mortality rate has been attributed to comorbidities such as infections, including HIV, as well as micronutrient deficiencies including anaemia that often affect children with SAM [6, 7].

Severe anaemia is one of the most common causes of admissions and mortality in Sub-Saharan Africa (SSA) and annually affects 9.6 million children globally [8, 9]. In Malawi, it was found that children with severe anaemia alone have a tenfold risk of dying within 18 months after the initial episode compared to children from the hospital and community who did not have severe anaemia [10]. Similar findings have been reported in Kenya and Uganda [11, 12]. Causes of severe anaemia are multifactorial and vary in different settings. In addition to infectious diseases, genetic factors and malignancies, nutritional deficiencies are a major factor [13–16].

Severe anaemia and any form of malnutrition are common and associated co-morbidities. Anaemia is the most common manifestation of micronutrient deficiency in malnourished children under 5 years old [17], with up to 67% of severely malnourished children found to be severely anaemic [18, 19]. In Malawi, up to 63% of malnourished children have some form of anaemia signified by a Haemoglobin (Hb) level of <11.0g/dl and of these, 22% are moderate to severely anaemic (Hb <7g/dl). On the other hand, 15.8% of severely anaemia children are found with SAM [2].

Severe anaemia is an important co-morbidity and determinant in the recovery of children with malnutrition, so much so that WHO recommends that children with kwashiorkor or marasmus should be assumed to be severely anaemic [20]. Many studies have reported the in-hospital and post-discharge mortality outcomes among children with SAM [5, 21], and children with severe anaemia [11, 22] separately. However, the added risk of dying when a child has both of these conditions; which we predict would be high has not previously reported. As MAM/SAM is a potentially treatable risk factor [3]; we aimed to evaluate its impact on mortality in severely anaemic children.

Materials and methods

This study was approved by the ethics committees of the College of Medicine, University of Malawi and the Liverpool School of Tropical Medicine, United Kingdom. In the SEVANA cohort study, children with severe anaemia and aged less than five years old were enrolled from Queen Elizabeth Central hospital and Chikhwawa district hospital in southern Malawi. Enrolment procedures have been extensively described elsewhere [14]. In summary, 382 children admitted with severe anaemia (defined as a haemoglobin concentration <5.0 g/dL) were enrolled and matched with one community and one hospital control. Each child was then followed up for 18 months.

In the present study, verbal and written informed consent was obtained from the legal guardians and children with severe anaemia who had a recorded weight, length and met the WHO classification of moderate to severe malnutrition defined as a child whose weight-for-length is less than <2 of the Z-scores and weight for age less that -2 of the z-scores [23]. An additional inclusion criterion was documented haemoglobin at enrolment and a documented date of outcome and status (died, completed, lost-to-follow up or withdrawn).

Information about the child's age, sex, residence, number of living and dead siblings, 24-hour dietary recall, family history of sickle cell disease (SCD), jaundice, bloody stool and urine, blood transfusion in the last two months, being on any medication, HIV infection and other previous medical history were obtained from the legal guardians at enrolment. Additional information included guardian's age, occupation and education level.

Other data points collected include physical examination findings at enrolment and laboratory records, which included parasitology, microbiology, haematology and biochemistry.

Power calculation

We did a power calculation to evaluate the statistical power of our study due to the limited sample size. Using open EPI version 3 (www.openepi.com), we computed the 95% two-sided confidence interval, risk ratio (2.1) and the number of children sampled in each study group (53 with MAM/SAM versus 275 without SAM/MAM). We found that our analysis gave us a power of 76.4%.

Statistical analyses

Data were coded, entered and analysed using STATA 15 (StataCorp, College Station, Texas, USA). Categorical variables have been summarized as frequencies and proportions, while continuous variables as means with standard deviations and medians with the interquartile ranges (IQR) reported. Death was our primary outcome. We examined risk of dying by calculating mortality rates in the children with moderate to severe acute malnutrition and those without. We measured time to death by survival analysis, using Kaplan-Meier curves to compare the probability of death between the two groups over the 18-month study period. Significance was calculated with a log-rank test. Incidence rates for the composite outcomes i.e. re-hospitalization, malaria and severe anaemia recurrence were also calculated for each group. For the malaria incidence rate, the time at risk was calculated by subtracting 14 days from the child-years follow-up with each case of clinical malaria treated with Lumefantrine-Artemether (AL). P values and 95% confidence intervals have also been included.

Results

Of the 1141 under-5 children enrolled in the SEVANA study between July 2002 and July 2004, 382 were severe anaemic cases admitted to the paediatric wards of QECH and Chikhwawa

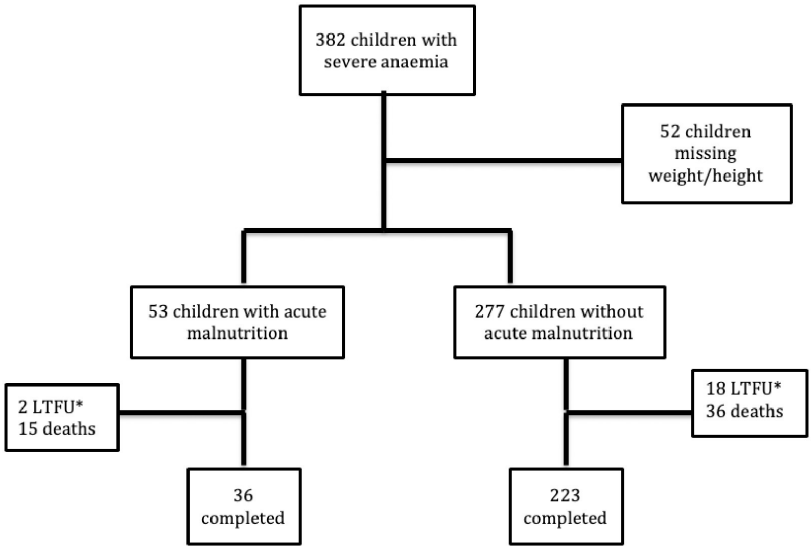

Fig 1. Study flowchart.

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district hospital and 759 were hospital or community controls without severe anaemia. Of the 382 children, 330 had their weight and heights measured and were included in the final analysis. A total of 53 children had a weight for height z-scores $\leq$ -2 (moderate to severe acute malnutrition) and 277 had a weight for height z-scores $>$ -2 (not malnourished). During the follow up period, twenty children were lost to follow up, 51 died and 259 children completed the study (Fig 1).

The baseline characteristics and examination findings of study participants was comparable between the two groups (Table 1). Moderate to severely malnourished children were significantly older with mean age, 24.3 months (SD 12.1) compared to 19.5 months (SD 12.4). The mean number of days hospitalised was not significantly different, 4.9 days (SD 8.1) compared to 3.9 days (SD 4.1). A higher proportion of non-malnourished children resided in a rural location, 52.4% compared to 45.3% in the malnourished group. The majority of parents of the children had received some formal education and about half of them had employment. A total of 34.0% of malnourished children had a sibling who died compared to 28.2% among children without ($p = 0.05$).

A total of 196 children (59.4%) had a positive blood smear for *P. Falciparum* malaria infection on admission, and of these 32 (60.4%) were children with MAM/SAM and 164 (59.2%) were children without MAM/SAM. C-reactive protein (CRP), a common marker of inflammation was raised ($\geq$10Mg/L) among 83% of the children with MAM/SAM compared to 82.7% of those without MAM/SAM. A total of 27.3% of all the children had iron deficiency. A higher proportion of children with vitamin A and vitamin B12 deficiency were those without MAM/SAM.

Table 1. Baseline characteristics of study participants.

Characteristic	Moderate to severe malnutrition	Severe anaemia alone	P-value
	n (%)	n (%)	
Age <24 months	**30 (56.6)**	**200 (72.2)**	**0.02**[a]
Mean age in months n (SD)	**24.3 (12.1)**	**19.5 (12.4)**	**0.01**[a]
Mean days in hospital n (SD)	4.9 (8.2)	3.9 (4.1)	0.18
Male gender	23 (43.4)	129 (46.6)	0.67
Rural location	24 (45.3)	145 (52.4)	0.35
One or more dead siblings	**18 (34.0)**	**78 (28.2)**	**0.05**[a]
Educated father	35 (66.0)	172 (62.1)	0.72
Teenage mother	8 (15.1)	71 (25.6)	0.15
Uneducated mother	**5 (9.4)**	**30 (10.8)**	**0.03**[a]
Jobless parent	**26 (49.1)**	**164 (59.2)**	**0.03**[a]
One dead parent	5 (9.4)	18 (6.5)	0.72
Previous blood transfusion	9 (17.0	38 (13.7)	0.53
Recent antimalarial use	31 (58.5)	175 (63.2)	0.72
History of bloody stool	6 (11.3)	19 (6.9)	0.45
History of bloody urine	1 (1.9)	5 (1.8)	0.97
Jaundiced	**6 (11.3)**	**10 (3.6)**	**0.02**[a]
Splenomegaly	33 (62.3)	178 (64.3)	0.49
Raised CRP (≥10Mg/L)	44 (83.0)	229 (82.7)	0.96
Median CRP n (IQR)	111.6 (65.2–183.2)	93.6 (37.8–150.5)	0.27
Mean Haemoglobin n (SD)	3.6 (0.8)	3.4 (1.0)	0.13
Low Vitamin B12 (<118pmol/L)	13 (24.5)	71 (25.6)	0.97
Iron deficiency	14 (26.4)	76 (27.4)	0.99
Malaria infection at enrolment	32 (60.4)	164 (59.2)	0.87
HIV infected	7 (13.2)	29 (10.5)	0.30
CMV infection	3 (1.1)	0 (0.0)	0.52
EBV infection	11 (20.8)	63 (22.7)	0.66
Bacteraemia	4 (7.6)	36 (13.0)	0.48
Sickle cell disease	1 (1.9)	3 (1.1)	0.88

[a] P-value which are significant at alpha = 0.05

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During the 18-month study period, the mean observation days was 383 in the severely anaemic children with MAM/SAM and 456 days in the severely anaemic alone group respectively (Fig 2 and Table 2).

The cumulative proportions of children who died during the entire 18 month study period was 51 (15.4%) with 27 (8.2%) dying within one month of admission. Of the 51 deaths, 15 (28.3%) occurred in children with MAM/SAM compared to 36 (13.0%) who did not. The overall incidence rate of death with the 95% CI was 3.0 (2.2,4.0) children per 1000 person days observed. The incidence rates for death were 5.4 (3.0,9.8) and 2.6 (1.9,3.7) among children with MAS/SAM and those without respectively. This shows that children with MAM/SAM had a twofold risk of dying compared to children who has severe anaemia without MAM/SAM (RR 2.1; CI 0.9–4.2,p = 0.03). Similarly, severely anaemic children who were underweight had almost a 3-fold risk of dying compared to those with severe anaemia alone (RR 2.8; CI 1.5–5.2, p = 0.0006).

The survival curves for the two groups showed a statistically non-significant difference in the two mortality rates (log rank = 2.9, p = 0.098) (Fig 2). However, there was a significant

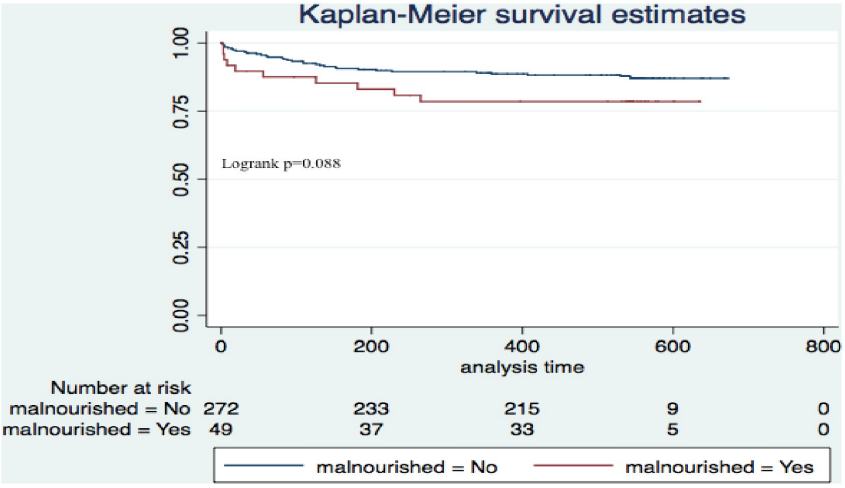

Fig 2. Kaplan Meier survival curves of severely anemic children with moderate to severe acute malnutrition compared to those with severe anaemia alone.

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difference in mortality when we compared severely anaemic children who were underweight compared to those who were not, p = 0.001 (Fig 3).

During the follow up period, there were a total of 679 confirmed malaria cases, 16 of which were complicated malaria. There were significantly more children who reported malaria infection among those with MAM/SAM 106 (40.8%) compared to 573 (32.3%) (p = 0.01) with severe anaemia alone (IRR 1.3; CI 1.04–1.6, p = 0.02). There were more hospital readmissions among children who had severe anaemia alone compared to those with moderate to severe acute malnutrition (4.4% versus 3.5%), (IRR 0.8; CI 0.4–1.7,p = 0.62), but this was not statistically significant. In addition, the recurrence of severe anaemia was similarly low between children with moderate to severe malnutrition compared to those who had severe anaemia alone (IRR 1.1, CI 0.3–2.8, p = 0.8) over the entire study period.

Table 2. Post-discharge morbidity and mortality among severely anaemic children with moderate to severe malnutrition compared to those with severe anaemia alone.

Event	Moderate to severe malnutrition		Severe anaemia alone			
	Total events	Incidence rate (1000 person- days)	Total events	Incidence rate (1000 person- days)	Rate ratio	p-value
	N = 53		N = 277		n (CI)	
Deaths n (%)	15 (28.3)	5.4	36 (13.0)	2.6	2.1 (0.9, 4.2)	0.03[a]
Hospitalisation n (%)	9 (3.5)	1.5	76 (4.4)	1.8	0.8 (0.4, 1.7)	0.62
Malaria incidence n (%)	106 (40.8)	17.3	573 (32.3)	13.0	1.3 (1.04, 1.6)	0.02[a]
Severe anaemia recurrence n (%)	5 (1.6)	0.8	32 (1.6)	0.7	1.1 (0.3, 2.8)	0.81

[a] P-value which are significant at alpha = 0.05

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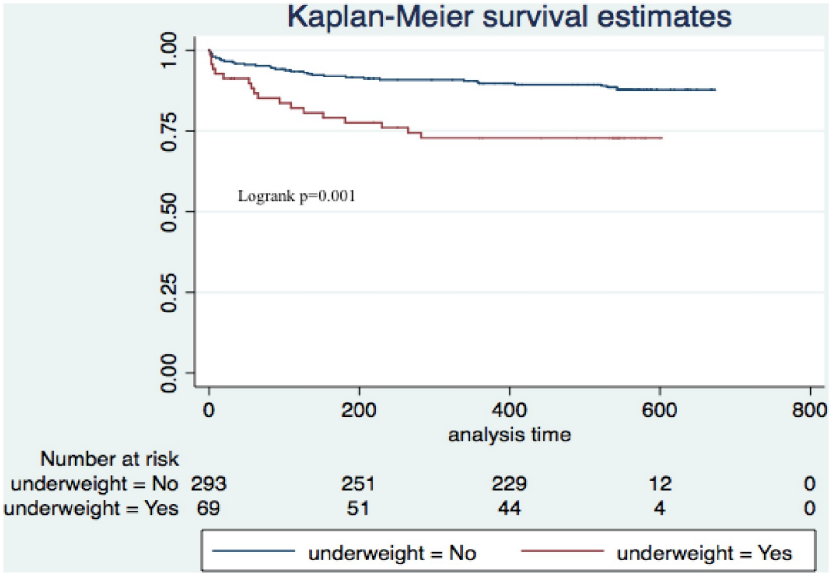

Fig 3. Kaplan Meir survival estimates comparing severely anaemic children who are underweight and those that have severe anaemia alone.

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Discussion

To our knowledge, no cohort studies investigating mortality outcomes in children with both severe anaemia and MAM/SAM have been conducted in SSA. We found that severely anaemic children with MAM/SAM are two times more likely to die compared to severely anaemic children without MAM/SAM during 18 months follow-up. High mortality rates have been reported among hospitalized children with severe anaemia and MAM/SAM separately in other African countries [24]. However, our findings show a much higher mortality rate than those reported in studies in children with severe anaemia in Ethiopia and Gambia [22, 25]. This higher mortality could be attributed to the fact that children included in our study had both conditions, which independently are major causes of mortality in children.

There are few cohort studies that have investigated mortality outcomes in children with both severe anaemia and MAM/SAM. Most of these have reported varying ranges of the burden of these two co-morbidities but there is limited data on impact. One study in Ethiopia reported that there was no significant difference in recovery among severe malnourished children with anaemia compared to those without anaemia [26]. On the other hand another study in Ethiopia found that children with SAM and anaemia had less chance of recovering compared to those who had SAM and no anaemia [27], which was similar to findings of a study in Kenya (Kwambai et al, Unpublished). However, this study did not have a comparison group. These findings are important because children admitted to hospital with severe anaemia are not routinely screened for MAM/SAM [28–30]. This has the implication that these children will not be checked for MAM/SAM, as it may be a treatable factor associated with high mortality.

The interplay between MAM/SAM, severe anaemia and the risk of mortality is multifactorial. It is believed that malnutrition lowers immunity, which leads to susceptibility to infections [31]. In addition, it is also possible that children with MAM/SAM are more likely to have micronutrient deficiency leading to cell damage that makes infections worse and leads to poor outcomes. Studies have attributed poor recovery outcomes in children with either MAM/SAM or severe anaemia to many factors including infections such as malaria [32–34]. We found that there was significantly higher malaria incidence among severely anaemic children with moderate to severe acute malnutrition compared to those with severe anaemia alone. The association between malnutrition and malaria has been inconclusive and conflicting [34]. In malaria endemic regions, malaria infection is associated with anaemia although it may not be the primary cause of it [35]. This finding is similar to other studies in Cameroon, Ghana and Gambia, where under-nutrition was associated with increased risk of malaria-associated mortality and multiple malaria infections [36–38].

Compared to other studies among children with severe anaemia or malnutrition, we did not find significant differences in hospital re admissions or recurrent severe anaemia. We had few fewer re-hospitalisations to detect meaningful differences. Although we did not make associations with other risk factors, our findings are important for exploring interventions that may reduce the additional burden that exists among severely anaemic children with malnutrition.

Our study had limitations. Our sample size was limited and we collected data from existing data that are now 16 to 18 years old. This might have an effect on the findings and their interpretation within the current context. Considering that mortality is a relatively rare outcome and the number of deaths was small, the confidence intervals for the mortality risks are relatively wide. However, we were able to detect significant and meaningful differences in mortality between the two groups of children.

Conclusions and recommendations

Severe anaemic children who also have moderate to severe malnutrition have a higher risk of death than those with severe anaemia alone, even after discharge from hospital. It is therefore crucial to carefully screen for acute malnutrition in children admitted with severe anaemia, as this may be a treatable factor associated with high mortality. Prospective cohort studies may be utilised to evaluate effects of interventions that may be used to reduce mortality among severely anaemic children with moderate to severe acute malnutrition.

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Adherence to community versus facility-based delivery of monthly malaria chemoprevention with dihydroartemisinin-piperaquine for the post-discharge management of severe anaemia in Malawian children: A cluster randomized trial

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Abstract

Background: The provision of post-discharge malaria chemoprevention (PMC) in children recently admitted with severe anemia reduces the risk of death and re-admissions in malaria endemic countries. The main objective of this trial was to identify the most effective method of delivering dihydroartemesinin-piperaquine to children recovering from severe anemia.

Methods: This was a 5-arm, cluster-randomized trial among under-5 children hospitalized with severe anemia at Zomba Central Hospital in Southern Malawi. Children were randomized to receive three day treatment doses of dihydroartemesinin-piperaquine monthly either; 1) in the community without a short text reminder; 2) in the community with a short message reminder; 3) in the community with a community health worker reminder; 4) at the facility without a short text reminder; or 5) at the facility with a short message reminder. The primary outcome measure was adherence to all treatment doses of dihydroartemesinin-piperaquine and this was assessed by pill-counts done by field workers during home visits. Poisson regression was utilized for analysis.

Results: Between March 2016 and October 2018, 1460 clusters were randomized. A total of 667 children were screened and 375 from 329 clusters were eligible and enrolled from the hospital.Adherence was higher in all three community-based compared to the two facility-based delivery (156/221 [70·6%] vs. 78/150 [52·0%], IRR=1·24,95%CI 1·06-1·44, p=0·006). This was observed in both the SMS group (IRR=1·41,1·21-1·64, p<0·001) and in the non-SMS group (IRR=1·37,1·18-1·61, p<0·001). Although adherence was higher among SMS recipients (98/148 66·2%] vs. non-SMS 82/144 (56·9%), there was no statistical evidence that SMS reminders resulted in greater adherence ([IRR=1·03,0·88-1·21, p=0·68). When compared to the facility-based non-SMS arm (control arm), community-based delivery utilizing CHWs resulted in higher adherence [39/76 (51·3%) vs. 54/79 (68·4%), IRR=1·32, 1·14-1·54, p<0·001].

Interpretation: Community-based delivery of dihydroartemesinin-piperaquine for post-discharge malaria chemoprevention in children recovering from severe anemia resulted in higher adherence compared to facility-based methods.

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Introduction

Severe anaemia is defined as low hemoglobin level of less than 5mg/dl. It affects over 10 million children globally and is one of the leading causes of paediatric hospital admissions and mortality in sub-Saharan Africa (SSA).[1] Children admitted to hospital with severe anaemia are at high risk of dying not only during the acute phase but also after discharge from hospital.[2, 3] One prospective study in Malawi reported that 8% of hospitalized children with severe anaemia were re-admitted or died within six months after discharge compared to none of the community controls.[4] Post-discharge mortality rates as high as 17·9% and 36·5% have been reported in other African countries such as Kenya and Uganda.[3, 5] In malaria endemic African countries, malaria infection is a major contributor of severe anaemia and is a risk factor for slow haematological recovery that occurs in the community where the risk remains high.[6-9]

Post-discharge malaria chemoprevention (PMC) is the targeted use of antimalarials in children with severe anaemia to create a malaria prophylactic window period post-transfusion and during recovery.[Kwambai, 2018 #499] Similar to seasonal malaria chemoprevention (SMC), PMC clears existing infections and provides prolonged prophylaxis against new infections.[10-13] A randomised clinical trial conducted in Malawi reported that provision of PMC to children aged less than 5 years with long-acting ACTs during recovery from severe anemia prevented up to 21% of deaths or hospital readmissions within 6 months after discharge.[Phiri, 2012 #85] More recently trials in Uganda and Kenya found that PMC resulted in 65% reduction in malaria incidence during the three months intervention period after successful treatment with blood transfusion and parenteral antimalarial drugs.[Kwambai, 2018 #499][Kwambai, 2020 #555]

Utilizing community health workers (CHW) to deliver interventions for childhood diseases such as pneumonia and malaria has been reported to be effective in reducing childhood mortality and improved access.[15] Compared to facility-based delivery, provision of intermittent preventive therapy (IPT) in pregnant women and children by CHWs in the community, has also been shown to reduce malaria prevalence and incidence.[16, 17] However, this delivery strategy may have some challenges with sustainability due to inadequate supervision, low remuneration and irregular supplies among others.[18] Although facility based interventions have been effective at reducing disease complications,[16] they are costly and challenging to deliver for the health system.[19]

PMC is an intervention that could offer substantial public health gains in managing under-five children who are at risk of dying. Although PMC is a relatively simple intervention, implementation will require appropriate delivery strategies so that it reaches the population that need it most. However, a major concern is how it can be delivered in an effective and sustainable way.[14] However, unlike other health interventions delivered to children through established health systems such as the expanded programme on immunization, there is no existing delivery mechanism for PMC.

The aim of this trial was to identify the most effective delivery mechanism for PMC by comparing community and facility-based delivery systems with and without reminders using short-text message service (SMS) and the role of using CHWs also known as health surveillance assistants (HSAs) in Malawi.

Methods

Study site

The study was conducted at Zomba central hospital (ZCH), a referral government hospital with high paediatric admissions rates due to severe malarial anaemia located in southern Malawi with perennial malaria transmission. The hospital provides health services to a population of over one million and it is the only government health facility that provides blood transfusions and health services in Zomba district free of charge. Zomba Central Hospital was selected because previous related studies had been conducted there and is was particularly suitable for the delivery trial because of the existing linkages with community based health care providers and rural clinics within their catchment areas

Study design and participants

This was a five-arm open label cluster-randomized trial. Children aged less than five years who were admitted to ZCH pediatric unit were included if they had severe anaemia (defined as a haemoglobin (Hb) concentration of <5g/dL with a confirmed malaria diagnosis either by rapid diagnostic test or microscopy) and having received the standard in-hospital care for severe anaemia which included a blood transfusion, intravenous artesunate and antibiotics, if bacterial infection was suspected. Once stable, all children received oral lumefantrine-artemether (AL) and caregivers were provided with information regarding the trial procedures, medication and follow up. We excluded children with other

specific causes of anaemia such as trauma, those with confirmed sickle cell or heart disease and those who resided out of the catchment area. After obtaining informed consent in the local language of Chichewa from their legal guardians, we collected socio-demographic information and medical history using questionnaires and performed a physical examination. We collected a blood sample from a finger prick to check Hb using the hemocue 301 (Angelholm, Sweden) and malaria slides for microscopy. After enrolment, the study participants were traced to their home to collect GPRS positions for follow up and ascertain distance from the hospital.

Randomization and procedures

The unit of randomization was the village in the catchment area of the hospital. Randomization of the village clusters was computer-generated prior to the trial by the trial statistician. All 1460 villages within Zomba which were in the catchment area of ZCH were randomised, as it was not known which village prospective participants would reside prior to the study. Therefore, children residing in the same village cluster were assigned to the same delivery arm. The villages were randomized to one of the following five arms: 1) community-based without an SMS reminder (Com + No SMS); 2) community-based with an SMS reminder (Com+SMS); 3) community-based with an HSA reminder instead of SMS reminder (Com+HSA); 4) facility-based delivery without SMS reminder (Fac-SMS); or 5) facility-based delivery with SMS reminder (Fac+SMS). Detailed descriptions of the methods have been provided in table 1 and published elsewhere.[20]

Text message reminder

In the SMS arms, the text of the SMS was customised for each child with the following message "Remember to give (child's name) medication starting from tomorrow for three days." It was translated into the local language of Chichewa, the most widely spoken language in Malawi. The reminder was pre-tested on a random sample of caregivers coming with their children to the pediatric out-patient department prior to commencement of the trial. Considering that this was an implementation trial, we wanted to reflect the "real life" situation and therefore mobile phones were not provided to caregivers. However, for all study participants; we collected mobile phone numbers of the nearest contact person. Consenting caregivers were instructed to inform the owners of the mobile phone numbers that their child was participating in the trial Caregivers and study staff was aware of the allocation. However, the study statistician who performed the analyses was blinded to treatment allocation.

Table 1. Detailed description of delivery methods of PMC

Method	Arm	Description
Community-based	Com+ No SMS	**PMC drugs given at discharge without SMS reminders:** The guardian received all drugs for PMC-1, PMC-2 and PMC-3. They were instructed on how and when to give these drugs to the child when being discharged from the hospital.
	Com+SMS	**PMC drugs given at discharge with SMS reminders:** The guardian received all drugs for PMC-1, PMC-2 and PMC-3 and was instructed on how and when to give the drugs to the child. Additionally, they were reminded via SMS to give the drugs to the child a day before each treatment course was due.
	Com+HSA	**PMC drugs given at discharge with HSA reminders:** The guardian receives all drugs for PMC-1, PMC-2 and PMC-3 and was instructed on how and when to give the drugs to the child. Additionally, HSAs who are officially government-supported community-based health workers were reminded via SMS to go and remind the guardian to give the drugs to the child a day before each treatment course was due.
Facility-based	Fac-SMS	**PMC drugs collected from the hospital:** At discharge, the guardian was requested to return to the outpatient department (OPD) of the hospital each month to collect drugs (a treatment course at each time) for PMC-1, PMC-2 and PMC-3. They did not receive any form of reminder other than what was documented in the child's health card.
	Fac+SMS	**PMC drugs collected from the hospital with SMS reminders:** At discharge, the guardian was requested to return to the OPD each month to collect drugs (a treatment course at each time) for PMC-1, PMC-2 and PMC-3. Additionally, they were reminded via SMS to come to the clinic to collect drugs a day before each treatment course was due.

Study medication

Co-formulated dihydroartemisinin-piperaquine dispersible tablets containing 20 mg dihydro-artemesinin and 160 mg piperaquine was given as a treatment course over three days (Eurartesim®, Sigma-Tau, Italy). It was prescribed in standard doses according to the weight of the child (supplementary table 1 for specific doses). Three full monthly treatment courses were prescribed at two (PMC-1), six (PMC-2) and ten weeks (PMC-3) post-discharge regardless of the presence of symptoms. The maximum number of doses that could be administered was nine. Standardized verbal instructions about administration and frequency were given to the primary caregiver and specific dates of administration were documented in the child's health book. The drug blister pack also contained administration instructions in Chichewa. All the caregivers regardless of assigned arm were requested to come back to the study clinic for the end of study assessment at 14-15 weeks after enrolment.

One to three days after administration of the last dose of each course of medication, field workers made unannounced home visits to collect blister packs and assess if study medication was indeed given to the child participating in the trial. If the caregiver was not at home, they were contacted and visits were made when they were at home. The number of tablets remaining in the blister packs was recorded and if none were remaining "0" was recorded. If the blister pack was missing the field worker probed to

assess if the medicine was given to the child or not. In addition, assessment for adverse events was made and children were referred to the nearest health facility if they were sick. Data were entered directly into questionnaires in handheld tablets programmed with open data kit (ODK) electronic case report forms (eCRF). Stata 15 was used for analysis.

Sample size

The study was designed to determine whether delivery of PMC through community-based methods resulted in higher adherence than when delivered through facility-based methods and the sample size was based on this. Although a 2x2 factorial design was used, only the main effects of "place of delivery" and "use of mobile phone reminders" were of primary interest. It was estimated that each village cluster would contribute 2 to 4 children with severe anemia. We assumed an intra-cluster correlation coefficient (ICC) of 0.1 and allowing for 20% loss-to-follow-up or efficiency loss due to varying cluster sizes, a sample size of 125 clusters (villages) of an average of 3 children per village (i.e. 75 children per arm and 375 overall), had 80% power to detect a 25% absolute increase in coverage from an estimated 50% in the standard out-patient groups to 75% in the arms supported by mobile phone reminders (α=0.05). The ICC of 0.1 is slightly more conservative than the ICC in a previous trial of delivery approaches for IPTc in the Gambia (0.08). A statistical analysis plan (SAP) was written and agreed upon by all investigators before the data were analysed. However, additional analyses were included in the SAP during analysis to explore effects of different cut offs of adherence.

Statistical considerations

We used appropriate descriptive statistics to summarize data, with mean or median (IQR) for continuous data, and frequencies and percentages for categorical data. For the primary outcome, our analysis was by intention to treat at cluster and participant levels. We used Poisson regression for the total number of doses administered. The unadjusted and adjusted incidence rate ratios (IRR) measuring the percentage of children receiving PMC according to schedule in each arm were obtained and compared between arms and the 95% CI for the IRR have been reported. The estimates of the IRR

were adjusted for baseline characteristics using Poisson regression and accounted for clustering. 95% CIs are provided for all measures of effect.

We also employed a factorial design analysis to investigate the interaction between the effects of community compared to facility delivery and the pooled effect of SMS; and interaction terms were included in models to assess the strength of interaction. We also did several subgroup analyses for the primary and secondary outcomes adjusted for clustering, socioeconomic and demographic variables stratified by each intervention arm with the Fac-SMS group as the reference group.

Our primary outcome of the study adherence to 7 to 9 doses of the study drugs. The secondary outcomes of the trial were: 1) the proportion of those with medium adherence defined as administration of 4 to 6 doses of the study drug; 2) the proportion of those with low adherence defined as the administration of less than 3 doses of the study drugs; 3) all-cause mortality and 4) all cause sick visits.

For the secondary outcomes, the levels of adherence were compared between the five groups. Full details of the study design and statistical methods are provided in detail in the protocol, [20] and statistical analysis plan, which is available as supplementary material.

Ethical approval

The study was approved by the research ethics committees of the College of Medicine in Malawi (COMREC, approval number P·02/15/1679 and the Regional Ethics Committee of Norway, approval number 2015/537 (REK Vest). Written informed consent was obtained from legal guardians of the study participants prior to enrolment. The trial was registered at ClinicalTrials.gov (identifier: NCT02721420).

Role of funding source

The funder had no role in the design, data collection, data analysis and interpretation or writing of the report; and in the decision to submit the paper for publication. The corresponding author had full access to the data and had the final responsibility for the decision to submit for publication.

Results

Between 24 March 2016 and 09 October 2018, a total of 667 children hospitalized with severe anaemia were screened for eligibility and 375 children from 329 villages were eligible and enrolled (Com+ No

SMS=69; Com+SMS=75; Com+HSA=79; Fac-SMS=77; Fac+SMS=75) and 71 villages did not have children who met the legibility criteria. Overall, 351 children (93.6%) were followed successfully until the end of the study; caregivers of four children (1.1%) withdrew consent prior to the first home visit while four children died and twenty did not attend the end of study visit at 15 weeks (Figure1).

Figure 1. Consolidated Standards of Reporting Trials (CONSORT) flow diagram of the PMC delivery trial

There was a good balance in the baseline characteristics across the arms. The overall median age and weight for all the participants were 29 (IQR 19–39) months and 11.3 (IQR 9.6–13.2) kg, respectively. There were generally more males in each arm except in the Fac+SMS arm (48% male). The proportion of participants with a history of having had a blood transfusion in the preceding month to recruitment was low (1.6%) across all the arms (Table 1). Over three quarter of children used insecticide-treated nets (ITN) the previous night prior to admission. None of the households had insecticide residual spraying. Fever was the most common presenting symptom and the mean hemoglobin was 7.9g/dL (sd 1.4).

Table 2. Baseline characteristics of trial participants

Characteristic	Com-SMS	Com+SMS	Com+HSA	Fac-SMS	Fac+SMS	Overall
	N=69	N=75	N=79	N=77	N=75	N=375
Participant age in months, median (IQR)	30 (19–40)	30 (23–38)	28 (18–39)	29 (20–38)	28 (16–38)	29 (19–39)
Weight in kg, median (IQR)	12.0 (9.9–3.9)	11.4 (10.0–13.5)	11.4 (9.9–12.5)	11.0 (9.9–12.7)	11.3 (9.6–13.2)	11.3 (9.6–13.9)
Height in cm, median (IQR)	86 (78–92)	84 (79–89)	84 (75–91)	83 (77–90)	84 (77–91)	84 (77–91)
Male, n (%)	37 (53.6)	48 (64.0)	49 (62.0)	42 (54.6)	36 (48.0)	212 (56.5)
Previous transfusion, n (%)	1 (1.5)	2 (2.7)	0 (0.0)	1 (1.4)	2 (2.7)	6 (1.6)
Malaria in previous month n (%)	10 (14.5)	9 (12.2)	6 (7.5)	5 (6.9)	4 (5.5)	34 (9.2)
Slept under ITN previous night, n (%)	52 (75.4)	54 (72.0)	64 (81.0)	62 (80.5)	55 (73.3)	287 (76.5)
Diarrhoea on admission, n (%)	11 (15.9)	12 (16.2)	18 (22.7)	15 (20.6)	14 (19.2)	70 (19.0)
Fever on admission, n (%)	63 (91.3)	69 (92.0)	74 (93.7)	60 (78.0)	69 (92.0)	335 (89.3)
Vomiting on admission, n (%)	26 (37.7)	24 (32.4)	31 (39.2)	17 (23.3)	29 (39.7)	127 (34.5)
Received at three doses of parenteral artesunate, n (%)	69 (100)	75 (100)	79 (100)	77 (100)	75 (100)	375 (100)
Difficulty taking medication, n (%)	14 (22.2)	22 (34.4)	21 (28.7)	19 (29.7)	14 (21.5)	90 (27.4)
Hb at enrolment in g/L, mean (Sd)	7.7 (1.3)	7.9 (1.5)	8.1 (1.6)	7.9 (1.3)	8.1 (1.3)	7.9 (1.4)
Hb at end of study in g/L, mean (Sd)	11.3 (1.5)	11.7 (1.4)	11.6 (1.4)	11.5 (1.5)	11.3 (1.8)	11.5 (1.5)
Guardian age in years, median (IQR)	28 (23–36)	26 (22–34)	27 (23–33)	27 (23–35)	27 (22–34)	27 (22–34)
Literate legal guardian, n (%)	50 (72.5)	46 (63.0)	54 (68.4)	50 (67.6)	52 (72.6)	253 (68.8)
Ownership of mobile phone, n (%)	28 (40.6)	28 (38.4)	28 (35.4)	29 (39.2)	33 (45.2)	146 (39.7)
Wealthy SES, n (%)	10 (14.5)	16 (21.6)	13 (16.5)	15 (20.6)	19 (26.0)	73 (19.8)
Distance to hospital in km, mean (Sd)	19.6 (8.9)	19.4 (8.9)	19.5 (10.2)	20.5 (8.5)	18.2 (9.5)	19.7 (9.2)
Receipt of ≥ 1 SMS, n (%)	-	10 (14.5)	-	-	15 (21.4)	25 (18.0)

Mobile phone ownership in the household or with a neighbour was reported in 39.7% of the caregivers, with the Fac+SMS arm reporting highest (45.2%). The mean distance to the hospital was similar among all the arms (19.7 ±SD 9.5 km). Out of the 150 participants who were expected to receive SMS reminders, only 25 (18.0%) reported to have received at least one SMS.

Adherence

Adherence to all PMC courses was reported in 63.1% of all the children. A higher proportion of children in the community-based arms reported full adherence to compared to facility-based arms (70.6% versus 52.7%, IRR=1.24, 95% CI 1.06-1.44, p =0.006). Children receiving PMC in the community in the SMS arm reported the highest proportion of full adherence (79.7%) compared to those in the community but receiving no SMS (63.2%), Com+HSA (68.4%), Fac-SMS (51.3%) and Fac+SMS (52. %). The proportion that was administered at least six doses representing medium adherence was 22.1% among all the children and Fac-SMS arm had the highest proportion of medium adherence (27.6%), and Com+SMS arm (12.2%) lowest for medium adherence. On the other hand, only 2.9 % of the children reported very low adherence which was representing less than 30% of the total doses (Table2 and Figure2).

Table 3. Levels of adherence to DHP across all the trial arms

Level of adherence	Total doses	Com+ No SMS n (%)	Com+ SMS n (%)	Com+ HSA n (%)	Fac-SMS n (%)	Fac+ SMS n (%)	Total n (%)
Very low (< 30 % uptake)	0	1 (1.5)	2 (2.7)	1 (1.3)	4 (5.3)	2 (2.7)	10 (2.7)
	1	0 (0)	0 (0)	1 (1.3)	0 (0)	0 (0)	1 (0.3)
	2	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	Total	**1 (1.5)**	**2 (2.7)**	**2 (2.6)**	**4 (5.3)**	**2 (2.7)**	**11 (2.9)**
Low (30% uptake)	3	7 (10.3)	4 (5.4)	6 (7.6)	11 (14.5)	13 (17.6)	41 (11.1)
	4	0 (0)	0 (0)	0 (0)	0 (0)	0(0)	0 (0)
	5	1 (1.5)	0 (0)	0 (0)	1 (1.3)	1 (1.4)	3 (0.8)
	Total	**8 (11.8)**	**4 (5.4)**	**6 (7.6)**	**12 (15.8)**	**14 (18.9)**	**44 (11.9)**
Medium (60% uptake)	6	15 (22.1)	9 (12.2)	16 (20.3)	21 (27.6)	18 (24.3)	79 (21.3)
	7	1 (1.5)	0 (0)	0 (0)	0 (0)	1 (1.4)	2 (0.5)
	8	0 (0)	0 (0)	1 (1.3)	0 (0)	0 (0)	1 (0·3)
	Total	**16 (23.5)**	**9 (12·2)**	**17 (21.5)**	**21 (27.6)**	**19 (25.7)**	**82 (22.1)**
Full (100% uptake)	9	43 (63.2)	59 (79.7)	54 (68.4)	39 (51.3)	39 (52.7)	234 (63.1)
	Total	**43 (63.2)**	**59 (79.7)**	**54 (68.4)**	**39 (51.3)**	**39 (52.7)**	**234 (63.1)**
Total		68 (100)	74 (100)	79 (100)	76 (100)	74 (100)	371 (100)

When PMC was delivered through the community-based methods, adherence was greater than facility-based methods (IRR=1.24; 95%CI 1.10, 1.44 p=0.001) and this was observed in both the SMS recipients (IRR=1.41; 95%CI 1.21, 1·64, p<0.001) and in the non-SMS recipients (IRR=1.37; 95%CI 1.18, 1.61, p<0.001) (Figure 3, Tables 6).

Table 4. Description of the total number of doses administered for each course of PMC

Course	No. of doses	Com-SMS n/N (%)	Com+SMS n/N (%)	Com+HSA n/N (%)	Fac-SMS n/N (%)	Fac+SMS n/N (%)	Total n/N (%)
PMC 1	0	15/68 (22.1)	11/74 (14.9)	10/79 (12.7)	10/76 (13.2)	10/74 (13.5)	56/371 (15.1)
	1	0/68 (0)	0/74 (0)	1/79 (1.3)	0/76 (0)	0/74 (0)	1/371 (0.3)
	2	1/68 (1.5)	0/74 (0)	0/79 (0)	1/76 (1.3)	2/74 (2.7)	4/371 (1.1)
	3	52/68 (76.5)	63/74 (85·1)	68/79 (86·1)	65/76 (85·5)	62/74 (83·8)	310/371 (83·6)
PMC 2	0	7/66 (10.6)	4/74 (5.4)	10/79 (12.7)	17/76 (22.3)	16/73 (21.6)	56/368 (15.1)
	1	1/66 (1.5)	0/74 (0)	0/79 (0)	0/76 (0)	0/73 (0)	1/368 (0.3)
	2	0/66 (0)	0/74 (0)	1/79 (1·3)	0/76 (0)	0/73 (0)	1/368 (0.3)
	3	58/66 (87.9)	70/74 (94.6)	68/79 (86.1)	59/76 (77.6)	57/73 (77.0)	312/368 (84.1)
PMC 3	0	7/66 (10.6)	8/74 (10.8)	13/79 (16.5)	29/76 (38.2)	24/73 (32.9)	81/368 (22.0)
	1	0/66 (0)	0/74 (0)	0/79 (0)	0/76(0)	0/73(0)	0/368 (0)
	2	0/66 (0)	0/74 (0)	0/79 (0)	0/76(0)	0/74(0)	0/368 (0)
	3	59/66 (89·.)	66/74 (89.2)	66/79 (83.5)	47/76(61.8)	49/73(67.2)	287/368 (78.0)

Overall, a total of 83.6%, 84.1% and 78.0% of the children received complete courses of PMC1, PMC2 and PMC3 respectively. Generally, most of the children who received the first dose of each PMC course also received the second and the third dose. A small proportion (1.3%) received the first and second dose but not the third dose of PMC 1, only one participant (0·3%) took only the first dose of PMC 2 and another one (0.3%) took only the first and second doses of PMC 2. All participants who took the first course of PMC 3 completed all the three doses.

Table 5. The distribution of the timing of each dose of PMC per course administered in each trial arm

Course		Com+ No SMS n/N (%)	Com+SMS n/N (%)	Com+HSA n/N (%)	Fac-SMS n/N (%)	Fac+SMS n/N (%)	Overall
PMC 1	1st dose	53/68 (77.9)	63/74 (85.1)	69/79 (87.3)	66/76 (86.8)	64/74 (86.5)	310 (83.6)
	2nd dose	53/68 (77.9)	63/74 (85.1)	68/79 (86.1)	66/76 (86.8)	64/74 (86.5)	
	3rd dose	52/68 (76.5)	63/74 (85.1)	68/79 (86.1)	65/76 (85.5)	62/74 (83.8)	
PMC 2	1st dose	59/66 (89.4)	70/74 (94.6)	69/79 (87.3)	59/76 (77.6)	57/73 (77.0)	312 (84.1)
	2nd dose	58/66 (87.9)	70/74 (94.6)	69/79 (87.3)	59/76 (77.6)	57/73 (77.0)	
	3rd dose	58/66 (87.9)	70/74 (94.6)	68/79 (86.1)	59/76 (77.6)	57/73 (77.0)	
PMC 3	1st dose	59/66 (89.4)	66/74 (89.2)	66/79 (83.5)	47/76 (61.8)	49/73 (67.1)	287 (78.0)
	2nd dose	59/66 (89.4)	66/74 (89.2)	66/79 (83.5)	47/76 (61.8)	49/73 (67.1)	

3hs dose	59/66 (89.4)	66/74 (89.2)	66/79 (83.5)	47/76 (61.8)	49.73 (67.1)

Community-based delivery arms had the highest proportions of participants receiving PMC2; (86.4 to 91.9%) and PMC3 (78.4 to 89.4%) compared to facility-based arms; who reported up to 78.7% receiving PMC2 and less than 70% for PMC 3. There were no significant differences in the proportion of participants across the arms in administration taking the PMC1 (p=0·56) and PMC2 (p=0·08) but administration of PMC 3 was statistically different across all the groups.

Figure 2. Kaplan Meir curves illustrating the adherence by the total number of PMC doses that were administered in each trial arm

Community delivery utilizing HSA reminders resulted in higher adherence compared to delivery in the health facility (IRR=1.32; 95%CI 1.14, 1.54, p<0.001). However, there was no evidence that SMS reminders resulted in greater adherence compare to the arms that did not receive the SMS (IRR=1.03; 95%CI 0.88, 1.21, p=0.7) [figure3 & table6].

Table 6. Poisson regression model excluding PMC 1 with an interaction term in factorial design analysis for adherence between a) community compared to facility and b) SMS compared to no SMS

Strategy		Crude		Adjusted	
		IRR (95% CI)	**p-value**	**IRR (95% CI)**	**p-value**
Pooled					
	Facility	Reference	-	1	-
	Community	-	-	1.24 (1.06, 1.44)	0.006
	No SMS	Reference	-	1	
	SMS	-		1.03 (0.88, 1.21)	0.677
By arm					
	Fac-SMS (Ref)	Reference	-	1	-
	Com+ No SMS	1.33 (1.14,1.54)	<0.001	1.37 (1.18,1.61)	<0.001
	Com+SMS	1.37 (1.19,1.59)	<0.001	1.41 (1.21,1.64)	<0.001
	Com+HSA	1.29 (1.12,1.5)	0.001	1.32 (1.14,1.54)	<0.001
	Fac+SMS	1.12 (0.96,1.31)	0.140	1.16 (0.99,1.37)	0.066

There was no difference in adherence between facility-based delivery with SMS and without SMS (IRR=1.16; 95%CI 0.99,1.37, p=0.07) (figure 3) and there was no evidence of interaction between the use of SMS and delivery strategy (Facility/community) (p=0.88).

Figure 3. Forest plots illustrating adherence to PMC in each trial arm

Table 7 summarizes sick visits that occurred during the follow-up period. There were total of four deaths (overall mortality of 1.1%); two each in the Com-SMS and Fac+SMS. Two deaths were caused by severe anaemia; one due to sepsis and one death caused by drowning. The total number of reported sick visits was 90 of which 46.7% were due to uncomplicated malaria. The lowest number of adverse events was observed in the Com+HSA arm. The number of deaths was too low to make meaningful association to adherence.

Table 7. A summary of all sick visits

Diagnosis	Com+SMS n	Com+SMS n	Com+HSA n	Fac-SMS n	Fac+SMS n	Total
Septicemia	1	0	2	1	1	**5**
Severe anaemia	1	0	0	1	0	**2**
Moderate anaemia	0	0	0	1	0	**1**
Uncomplicated malaria	7	12	4	12	7	**42**
Complicated malaria	1	0	1	1	0	**3**
Respiratory infections	5	4	2	4	10	**25**
Total	**15**	**16**	**9**	**20**	**18**	**78**

Discussion

In this study, we found that children who had their monthly DHP in the community provided by caregivers irrespective of reminders resulted in 24% higher adherence compared to facility-based delivery where caretakers were asked to return to the clinic to collect their 2nd and 3rd course of PMC. These findings are consistent with findings reported from other African countries. Studies in Kenya, Uganda and Ghana reported that malaria treatment distributed by CHWs resulted in reduced malaria incidence and increased access to treatment.[19, 21, 22] Similarly, in Malawi, community delivery of sulfadoxine-pyrimethamine (SP) for intermittent preventive therapy in pregnancy IPTp by CHWs improved coverage from 41.5% to 82.9% however it was noted that this led to a reduction in antenatal care (ANC) attendance.[23] In the Gambia, delivery of intermittent preventive therapy in children (IPTc) by CHWs also achieved higher coverage, cost-effectiveness and reduced symptomatic malaria cases.[17]

Although utilizing CHWs has been supported by WHO and has proved to be effective for high adherence and reduced incidence of disease, the effectiveness has shown to decline for subsequent

doses. In Mali, seasonal malaria chemoprevention (SMC) delivered through routine programmes utilizing existing CHWs reduced malaria prevalence; 84% of the targeted children received the first course but only 54% received four complete SMC courses.[24] Another study reported that completion of all the three doses of IPTc was similar (91.6% versus 91.7%) in community delivery compared to delivery at health centres.[25] Utilizing HSAs has its own challenges and requires additional resources for training, supervision and incentives and this may be challenging for PMC delivery.[17, 26] In addition, children receiving PMC will not be in the scheduled work plans for HSAs to incorporate. In our setting, it has been reported that HSAs are motivated to provide reminders for PMC.[27] However, despite this motivation, our study still showed that less than half of the HSAs conducted the required home visit reminders. Many of the reported challenges include inability to locate the child, high existing workload, limited training, supervision and poor community acceptance.[27, 28]

Whereby there are limited studies that have examined adherence to medication when utilizing caregivers to administer longer-term malaria interventions at home, in our study, we found that community-delivery utilizing caregivers resulted similar adherence without requiring HSA reminders. One study in Sierra Leone reported that caregivers are capable of administering anti-malarial medication to the children with basic instructions and supervision of the first dose by the CHW.[29] Caregivers were able to administer monthly doses without additional reminders and this is important because it does not require additional resources. A qualitative study examining the acceptance of PMC among caregivers in Malawi reported that caregivers had a higher preference and confidence to be given all the medication to administer to their children without any additional reminder because HSAs and phones were unreliable and collecting medication from the hospital was very challenging.[30] However, the concern with this method is poor storage conditions, ensuring that medication will be only be administered as prescribed to the child and not others and possible side effects of the drugs.[30]

Use of mobile phone reminders has been hailed as an important tool to achieve adherence, optimal treatment response, case management and outcomes in resource poor settings such as SSA.[31, 32] However, we found that SMS did not have that added effect on adherence. In rural Malawi, provision of SMS to health workers or mothers has been reported to not have a significant effect on adherence and improvement of management of common childhood illnesses with only up to 46·5% receiving SMSs.[33, 34] This is rather low compared to similar trials in Kenya where providing SMS was effective when 91% received them.[35, 36] Challenges reported with implementing mobile health (mhealth)

interventions in resource poor settings such as Malawi include poor network coverage, access, and inability to charge mobile phones, literacy and low phone ownership.[37]

Our findings are important because PMC is a relatively new intervention in the Malawian and other developing countries health care system where established delivery systems currently do not exist. Because the timing of PMC medication administration is sensitive, it would be a challenge for a caregiver to rely on receiving timely reminders on a personal phone or rely on others to receive the reminder and pass on the message. A study in Tanzania reported that unsupervised malaria treatment given at home by caregivers was effective without the utilization of any reminders.[26] Contrasting to this, caregivers have a higher preference and confidence to be given all PMC medication to administer at home without any reminders.[30] In this case, community-based delivery strategies where the medication is given to the caregivers may be the most successful strategy for this promising intervention.

Conclusion

This is the first study to assess adherence to PMC, which is an innovative intervention for managing sick children during the post-discharge period. We found that using community-based strategies, caregivers were able to administer PMC medication to their children without additional reminders. As they routinely administer medication to their children at home, this may be a cost-effective strategy for delivery of PMC. Although utilizing HSAs has proven to be effective for improving adherence for other malaria interventions, adherence to subsequent doses has tended to decline and may remain challenging for PMC delivery utilizing HSAs reminders, which is interval sensitive. Although we found that SMS reminders had no effect on adherence, it must be noted that the proportion of caregivers that reported received the SMS reminder was very low. As such we are not able to conclusively state that they are not effective in improving adherence regards to PMC in our setting.

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Introducing post-discharge malaria chemoprevention (PMC) for management of severe anemia in Malawian children: a qualitative study of community health workers' perceptions and motivation

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Abstract

Background: Severe malarial anaemia is one of the leading causes of paediatric hospital admissions in Malawi. Post-discharge malaria chemoprevention (PMC) is the intermittent administration of full treatment courses of antimalarial to children recovering from severe anaemia and findings suggest that this intervention significantly reduces readmissions and deaths in these children. Community delivery of health interventions utilizing community health workers (CHWs) has been successful in some programmes and not very positive in others. In Malawi, there is an on-going cluster randomised trial that aims to find the optimum strategy for delivery of dihydroartemesinin-piperaquine (DHP) for PMC in children with severe anaemia. Our qualitative study aimed to explore the feasibility of utilizing CHWs also known as health surveillance assistants (HSAs) to remind caregivers to administer PMC medication in the existing Malawian health system.

Methods: Between December 2016 and March 2018, 20 individual in-depth-interviews (IDIs) and 2 focus group discussions (FGDs) were conducted with 39 HSAs who had the responsibility of conducting home visits to remind caregivers of children who were prescribed PMC medication in the trial. All interviews were conducted in the local language, transcribed verbatim, and translated into English. The transcripts were uploaded to NVIVO 11 and analysed using the thematic framework analysis method.

Results: Although intrinsic motivation was reportedly high, adherence to the required number of home visits was very poor with only 10 HSAs reporting full adherence. Positive factors for adherence were the knowledge and perception of the effectiveness of PMC and the recognition from the community as well as health system. Poor training, lack of supervision, high workload, as well as technical and structural difficulties; were reported barriers to adherence by the HSAs.

Conclusions: Post-discharge malaria chemoprevention with DHP is perceived as a positive approach to manage children recovering from severe anaemia by HSAs in Malawi. However, adherence to home visit reminders was very poor and the involvement of HSAs in a scale up of this intervention may pose a challenge in the existing Malawian health system.

Trial registration: ClinicalTrials.gov identifier NCT02721420. The trial was registered on 26 March 2016.

Keywords: Anaemia, Malaria, Secondary prevention, Community health workers, Social perception, Malawi

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Background

In sub- Saharan Africa, between 17 and 54% of malaria-attributable deaths are estimated to be due to severe anaemia [1]. Severe anaemia is a condition in which the number of red blood cells or their oxygen-carrying capacity is insufficient to meet physiological needs. Children with severe anaemia due to malaria are at risk of readmission and death within 6 months after discharge from hospital [2, 3]. Post-discharge malaria chemoprevention (PMC) is the intermittent administration of full treatment courses of antimalarial to children recovering from severe anaemia. Findings from studies in Malawi and other African countries suggest that PMC to children in the post-discharge period significantly reduces hospital re-admissions and deaths after discharge from hospital [2–19]. Although PMC is a relatively simple intervention, its implementation requires a feasible and acceptable delivery strategy [9, 20–25].

Community health workers (CHWs) and related cadres play a role in prevention, case management and health promotion delivery in many poor countries [26–28]. Delivering community-based programs using community health workers has been shown to be effective in achieving high coverage, improved access, and in reducing maternal, neonatal and child mortality in some resource-poor settings [9, 20–22, 29–38]. However, the global health literature has also identified a number of challenges related to the role of CHWs in different community-based interventions [38–42].

In the Malawian health care system, CHWs are known as Health Surveillance Assistants (HSAs). The HSAs are the lowest cadre in the Malawi health system and the Ministry of Health (MoH) pays them a monthly salary. In the villages, they work together with community leaders in providing some basic health and environmental health services to the community and it is estimated that each is expected to serve approximately 1000 people in a catchment area [43]. Their role is important, since it is estimated that only 54% of the Malawian population resides within 5 km radius of a health facility and even patients who do reach a health facility encounter a shortage of health workers [29]. Furthermore, the proportion of the population residing within 5 km of a health facility equipped to provide treatment of severe anaemia is far lower. HSAs have been reported to create a link between the health facility and the community and they have contributed to the delivery of health services in rural areas [44, 45].

The literature refers to a number of factors that influence CHW activity, motivation and continuation on the job [46–54]. Motivation can be defined as the "willingness to exert and maintain an effort towards goals" and is regarded to develop in individuals as a result of the interaction between individual, organizational and cultural determinants [55]. In Malawi, HSA motivation has been found to be driven by community interactions and opportunities for increased responsibility [29]. Other reported contributing factors to sustained motivation and job satisfaction are altruism, need for community respect and recognition, supportive supervision and monetary and non-monetary incentives [45]. However, the literature also shows that HSAs are not always conducting the activities that are expected from them. For example, a recent study of caregivers' perceptions of delivery of PMC showed that caregivers reported that HSAs were unreliable and mothers do not prefer them as a means to receive reminders [56].

The main objective of this study is to assess the feasibility of involving HSAs in the scaling up of PMC into the health system by exploring perceptions, experiences and motivation of the HSAs who were involved in an on-going trial in Malawi [57]. The study will contribute to the existing literature on the role of CHWs in low-income settings, and particularly to a better understanding of the interrelationship between motivation and structural factors for scaling up an intervention such as PMC.

Methods

Study place

The study was conducted in Zomba District, which is located in the southern region of the Republic of Malawi and has a population of approximately 883,200. Public health services in Malawi are provided mainly at village health posts, health centres and district and central hospitals. There are 32 health facilities in Zomba district and a total of 630 HSAs working for the Ministry of Health (MoH).

The design of the trial

This study is part of a trial that aims to find the optimum strategy for delivery of PMC. A total of 375 children aged less than 5 years are given an antimalarial medication; dihydroartemisinin-piperaquine (DP), over a period of 3 months during the recovery from severe anaemia. The delivery of the medication is divided into five different arms, of which two are facility-based and three community-based and the protocol for the trial has been described elsewhere [57]. This study focuses on one of the community-based study arms where the study medication is given to the caregiver upon discharge from the hospital, and she/he is instructed to give them to the child at two, six and ten weeks after discharge for 3 days at a time. The dates are noted on the child's health card.

The PMC trial recruits children from the Zomba central hospital (ZCH), which is the referral hospital for all neighbouring health centres and districts. On the day when the child is discharged, the caregiver is linked to the HSA in their catchment area. The HSA responsible

for the catchment area receives their contact details and are informed about the participant and the location of their home. In the case that the HSA is not available, he/she is contacted by phone, or by receiving a physical visit, with information about the participant's details, location and treatment procedures. One or two days prior to the scheduled date of drug administration, the HSA was expected to receive a short message service (SMS) reminder on his/her phone to go to the child's home to remind the caregiver to administer the study medication. The HSAs did not receive any other reminders or memory aids during the course of follow up and they were not paid specifically for this work because it was considered to be part of their regular duties. However, they received a lunch allowance during the initial training.

Prior to commencement of the trial, community engagement and briefing about the trial was conducted with all the 7 Traditional authorities (TAs) and their group village headmen. In Malawi, TAs are key community leaders. In these meetings, information about the trial objectives and methods were discussed and the leaders were expected to disseminate this information in their communities. In addition, 608 HSAs received a short training about PMC as an intervention for management of children with severe anaemia. The training included informing them about their role in the project whereby they were requested to visit the child and remind the caretakers to administer the study medication to the child. The HSAs were not shown the actual study medication during the training, and there was no formal assessment of knowledge attained.

Study participants and sampling

A total of 78 children were randomized to receive the intervention in the arm utilizing HSAs, and 60 HSAs participated in the trial. Of these, 21 were not interviewed since they had either relocated, were unreachable by phone, or had a child participating at the time of the study and could not be involved in the interviews to avoid influencing outcome measures of the trial. The remaining 39 HSAs were invited to participate in this study. In December 2016 we conducted 20 individual in-depth interviews (IDIs) with HSAs, and later, in March 2018, we conducted two focus group discussions (FGDs) with 19 HSAs at designated health centres. While saturation to a large degree was achieved with the first 20 IDIs, the two FGDs gave us an opportunity explore further the findings that had been identified in the initial analysis of the IDIs. The choice of the additional 2 FGDs was made in order to explore different experiences between adherent (FGD1) and non- adherent (FGD2) HSAs. Inclusion was not based on age or gender, but rather by caregiver's report at the exit visit of the main trial.

Data collection

The semi-structured interview technique was used utilising a guide with set topics, and an open-ended approach, which allowed the informant to speak without interruption. This was best suited for this study because we aimed to uncover the perceptions and understandings of PMC from the interviewees' point of view [58]. All interviews were conducted in the local language; Chichewa, by three experienced and independent research assistants. The interview guides were formulated in English and translated into Chichewa and piloted with the local nurses to ensure that the information gathered truly reflected the study objectives and ensured that probes were captured precisely (Additional files 1 and 2). Furthermore, all research assistants and the first author were Malawians, who speak fluent Chichewa. Since the first author is the medical researcher responsible for conducting the trial, she took part only in the interviews with HSAs that she did not have prior contact with to reduce the likelihood of biased responses. The information gathered was supplemented by her experiences and observations throughout the trial and field notes made during the interviews. All interviews were digitally recorded, transcribed verbatim and translated into English by the research assistants. Permission to conduct the trial was obtained from ZCH and Zomba DHO prior to commencement and written consent was obtained from all participants.

Data entry and analysis

The first author went through all the transcripts, observation notes and audio files for accuracy and reliability, and read each transcript carefully to familiarise herself with the data. The last author reviewed all the FGD transcripts. Transcripts were loaded into NVIVO 11 and a coding system was developed based on the research objectives and the analytical framework of motivation. The coding system was expanded during the coding process to capture emerging themes outside of the original study objectives. The first author coded each IDI and FGD and the last author reviewed the coding frame. Through this process the coding was refined and both agreed on the final themes. Thematic framework analysis was used because it is an appropriate, rigorous and systematic method for undertaking qualitative analysis [59, 60].

Results

Characteristics of participants

A total of seven women and thirteen men were interviewed in the IDIs. The HSA ages ranged from 27 to 45 years and the length of service as HSAs was between seven and 24 years. A total of thirteen HSAs served a health centre that was categorised as rural and seven

were from the urban or semi-urban health centres. FGD 1 comprised of three women and six men and seven women and three men in FGD 2 respectively. The ages ranged between 32 and 45 years in FGD 1 and 27 and 51 in FGD 2. In FGD 1, the range of service as HSAs was nine to twenty years and eight and seventeen years in FGD 2. All the discussants in FGD 1 reported to a rural health centre while six out of the ten reported to a rural health centre in FGD2. The range of duration of each IDI and FGD interviews was between 62 to 104 min. A majority of all had completed secondary school and attained a Malawi school certificate of education (MSCE), while four possessed a junior certificate of education (JCE), which is attained after completing 2 years of secondary school. The HSAs reported that their catchment populations ranged between 599 and 33,000. A summary of the characteristics of the IDI and FDG participants is provided below in Tables 1 and 2 respectively.

Adherence

HSAs were required to visit the child's home three times, at two, six and ten weeks after discharge from hospital. Information on adherence to home visits was collected at the exit interview with caregivers as part of the trial, and during IDIs and FGDs with HSAs. In FGD 1, all the nine HSAs were reported as adherent by caregivers. Out of the 9 HSAs, 3 of them report to have conducted at least one visit; 2 reported full adherence and 1 had partial adherence. The ten HSAs in FDG 2, in contrast, were reported to be non-adherent by caregivers. However, three of them claimed that they had made one or more visits to the child. In the IDIs, twelve HSAs reported adherence but two differed from what the caregiver reported. There may be several reasons reported for this discrepancy. Firstly, the HSA may have visited the child when the caregiver who was interviewed for the exit interview was not at home. Second, the caregivers or HSAs may not have reported correctly. Third, there may have been a social desirability effect; HSAs may have wanted to over-report their adherence. In this paper, we refer to the HSAs self-reported adherence. Tables 1 and 2 also summarize adherence level by HSA.

We define adherence level by the number of home visits the HSAs conducted. Those that conducted all three home visits are termed "adherent", those who made at least one visit are termed "partially adherent" and those that did not conduct any home visit are termed "non-adherent". Only ten HSAs, or about one in

Table 1 Characteristics of HSAs who participated in IDIs

HSA ID	Gender	Age	Location category	Population size	Length of service	No. Of visits	Level of adherence
HSAs with self- reported adherence ($N = 12$)							
ID1-HSA-01	Male	32	Urban	2219	9	1	Partially adherent
IDI-HSA-03	Male	40	Semi-urban	894	7	3[a]	Fully adherent
IDI-HSA-04	Female	37	Rural	3077	10	1	Partially adherent
IDI-HSA-05	Female	45	Urban	4050	24	3	Fully adherent
IDI-HSA-06	Female	36	Semi-rural	Unsure	9	2	Partially adherent
IDI-HSA-07	Male	35	Rural	3090	9	1	Partially adherent
IDI-HSA-09	Female	39	Semi-urban	1139	8	2	Partially adherent
IDI-HSA-10	Male	30	Rural	3299	10	1	Partially adherent
IDI-HSA-11	Male	39	Remote	2360	14	2	Partially adherent
IDI-HSA-14	Female	30	Semi-rural	2202	9	1	Partially adherent
IDI-HSA-17	Male	42	Semi-rural	4500	17	3	Fully adherent
IDI-HSA-18	Male	27	Urban	1160	9	1	Partially adherent
HSAs with self-reported non-adherence ($N = 8$)							
IDI-HSA-02	Female	27	Urban	884	9	0	Not adherent
IDI-HSA-08	Female	42	Urban	599	21	0	Not adherent
IDI-HSA-12	Male	33	Semi-rural	1276	9	0	Not adherent
IDI-HSA-13	Male	32	Rural	1356	8	0	Not adherent
IDI-HSA-15	Male	32	Rural	4000	7	0	Not adherent
IDI-HSA-16	Male	38	Remote rural	NA	10	0	Not adherent
IDI-HSA-19	Male	36	Remote	940	9	0	Not adherent
IDI-HSA-20	Male	40	Remote	3100	9	0	Not adherent

[a]This HSA had 2 children during the course of the study and he was fully adherent to both

Table 2 Characteristics of HSAs participating in two FGDs

HSA ID	Gender	Age	Location	Population	Length of service	Number of visits
FGD 1: HSAs with full or partial-adherence as reported by the caregiver						
FGD-HSA-01	F	32	Rural	982	10	2
FGD-HSA-02	M	42	Rural	3840	18	2
FGD-HSA-03	F	39	Remote	1796	20	3
FGD-HSA-04	M	35	Rural	1139	10	4
FGD-HSA-05	M	35	Rural	9808	12	3
FGD-HSA-06	M	38	Rural	2098	11	3
FGD-HSA-07	F	35	Rural	2876	10	2
FGD-HSA-08	M	34	Rural	3614	9	3
FGD-HSA-09	M	32	Rural	9300	10	2
FGD 2: HSAs with non-adherence as reported by the caregiver						
FGD-HSA-10	F	27	Rural	2070	10	0
FGD-HSA-11	F	35	Semi urban	890	8	0
FGD-HSA-12	F	45	Semi urban	883	10	0
FGD-HSA-13	M	29	Urban	1896	10	1
FGD-HSA-14	F	45	Urban	1982	10	0
FGD-HSA-15	M	38	Remote	1740	10	3
FGD-HSA-16	F	31	Semi urban	2339	10	0
FGD-HSA-17	F	32	Semi urban	1038	10	0
FGD-HSA-18	M	39	Remote	1935	10	0
FGD-HSA-19	F	51	Rural	2040	17	3

four, carried out all the three required home visits. Of the remaining three quarters of HSAs, fifteen were non-adherent and fourteen were partially adherent. We did not find any clear association between HSAs characteristics (age, sex, population size) and adherence, but we note that adherence was slightly higher among HSAs in rural communities (30%) compared to those who were based in urban areas (15%). Additionally, we noted that male HSAs had the highest reported adherence compared to female HSAs; but the sample was too small to make any generalization. Table 3 below summarizes the adherence levels among HSAs categorized by location.

In the following, we map out factors that appear to have influenced HSAs' adherence. We have categorized these factors into three main categories: Professional factors, structural factors, and community factors. For each of them, we describe a number of enabling and motivating factors reported by the HSAs. We also describe the barriers and demotivating factors that HSAs identified for each of these categories, which reportedly discouraged adherence.

Table 3 Adherence to PMC home visits by location

Location	Adherence	Total (%)
Rural ($N = 26$)	≥3	8 (30)
	1–2	10 (39)
	0	8 (30)
Urban ($N = 13$)	≥3	2 (15)
	1–2	4 (30)
	0	7 (54)

Professional factors

The belief that PMC is important and useful, gaining new knowledge, and opportunities to conduct other tasks were reported as motivating factors, while the lack of incentives was reported as a demotivating factor by some HSAs.

The belief that PMC is important and useful

All HSAs, regardless of adherence, expressed that malaria is a serious disease and is the most common cause of death among children in their communities. Regarding knowledge of severe anaemia, the HSAs explained that it is a complication of malaria and most described those with severe anaemia as "having white hands" and that this condition frequently leads to death.

All HSAs, including the non-adherent, perceived PMC as an important and beneficial intervention that will save the lives of many children. In addition, HSAs that were adherent to at least one visit expressed that the children

who took the medication did not get sick from malaria again:

This study has helped - the child's frequent malaria problems have ended. Even when the child doesn't look sick, the drugs are still given, to completely kill the malaria parasite. This would benefit the nation. (FGD1, male, 34 yrs, adherent)

Gaining new knowledge

Of the 39 participants, seven had not been part of the initial training. Of these seven, two had received information on the day that the child was taken home by the research team, while the other five had heard about it from their fellow HSAs. None of the HSAs had prior knowledge about the fact that there is medication that can be given to children in order to protect them from getting malaria. This knowledge was appreciated and considered novel by all HSAs regardless of adherence, but it was more important to the HSAs who were adherent. They said this knowledge gave them confidence in the medication and gave them a sense of pride to know something that even superiors at their facilities didn't know:

We have gained knowledge and the kids have been helped (FGD 1, male, 34 yrs, adherent)

They also said this knowledge was beneficial to other people than the children in the trial since they spread this information to other community members as well as health workers at their facilities. However, more than half of all the HSAs reported that the information received on the day of the initial training was too limited. They also argued that follow-up trainings would have been a big motivator for them because they would have gained refreshed knowledge and up-to-date information.

Everyone knew about this study, but the information was not clearly laid out to us. As my colleague has already pointed out, my plea is that next time there is a meeting, the information should be well delivered to us, and we should have enough details. The training should have been for a few days, or even a week. In my case, it turned out that the client had more information than me so it is sort of embarrassing. (FGD 1, male, 35 yrs, adherent)

Recognition by government or NGOs

Most of the adherent HSAs reported that the fact that they were recognised and considered to take part in reminding caretakers is a sign of respect to them and recognition of their importance in the health system. They expressed that they are often not involved during inception of similar projects and yet they are the ones who provide health care within the community:

As HSAs, we are supposed to be part of this because the people are ours, we live with them in the community, and we know them in and out. When they (hospital staff) come here they just register and leave. But we know their homes, how it is, what's there, their habits, maybe their eating habits, we visit their homes and we know. But then the problem is when things like these come; they involve clinicians, nurses and so when it gets hard, that's when they involve the HSAs at the end. (IDI-05, female, 45 yrs Adherent)

However, many of the non-adherent HSAs were not happy about being involved in projects organized by NGOs and research institutions. They felt that they were being "used" since there is no personal benefit to them:

To say the truth, I was supposed to deliver the message. But the benefit is not there for me because the study was just done with me, they have just used me. So it means much benefit is gained by those getting the support of drugs, and those doing the study. I was just supposed to be doing my job as I do. (IDI-12, male, 33 yrs, non-adherent)

Genuine love for the job, sense of obligation and altruism

Intrinsic motivating factors are factors that make an individual to carry out tasks without outside influence. Many participants reported that being an HSA was a calling and that it was their responsibility to ensure good health in their communities. Altruism can be described as the opposite of selfishness and it's the inert need to do good. Among the HSAs that conducted at least one visit this was an emerging theme. Several reported that the love for the job and the love for their community enabled them to help the children get better and that they had saved lives:

Of course, I like it because our role is to save people's lives. So, after you have followed up and you find that they are getting better, you feel that you had done the job on your own, but when the person is neglecting it and then they die, you feel like you haven't done your job, like you are the one who has killed them. (IDI-01, male, 32 yrs, partially adherent)

Many expressed that it is a calling and a privilege to serve the communities that they are part of, but some

were vocal that their motivation was also linked to financial rewards.

No personal rewards

Very few of the non-adherent HSAs reported that provision of additional incentives (other than those provided by the government as part of their job description), would improve their willingness to visit the children in their homes. Many HSAs however, both adherent and non-adherent, argued that they should get more training (which also means a per diem), and two of the HSAs wanted bicycles as a way to be motivated to conduct the task. When asked what kind of incentive that would be more motivating, the majority preferred incentives in the form of additional training with financial allowances rather than being paid per visit to the child, as this is not practical.

> *Just as my fellow HSA has said, getting these trainings will motivate us to do the work. We shouldn't be given allowances every time we visit a child but rather when we attend training. (FGD 2, female, 45 yrs, non-adherent)*

Structural factors

Structural factors are factors that are closely linked to the practicalities of the work tasks themselves. Many of the HSAs who were adherent reported that the task was easy, and/or that they knew the participant. However, we also identified a number of structural factors that were barriers to adherence. These barriers are factors that were reported by HSAs who were not adherent or partially adherent. We have categorized these factors into workload, inadequate training and lack of supervision, difficulties related to text messages, and lack of transport. Although the scope of our study was particularly expressed in the context of PMC activities, most of the reported structural barriers are true for the HSA's current daily work.

Ease of the task and opportunity to conduct other activities that are within job description

The majority of the HSAs who were adherent or partially adherent reported that the task was easy, uncomplicated and not time-consuming:

> *It was simple; I didn't spend much time, since it was just to go and remind them and I would come back, and continue with my work. (IDI-10, male, 30 yrs, partially adherent)*

They described that they went to the child's home and simply ensured that child was given medication. Most of them said that the entire visit took less than 10 min and was even easier than other tasks they do on a daily basis:

> *Since our job is mostly about visiting our people in the community, we are able to pass through the client's home whilst attending to other activities. (FGD 1, male, 35 yrs. adherent)*

Moreover, more than half of them had found that either the caregiver had already administered the medication or had already planned to do so. Although the task was easy, they felt that their visit was very important because it made a positive impact on the caregivers and in turn motivated them to remember to give medication to their children. A few also added that these visits gave them the opportunity to conduct other activities such as giving health counseling, nutritional assessments and family planning counseling to the caregivers and therefore they were able to incorporate it into their schedule:

> *It is not something that is done frequently, or eats up most of our time. When we visit the client we also encourage them to follow healthy methods of life such as building a toilet. Through these visits a bond is created between the clients and us. (FGD 1, male, 42 yrs, partially adherent)*

Knowing the participant, distances and transport

Adherence was highest among HSAs who knew the location of the family that they were to visit. HSAs in this group had either been informed or taken to the home by the research team or they received a message from their supervisor. Four of them made the effort to find the location prior to the scheduled visits when they received a message. Among these HSAs, all of them mentioned that as a result of knowing the location or the family, it was much easier to conduct the visits and they felt an obligation to make the home visits.

Similarly, most of those that were non-adherent, reported that they did not know the child or the location when they received the message. Nearly all of them said they did not make the effort thereafter to find the location. However, two of the non-adherent HSAs knew the study participants' home, but despite this they did not conduct the visits because they were informed to wait for SMSs, which they didn't receive:

> *Yes, I was given the client name and was told that I will receive a phone call but I didn't. I did not follow up the child even though I knew him, because I was waiting for more details. I will receive a message of when to go, but I did not receive any, hence I didn't visit the child. (FGD 2, male, 39 yrs, non-adherent)*

However, most of those that eventually become aware of the child and their home cited that the distance to the participant was too far to go at such short notice. They felt that they were not able to go a day or two after the specific date because it would be too late.

Transport was reported to be a challenge also by some of the adherent HSAs. One HSA who conducted all three visits mentioned that the child lived very far but he was only able to visit her because he decided to schedule clinics in a nearby village around the dates the PMC medication was due:

Actually, I have an outreach site close to her home. And the dates she was given for the dosage were corresponding to those when I was having my outreach nearby. Hence, once I was done with my activities, I would go visit the child. (FDG 2, male, 38 yrs, adherent)

He said this could only be achieved because he knew the schedule. Another HSA who also conducted all the visits reported that she would have liked to have a bicycle because the child's home was far away:

It was far. I had to go around a mountain to get to her place. (FGD 2, female 51 yrs, adherent)

Workload, PMC not part of HSAs regular work

Although all HSAs concurred that serving their community plays a major role in their motivation to work, most of the HSAs that were not adherent reported that at the time they were supposed to go to visit a child for PMC they were already expected to perform many other tasks, including tasks meant to be done by nurses and clinicians. One participant said he was aware about the child under his care, but he "simply forgot" to go because he had so much to do. Another HSA also said that PMC is not on his job description, just like another on-going project whereby they are requested to go and give vitamin supplements. They all agreed that it is very difficult to introduce new tasks for children aged less than 5 years, since they already entail a lot of activities such as vaccinations and vitamin supplementation that are scheduled on different dates.

We were all given work that does not even concern us but we just do it. When actually, it's not in line with our job description. It is not there. So, they pile a lot of work on you, yet the pay itself does not match the given jobs. (IDI-13, male, 32 yrs, non-adherent)

Although HSAs who were adherent reported that PMC visits were relatively simple they similarly expressed that it increased workload, which is particularly challenging since PMC reminders are time sensitive and therefore more difficult to combine with other duties. Two of the HSAs had the responsibility to remind more than one caregiver and both of them were adherent. One of them mentioned that although he did not find it difficult, visiting more than one child during the same time period in the case of an upscale of PMC would be too much work on top of the existing assigned tasks.

Inadequate training and lack of supervision

The majority of the HSAs were dissatisfied with the training that they received for the PMC study. They said that the training prior to the study was too short with too much information. In addition, the medication instructions were not very clear. This was a reported barrier even among those who were adherent. They complained that there was no follow-up training following the initial one. As a result, they had forgotten most of the content and some even said they thought the project was finished. They reported that they only followed instructions as per the short message reminder they received during the trial and not during the initial training.

A major complaint from HSAs was the fact that they saw the medicine for the first time only with the caregiver, because the medicine was not shown during the training:

The work is not demanding. My only problem was that I did not know the medicine that was administered to the child. None the less it was simple. (FGD 2, male, 29 yr, partially adherent)

Not having seen the medication was disappointing to the HSAs, because they did not want to look incompetent in front of the caregivers. They feared losing the confidence of the caretaker because as HSAs they are considered highly qualified and are expected to have all the answers. In this case, when they showed ignorance about the medication the caregiver was unsure whether to give the medication or not. This was expressed by both HSAs who made the visit, as well as those that didn't:

You could have informed us more about the medicine during the briefing. We had no idea how they look like; hence it would be a surprise to see that kind of medicine when we visit the client. We are like doctors to the clients and if they see our ignorance about the medicine, every guardian will question whether they should really give the dosage to their children. (FGD 2, female, 31 yrs, non-adherent)

Most of the HSAs reported that their supervisors were not involved in any way during the intervention. The

responsibility solely lied on the responsible HSA to ensure that home visits were conducted according to plan. They also complained that this supervision was lacking also from the research team. Most said it should be the supervisor who has to ensure that the work plan of each HSA reflects all activities assigned but none of the supervisors offered any guidance. One said the supervisor also had limited information and as such he was not able to go and visit the child:

I had to check with my supervisor for details. My supervisor did not have any concrete information about it as well; though he attended the meeting he said the training wasn't clear enough. (FGD 2, male, 39 yrs, non-adherent)

One HSA who did not conduct any home visit said she was away on maternity leave at the time the child was discharged and felt that had the supervisors been involved, another HSA could have taken over reminding the child on her behalf.

Difficulties related to text messages

Two or three days prior to drug administration, HSAs were to receive text messages to their personal phone from the study team with the following information translated into the local language: "Go and remind (child's name) to give medicine from tomorrow for three days". The majority of the HSAs, both those who were adherent and those who were not, reported that they did not receive all the monthly text message reminders. For some of the non-adherent, this was reported as one of the reasons why they had not visited the child:

I did not know the date that the medicine was supposed to be taken because the date was known by the project team so they were supposed to call me that the child is supposed to take the medicine tomorrow. And then I was supposed to go and see the child in the morning and tell them that the child is supposed to take medicine at this particular time. How would I go when I do not know the dates that the child is supposed to take the medicine? (IDI-6, female, 36, partially adherent)

Four non-adhering HSAs reported that they had been informed during the training to only visit the child when they received a text message, and because they did not receive it they did not conduct a single visit:

I couldn't do anything because we were told to wait for the phone messages. At least if they called us, we would have monitored the child. (FGD 2,male, 39 yrs, non-adherent)

The few who received the text message said that having received it was helpful, although not required. They instead relied on a schedule they developed after finding out the dosing schedule documented in the child's health book. It was reported that the content of the SMS was adequate and clear. Only one HSA expressed that the information on the reminder was not clear and therefore he did not know which child to visit.

Others reported difficulties with the text message was that the timing of the text message was very inconvenient because it came at a time when they had either concluded their daily activities or were away. One HSA who conducted only one visit reported that he received the text message once and that was the time when he was able to go and remind the caretaker. Another HSA decided to go even if he hadn't received the message:

The greatest problem I encountered was waiting to receive a message of reminder. I did not receive the message so I would go on my own to visit the client. (FGD, male, 38 yrs, adherent)

Another pointed out that he is not reachable by phone every time due to unreliable network coverage or inability to have the phone charged all the time since he lives in a remote village:

*Maybe sometimes you have been calling me but you couldn't get through, it is because my phone doesn't get through, since the phone is a phone by name (meaning the phone is unreliable). (*IDI-07, male, 35 yrs., partially adherent)

The majority of the participants expressed that more focus should be put on providing enough information including dose schedule to HSAs because having this information made it possible for them to incorporate it into their scheduled work plans and also to conduct the home visits even when text messages were missing. Similarly, HSAs who were non-adherent reported that if they had known the dosing schedule beforehand they would have been able to plan ahead, but otherwise they didn't know what was going on:

The first time I visited the child, I took the child's health card to check out the dates on which the drugs should be taken. So, I would remind the guardian on such given date. I was motivated even more when I would find the child has already been given the drugs. I did not receive any message of reminder. The first time I visited the client, I just got the dates on which I should be reminding them. (FGD 2, male, 29 yrs, partially adherent)

Overall, HSAs reported that the SMS reminders were not necessary due to their unreliability.

Community factors

In addition to professional and structural factors, factors that were related to the HSAs relationship with the community, such as their wish to maintain community trust was important for adherence.

Maintaining community trust

Another theme that was emerging was that all HSAs, regardless of adherence level, argued that they had a strong link with their villages and community members. They expressed that the recognition by their communities as "doctors" gives them pride. As mentioned before, we noted that adherence was highest among HSAs from rural locations of which most live within the communities they serve. They report that there is a level of trust and confidence that their communities hold for them and it is important to maintain it as they conduct their daily tasks:

> *To my understanding I have been able to help the clients and in return creating a bond with them. They will have a good perception about me and trust me when need arises. I am appreciated for the job I have done. (FGD 2, female, 51 yrs, adherent)*

For them, going to the child's homes for this project was no different and maintaining the confidence motivated them to go. Although those who were non-adherent talked in a similar way, they did not see this as a major determinant of motivation for them to go.

Caregivers see the benefit of PMC, but neighbours may be sceptical

When asked about community reception and attitudes towards the intervention, most adherent HSAs reported that caregivers of children taking PMC were generally very receptive and had a good understanding and information about the study medication, although some parents did not understand the idea of giving medication to children who are not sick or have recovered.

More than half of the HSAs reported that the caretakers had a better understanding of PMC than themselves and all fully adherent HSAs reported that they were certain that all prescribed doses were given to the child because caregivers were determined to improve their child's heath.

However, some of the HSAs reported that generally, there was a lack of information and understanding of PMC by community members who were not directly involved. Two HSAs specifically mentioned that as much as the caretakers whose children were receiving PMC were happy to give medication to their children, some of the neighbours were curious and suspicious:

> *To some people who don't know about this study, they were very suspicious about it. They would ask why the frequent visits to that house and why health officers keep coming there. Whenever I sat outside with the mother, some people would pretend to come greet me while they just want to eavesdrop on what's happening. I asked the lady if we could go inside, as this was irritating. The mother would feel uncomfortable about it but I had to remind her the importance of this study to her and the child. So, the challenge I had was the other people had a bad perception about the study. (FGD 1, male, 42 yrs, partially adherent)*

As a result of this, two of the HSAs reported that caregivers feared raising unwanted suspicion among their fellow community members as to why they were being repeatedly visited by the HSA, which would result in being stigmatized. One of them explained that the caregiver avoided being at home when the HSA was supposed to visit and he did not find her at home on two consecutive visits. The other HSA reported the same concerns but he simply encouraged the mother to continue giving her child medication:

> *Maybe the people may be wondering, "Why are they coming to see our children?" maybe they don't want you to come because of what people say. But yet in the end they may accept it. (IDI-07, male, 35 yrs partially adherent)*

Some of the HSAs also reported that there are some cultural and social beliefs that exist in the communities such as that a chronic illness in a child is often attributed to witchcraft or karma and that there are no medications for it. A few of the HSAs also mentioned that some community members believed that the medicine is given to the children so that they should be infertile. However, this was not presented as a major factor that affected adherence to conduct home visits but rather an observation that may result in caregivers not being adherent.

> *They just say "you are giving these things to the children with an aim of destroying them so that they should not have children in future. They should not do this and that." This is what most people ask and so you have to convince them that it is not like that. (IDI-04, female, 37 yrs,partially adherent)*

When presented with the idea that caregivers could be in full charge of the medication, some argued that HSAs should be central to this and that it would be better if the medication were kept by them and not by the caretakers to guarantee proper storage and administration:

If an HSA would be taught on how to dispense these drugs that they receive at the central hospital, they can be left at the facility, when the follow up date comes the HSA will take the drugs, go and give it to the mother and also see how the child is doing. (IDI-10, male 30 yrs, partially adherent)

Four of the adherent HSAs however, expressed that caregivers are capable of remembering to give medication and may not need to be reminded by HSAs because some of the caregivers had already given the study medication at the time when the HSA was visiting. The findings of this study have been summarized in Table 4 below.

Discussion

In this study we aimed to explore whether utilizing HSAs can be a feasible, practical and acceptable strategy in the delivery of PMC. We found that only one in four HSAs who were trained to incorporate PMC reminders into their normal duties were adherent to all three visits. However, despite this poor level of adherence, the great majority of the HSAs report that they are intrinsically motivated to remind caregivers to administer dihydroartemesinin-piperaquine to children in their community without any additional financial incentives.

We found that the main motivation for HSAs in this intervention came from their altruism and the recognition that they play a major role in provision of health services to the community and the appreciation they get from the caregivers. Kadzandira et al. and Kok et al. reported that HSAs are a link between the community and the health system in Malawi where their major strengths reported for motivation are team spirit, cooperation, knowledge of local culture, language and environment [44, 45]. The HSAs' need to attain and maintain the trust of the community gives them a sense of duty and responsibility because they have developed lasting bonds with the people within the community [51, 55, 61]. This was further outlined in our study in that they want to maintain that level of power by insisting that they need to be an integral part of this intervention. However, when it came to conducting the duties assigned for this intervention this motivation was not demonstrated.

In addition, the experience of actually seeing the impact of their work and benefits of the intervention play a major role on motivation, which was similarly reported by Winn et al. and Gilroy et al. in other malaria programmes [62, 63]. We found that most of the HSAs do not expect additional financial incentives to conduct home visits since similar visits are part of their normal duties anyway. Some studies have reported that financial incentives may represent a source of sustained motivation, while others have observed that they can negatively influence motivation [43, 55, 64]. On the other hand, a number of the HSAs stressed that lack of refresher training (with allowances) reduced their motivation to make PMC visits. This is consistent with findings reported by Mpembeni et al. and Prytherch et al. in studies from different community-based interventions [55, 64].

This suggests that some form of reward either financial or non-financial for the extra work is needed to drive their extrinsic motivation, as they genuinely want to do well in their communities. Financial incentives in the form of lunch allowances during trainings would have the added benefit of gaining new knowledge.

Table 4 Summary of findings

	Enabling and motivation factors	Barriers and demotivating factors
Professional factors	- The belief that PMC is useful - Gaining new knowledge - Maintain recognition from the government and NGOs - Genuine love for the job, altruism, sense of obligation	- Sense of PMC not being part of regular work duties - No personal reward - No provision of earmarked financial incentives or other incentives like air time, bicycle or additional training with allowances
Structural factors	- Ease of the task - Short distance to child's home - Knowing participant location and family - Being able to combine with other duties in the same area	- High workload - Not knowing participant or family location - Long distance to child's home, lack of transport - Inadequate information and lack of supervision - No refresher trainings - Not receiving SMS/No phone - Had not seen the study medication, fear of losing care takers' respect because of this
Community factors	- To maintain community trust and respect as 'doctors' - "Love for the community" - Care takers see the benefit for their child - Being informed by the care taker about the dosing schedule	- Curiousness and suspicion from neighbours - Caretakers may fear stigmatisation - Fear that the study medicine may be harmful

If intrinsic motivation is high then why was there such poor adherence?

Although awareness of the burden and impact of malaria and severe anaemia was high among the HSAs, the question is why there was poor adherence to an intervention that could potentially minimise morbidity and mortality in the communities? In line with other studies, our study found that the factors that influence HSAs motivation to carry out the PMC intervention activities are multilayered [48, 49]. Professional factors allow for good intentions to carry out the duties because most are interpersonal but structural and community factors are a hindrance to them. Some of the non-adherent and partly adherent participants in this study referred to a high workload as one reason why they had not conducted the visits. High workload has been reported as a barrier for CHWs also in other studies [43–45]. However, most said the task was simple, so perhaps in the event of a scale up there would not be the amount of resistance as demonstrated here. Moreover, in the event of an upscale, PMC will most probably be incorporated into the regular work description of the HSAs, and will not be seen as an additional task.

We have identified some significant structural barriers that contributed to poor adherence: difficulties with the text messages which meant that HSAs were not informed when to visit the child, inability to locate the child, and transportation challenges. The poor functioning of the SMS reminders suggests that one should not design a system that relies on the use of this technology in the event of an upscale in Malawi.

All HSAs received similar training, but there are other factors that come into play because with the same training some HSAs were adherent to all the required visits. Limited information and knowledge about the intervention meant that the HSAs did not have a proper understanding of their role and expectations. There was no follow up supervision because we didn't want to affect adherence, which is a major outcome of the main trial. Many studies have shown similar findings, that training improves outcomes because without retraining acquired skills and knowledge are lost over time [43, 61, 63, 65–69]. The finding that the majority of the HSAs felt that they needed follow-up trainings, suggests in the event of an upscale, that resources should be placed into conducting more frequent training as a way of providing additional knowledge and feedback [66].

Strengthening supportive supervision has also been shown to improve effectiveness of utilising CHWs in similar contexts. Good supervision has been shown to be an effective way to boost team spirit and improve the work environment through a continuing dialogue in similar contexts [64, 66, 68–70]. Clarity of chains of command and accountability are reported as sources of extrinsic motivation, since one fears rebuke and loss of professional respect. When it comes to anchoring PMC reminders, it would be better if there were existing chains of command. However, introducing such lines of command in the current study, might have had an undesired impact on the main trial outcomes because this would falsely represent an existing operational system for supervision of HSAs.

Reminding caregivers to give PMC medication is reportedly simple and requires minimal resources in the cases when the child lives nearby, but most of the challenges were related to identifying the child and incorporating that into their routine scheduled work plans. Locating the child was a challenge for some. In the cases that the HSAs were available, they were driven to the child's home by the research team. However, in the event of a scale-up, HSAs will not be driven to the child's home. Therefore, to address this, establishing and strengthening existing supportive supervision is important.

HSAs in this study report having strong relationships with their community who depend on them for guidance and community health needs. Caregivers in the trial preferred to use reminders documented in the child's health book rather than the HSAs reminding them. They report that their HSAs were unreliable and often unavailable [56]. However, other reports have shown this to be opposite in that HSAs have close ties with the community and is an important driver for carrying out their duties [20, 49]. Interestingly, the HSAs themselves report that most of the times the caregivers were capable of administering the medicine to their children without reminders from them. However, the main concern and reason for being part of for this would be to reduce misuse in terms of administration of the medicine to another child and poor storage conditions due to the limited community understanding. They therefore believe that they should be an integral part of this and work hand in hand with the caregiver.

Study limitations

Our study was done in the context of a clinical trial, which may have affected our findings in several ways. First, some HSAs may have felt that since PMC was an add-on to their regular work which they were not given any extra compensation for, they were not "obliged" to be adherent, and an integration with regular chain of command in a national scale up might potentially improve adherence. Second, and pulling in the opposite direction, in the event of a national upscale, HSAs will not be transported to the child's home and adherence may therefore be even lower than what we found. The feasibility of sending a customized SMS with the specific child's name may also not be sustainable in the long run, given the constraints facing the health system. Finally,

the results have probably been affected by the social desirability effect whereby the HSAs might have over-reported their enthusiasm and willingness to conduct the visits.

Conclusion

This study has explored the feasibility of delivering the PMC intervention by utilizing HSAs to remind caretakers in the delivery of PMC as a strategy of management of severe anaemia during the post discharge period. We found that HSAs in Malawi perceive PMC with dihydroartemesinin-piperaquine as an important intervention and that they are intrinsically motivated to conduct home visits to remind caregivers to administer the medication to their children. Nevertheless, adherence to the visits was poor.

Difficulties with the SMS reminders, not knowing the location of the child and/or long distances, and lack of information about the medicine currently limits motivation, gives practical challenges and reduces adherence. In the event of a national scale up of the intervention, the responsibility for delivering PMC should not be anchored with HSAs, but HSAs can provide an additional support to care takers as long as this is included in their job description, and the supervision system is strengthened. Provision of regular trainings, which provide a lunch allowance, may provide sustained motivation and provide the opportunity to enhance their knowledge. However, addressing most of these challenges will be difficult in the current health system. Unless additional resources are invested, utilizing HSAs to remind caregivers as a delivery strategy for PMC may not be feasible.

Additional files

Additional file 1: HSA interview guide; Interview guide for in-depth inter-views with health surveillance assistants in the post discharge malaria chemoprevention study. (DOCX 29.0 kb)

Additional file 2: HSA _FGD interview guide; Interview guide for focus group discussions with health surveillance assistants in the post discharge malaria chemoprevention study. (DOCX 28.0 kb)

Abbreviations

CHW: Community health worker; DHMT: District health management team; DHO: District health office; DP: Dihydroartemesinin-piperaquine; FGD: Focus Group discussions; HSA: Health surveillance assistant; IDI: In-depth-interviews; IPTc: Intermittent preventive therapy in children; IPTi: Intermittent preventive therapy in infants; IPTp: Intermittent preventive therapy in pregnancy; IPTpd: Intermittent preventive therapy post-discharge; PMC: Post-discharge malaria chemoprevention; SMC: Seasonal malaria chemoprevention; SMS: Short message service; WHO: World Health organization; ZCH: Zomba Central hospital

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Availability of data and materials

The data used and analyzed during the current study are currently not available to the public, but may be obtained from the corresponding author on reasonable request.

Authors' contributions

TG and SL designed the qualitative study. TG conducted the study and supervised the data collection. TG analysed the data and wrote the first draft of the manuscript with supervision from SL. All authors contributed to the interpretation of the study findings. All authors reviewed the manuscript and read and approved the final manuscript.

Ethics approval and consent to participate

Prior to collection of data ethical clearance for the qualitative research was obtained from the regional committee for medical and health research ethics in Western Norway (REC 2015/537) and from the University of Malawi, College of Medicine Research Ethics Committee (COMREC no.P.2/15/1679). Written and verbal informed consent was obtained in the local language from all the HSAs.

Consent for publication

Consent for publication of study findings was obtained from all the HSAs involved.

Competing interests

The authors declare that they have no competing interests.

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16 Appendices

1. Protocol paper
2. Data collection forms for SAM study
3. Data collection forms for PMC trial
4. Interview guides for IDIs and FGDs
5. Ethical clearance

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STUDY PROTOCOL Open Access

Delivery strategies for malaria chemoprevention with monthly dihydroartemisinin-piperaquine for the post-discharge management of severe anaemia in children aged less than 5 years old in Malawi: a protocol for a cluster randomized trial

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Abstract

Background: Children initially hospitalized with severe anaemia in Africa are at high risk of readmission or death within 6 months after discharge. No intervention strategy specifically protects children during the post-discharge period. Recent evidence from Malawi shows that 3 months of post-discharge malaria chemoprevention (PMC) with monthly treatment with artemether-lumefantrine in children with severe malarial anaemia prevented 31% of deaths and readmissions. While a confirmatory multi-centre trial for PMC with dihydroartemisinin-piperaquine is on going in Kenya and Uganda, there is a need to design and evaluate an effective delivery strategy for this promising intervention.

Methods: This is a cluster-randomized trial with 5 arms, each representing a unique PMC delivery strategy. Convalescent children aged less than 5 years and weighing more than 5 kg admitted with severe anaemia and clinically stable are included. All eligible children will receive dihydroartemisinin-piperaquine at 2, 6 and 10 weeks after discharge either: 1) in the community without an SMS reminder; 2) in the community with an SMS reminder; 3) in the community with a community health worker reminder; 4) at the hospital with an SMS reminder; or 5) at the hospital without an SMS reminder. For community-based strategies (1, 2 and 3), mothers will be given all the PMC doses at the time of discharge while for hospital-based strategies (4 and 5) mothers will be required to visit the hospital each month. Each arm will consist of 25 clusters with an average of 3 children per cluster giving approximately 75 children and will be followed up for 15 weeks. The primary outcome measure is uptake of complete courses of PMC drugs.

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Discussion: The proposed study will help to identify the most effective, cost-effective, acceptable and feasible strategy for delivering malaria chemoprevention for post-discharge management of severe anaemia in under-five children in the Malawian context. This information is important for policy decision in the quest for new strategies for malaria control in children in similar contexts.

Trial registration: ClinicalTrials.gov: NCT02721420. Protocol registered on 29 March 2016.The study was not retrospectively registered but there was a delay between date of submission and the date it first became available on the registry.

Keywords: Children, Severe anaemia, Post-discharge malaria chemoprevention, Malaria, Dihydroartemisinin-piperaquine, Cluster randomised trial

Background

Severe anaemia is a reduction in haemoglobin (Hb) concentration below 5 g/dL or haematocrit below 15%. Globally, 43% of children have anaemia and in Africa 3.6% have severe anaemia [1]. Severe anaemia is a leading cause of hospital admissions contributing substantially to paediatric mortality in Africa. Hospitalized children with severe anaemia are particularly at risk within the first 3 months post-discharge, mostly due to a combination of environmental, behavioural, nutritional and genetic risk factors [2–6]. A case-control study in Malawian children indicated that children aged less than 5 years admitted with severe anaemia were not only at high risk of dying during the acute phase in-hospital but also for several months after discharge from the hospital. 17.2% of children with severe anaemia experienced an all cause mortality compared to 2% of controls without severe anaemia [7].

By 18 months post discharge, 10.2% of children with severe anaemia were re-admitted with rebound severe anaemia and 12.6% had died, which is nine times higher than the mortality in community-based, age matched children with mild anaemia. High rates of post-discharge morbidity and mortality have also been reported in western Kenya and Uganda, where 36.5% of children aged less than 5 years admitted with severe anaemia died after 18 months of follow up [3, 7].

Previous observational studies in western Kenya and a recent intervention study in a high transmission areas in Malawi showed that malaria in the post-discharge period is an important contributor responsible for a slow haematological recovery, rebound severe anaemia and morbidity [3, 5, 7]. Many children in these areas experience episodes of new or recrudescent malaria infections after discharge, which negates the initial rise in haemoglobin (Hb) achieved by blood transfusion in hospital [3, 8]. Haematological recovery from malaria-associated anaemia is known to take at least 6 weeks. This period may be prolonged in those with persistent or new malaria infections due to on-going red cell destruction and red blood cell production failure [9].

Standard treatment guidelines for severe anaemia in many countries in sub-Saharan Africa consists of a blood transfusion combined with presumptive intravenous anti-malarial treatment (quinine or artesunate) plus antibiotics if bacterial infections are suspected. Once children have stabilized and can be switched to oral treatment, they receive a 3-day treatment course with artemisinin-based combination therapy (ACT), usually artemether-lumefantrine (AL). Children are often discharged with a short course of iron and folate, typically with no scheduled follow-up [8]. Creating a prophylactic time-window post-transfusion, is suggested to allow time for the bone marrow to recover, resulting in a more sustained haematological recovery post-discharge. Data from a previous study in Malawi show that this process takes 2–3 months in children with severe anaemia [3, 7]. Recently, the use of Intermittent Preventive Treatment (IPT) in children with severe anaemia during the rainy season reduced clinical attacks of malaria by more than 80% in areas with highly seasonal transmission [10]. PMC is a version of IPT designed to clear existing infections and provide prolonged prophylaxis against new infections.

A study in Malawi showed that provision of 3 months of chemoprevention with 3 full treatment courses of artemether-lumefantrine (AL), given in-hospital for initial malaria episode and at 1 and 2 months post-discharge, prevented 41% of deaths or readmissions due to severe anaemia or severe malaria during a 6 months follow-up period [2, 7, 11, 12]. These results are consistent with studies of children with severe anaemia in Gambia, who received chemoprevention given as monthly intermittent preventive therapy with SP or as weekly prophylaxis with pyrimethamine-dapsone targeted during the malaria transmission season [12]. For these children, the rate of clinical malaria was halved and all-cause hospital readmission was reduced by 78% in one trial, and recurrence of severe anaemia was reduced by 78% in the other [12–14]. These data indicate that IPT in the post-discharge period may potentially provide substantial health benefits [13].

Rationale

In the past two decades, most research on severe anaemia and severe malaria have focused on reducing in-hospital mortality. A major and potentially preventable component of the disease burden occurs after discharge from hospital and a proactive approach using PMC could offer substantial public health gains [11], and is a priority area for research. There is, however, no specific delivery strategy that has been scaled up to address this high-risk post-discharge period. Despite being a relatively simple intervention, the implementation of PMC in African settings may face challenges due to weak healthcare systems that are unique in different contexts. PMC requires appropriately designed delivery strategies because treatment must be administered for 3 days at different pre-specified intervals post-discharge.

Delivery of PMC to the target population will require new systems to be established that are sustainable and cost-effective. In contrast to IPT strategies in infants (IPTi) and pregnant women (IPTp), which are delivered through the expanded programme on immunization (EPI) and antenatal clinics, the delivery strategies for PMC are not yet in place. Some evidence shows that delivery of IPT to children (IPTc) through community health workers is feasible and well accepted in rural West Africa [12]. In Malawi, the health system also include village health volunteers (VHVs) and Health Surveillance Assistants (HSAs) who could deliver PMC or schedule post-discharge visits to clinics or hospital outpatient departments for subsequent PMC doses [14]. Since PMC targets a very high-risk group of hospitalized children who already have contact with the health-care system, the point of entry is already established [2, 12]. This trial is part of a larger project under the PMC consortium with 5 main activities in Malawi, Kenya and Uganda that aim to address the gaps in knowledge on whether PMC should be recommended as a strategy for the post-discharge management of children with severe anaemia to the WHO. The PMC trial in Malawi specifically aims to identify the most effective, acceptable and cost-effective strategy for delivering PMC and if use of short message service has additional benefits.

Study aims and objectives

The primary objective of the trial is to determine the optimum PMC delivery strategy by comparing community-based versus health facility-based strategies in order to inform policy decision. Specifically we aim to compare PMC uptake (adherence) levels and safety between community-based versus health facility-based strategies. To determine and compare health system and family/household costs of delivering and receiving PMC using the alternative proposed strategies. To assess the feasibility and acceptability of delivering and receiving PMC in a typical Malawi health system setting. To determine whether SMS or Health Surveillance Assistant (HSA) reminder has additional benefit on PMC uptake (adherence) levels. To estimate the incremental cost-effectiveness and equity impact of the alternative delivery strategies.

Methods

Study design

This is a single-centre open label cluster randomized clinical trial with 5-arms. A cluster represents a village, which is the smallest administrative unit and overseen by a village headman. A total of 1387 villages in the catchment areas of Zomba Central hospital in southern Malawi will be involved in this study.

Trial drug

The study drug used in this trial is Eurartesim® manufactured by Sigma-Tau pharmaceuticals. This is a GMP certified co-formulated artemisin-based antimalarial combination, which contains 20 mg Dihydro-Artemesinin and 160 mg Piperaquine. It is administered according to body weight 2 (PMC-1), 6 (PMC-2) and 10 weeks (PMC-3) after discharge from hospital, each course for three consecutive days.

Study participants

Children aged 4 to 59 months admitted to Zomba central hospital with a diagnosis of severe anaemia either by haemoglobin of < 5 g/dl or clinically assessed as severely anaemic but clinically stable and have received all treatments according to the hospital standard of care are screened for inclusion in the trial at the time of discharge from hospital. Caretakers of children who meet the eligibility criteria are given general information about the trial and those who are interested are required to give written consent for the child to participate into the study.

Interventions

All children receive DHP and hence there are no placebo arms in this trial. However, children are randomized to receive PMC as follows:

Community-based arms

Arm 1

PMC drugs given at discharge without SMS reminder: The guardian receives all drugs for PMC-1, PMC-2 and PMC-3. They are instructed on how and when to give these drugs to the children when being discharged from hospital. The dates for each course are documented in the child's health book.

Arm 2

PMC drugs given at discharge with SMS reminders: The guardian receives all drugs for PMC-1, PMC-2 and

PMC-3 and is instructed on how and when to give these drugs. Additionally they are reminded via SMS to give the drugs to the child one day before each treatment course is due.

Arm 3

PMC drugs at discharge with Health Surveillance Assistant (HSA) reminders: The guardian receives all drugs for PMC-1, PMC-2 and PMC-3 and is instructed on how and when to give these drugs. Additionally, HSAs which are part of existing networks of community-based volunteers taking part in village health committees are reminded via SMS to go and remind the guardian to give the drugs to the child one day before each treatment course is due.

Hospital/facility based arms

Arm 4

PMC drugs collected from the hospital: At discharge, the guardian is instructed to return to the outpatient department (OPD) of the hospital each month to collect drugs for PMC-1, PMC-2 and PMC-3. They do not receive any form of reminder other than what has been documented in the child's health card.

Arm 5

PMC drugs at hospital with SMS reminders: At discharge, the guardian is requested to return to the OPD to collect drugs for PMC-1, PMC-2 and PMC-3. Additionally they will be reminded via SMS to come to the clinic to collect drugs one day before each treatment course is due.

Recruitment and follow up

Figure 1 shows the study flowchart from the standard protocol items: recommendations for interventional trials (SPIRIT). Every morning, the study staff at Zomba Central Hospital goes through all newly admitted children's files in order to identify and pre-screen children who meet the study criteria. During this acute phase of

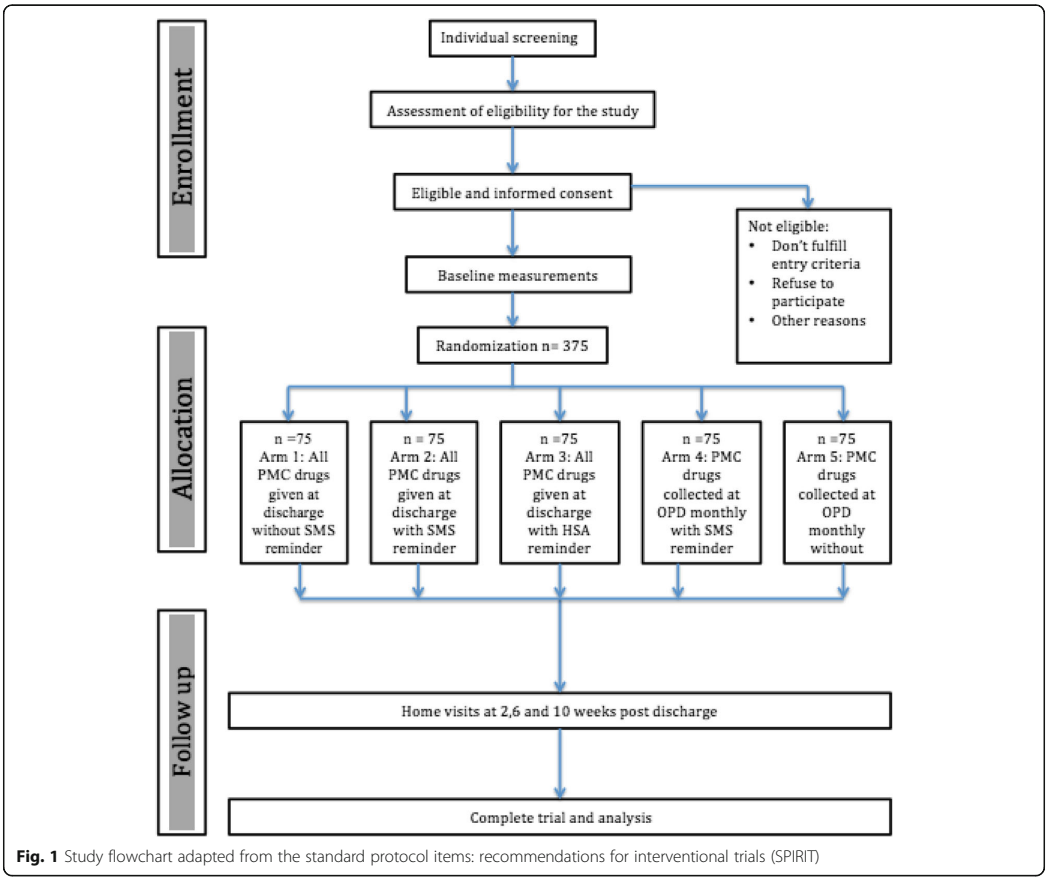

Fig. 1 Study flowchart adapted from the standard protocol items: recommendations for interventional trials (SPIRIT)

illness, pre-study screening involves confirming the study criteria and provision of routine standard of care treatment. No study specific information or samples are collected in this point of time. The role of the study team during pre-study screening is to review the diagnosis and ensure that the potential study participants get the standard quality of care for severe malarial anaemia.

Each pre-screened subject is assigned a pre-screening number in sequential order regardless of whether they fulfil the pre-screening eligibility criteria. After the child has recovered sufficiently, the caretaker is approached for further screening for eligibility. Caretakers of children who fulfil the eligibility criteria and who agree to participate in the research provide written informed consent before enrolling into the study. The study participant's demographic data, relevant clinical information, including the previous and current medical history, and laboratory information is collected simultaneously. Furthermore, a physical and clinical examination is performed and captured on the enrolment case report forms (CRFs).

Randomization and allocation methods

The unit of randomization is villages within the catchment area of Zomba central hospital. 400 out of the 1387 villages were randomly selected and randomized to one of the study arms, where each arm represents a different implementation alternative. When a child is enrolled and all study procedures have been done, the study data officer enters the name of the village where the child resides into a pre-programed database and this automatically generates the study arm and study identification number. The participants and the study staff are aware of the study arm assigned. However, the study statistician who will perform the final analyses will be blinded to the allocated treatment arm.

Follow up procedures

Table 1 summarises the recruitment and follow up procedures for the study. Depending on the trial arm to which the child is allocated, the caretaker is either scheduled to return to OPD clinic for PMC drugs at two, six and ten weeks (facility based strategies), or be given all the courses of drugs at discharge to administer them at home also at two, six and ten weeks (community based strategies). This information is documented in the child's health book. All participants, irrespective of arm, are visited at home shortly after the two, six and ten scheduled PMC treatments to assess DHP uptake. These home visits are for adherence assessment, vital registration and health economic assessments only, and not for clinical assessment. The PMC follow up period

Table 1 Recruitment and follow-up procedures

	Enrolment	Allocation	Follow up			
TIMEPOINT	*-t_{-} 2 wks.*	0	*t = 2 wks.*	*t = 6 wks.*	*t = 10 wks.*	*t = 15 wks./study end*
ENROLMENT						
Eligibility screen	X					
Informed consent	X					
Baseline measurements	X					
Allocation		X				
INTERVENTIONS:						
Arm 1: All PMC drugs given at discharge without monthly SMS reminder			X	X	X	
Arm2: all PMC drugs given at discharge with monthly SMS reminder			X	X	X	
Arm 3: All PMC drugs given at discharge with HAS reminder.			X	X	X	
Arm 4: PMC drugs collected monthly at the OPD with SMS reminder.			X	X	X	
Arm 5: PMC drugs collected monthly at the OPD without SMS reminder			X	X	X	
ASSESSMENTS:						
Physical examination	X					X
Blood samples	X					X
Adverse event assessment	X	X	X	X	X	X
OUTCOMES						
Adherence						X
Clinical safety			X	X	X	X
Cost-effectiveness						X
Acceptability and feasibility						X

ends at 15 weeks after enrolment, which is four weeks after the third scheduled PMC course. Participants are then requested to come to the clinic 15 weeks after enrolment for an end of study assessment. Transport is reimbursed for the study end visit. In addition, subject's parent or guardian are instructed to return his/her child to the study clinic for evaluation free of charge at any time if their condition warrants medical attention during the 15 weeks follow-up period after discharge.

Data collection and outcome measures

Adherence outcome measures

The primary outcome is the level of uptake of PMC drugs which will be assessed by unannounced home visits after each course whereby pill counts will be done. Hundred percent uptake of PMC drugs will be defined as administration of all 3-day treatment courses (i.e. 9 doses), given at 2, 6 and 10 weeks after discharge from hospital. Sixty percent of PMC drugs are defined as administration of 6 or more (but less than 9) of the daily dosages out of the total of 9.30% of PMC drugs will be defined as administration of 3 or more (but less than 6) of the daily dosages out of the total of 9. Less than 30% of PMC drugs is defined as administration of less than 3 of the daily dosages out of the total of 9, given 2, 6 and 10 weeks after discharge.

Clinical outcomes

Study instruments include structured forms for clinical history, physical assessment, laboratory evaluations and clinical information collected on history of current and previous illnesses and hospital admissions is collected in addition to hospitalizations and mortality. For children who are hospitalized during the follow-up period, data is collected on the length of hospitalization, diagnosis, treatments provided, laboratory results, and participant outcomes. Physical examination and laboratory tests include: height, weight, mid-upper arm circumference, malaria rapid test results, blood slide results, parasitaemia level, and haemoglobin concentration. This will be used to assess all-cause mortality, incidence rate of all-cause hospital readmissions, incidence rate of readmissions due to severe anaemia (Hb < 5 g/dL) or severe malaria defined by the administration of parenteral Artesunate or Quinine, incidence rate of non-severe all-cause sick-child clinic visits, specifically incidence rate of clinic visit due to RDT/microscopy confirmed non-severe malaria during the study period.

Cost and economic evaluation outcomes

Information about expenses, resource and time use with open-ended fields for unanticipated findings and place for comments will be collected. Demographic information on children is collected including age, sex, while religion, village of residence and socioeconomic features of their household is also recorded as well as cost information for the economic evaluation. This will assess health provider's cost of delivering the PMC services, caretakers' cost of receiving the PMC services, incremental cost-effectiveness ratio (ICER) of PMC delivery strategies and equity impact by socioeconomic status of PMC delivery strategies on main and secondary outcomes.

Acceptability and feasibility outcomes

In addition there will be interview guides for in-depth interviews and focus group discussions with a selection of caretakers and health workers who have been involved in the PMC trial. This information will be used to assess the acceptability of PMC, adaptations to health workers' working practices required to implement PMC, perceptions of implementing PMC through different delivery strategies, and recommendations on effective implementation.

Sample size

The sample size calculation has been adjusted for the design effect using the coefficient of variation method in order to account for the Intra-cluster Correlations (ICC) [15, 16]. We assumed that the cluster sizes would be uniformly distributed between 2 and 4 children [2, 4]. This gives a mean cluster size of 3 children per village per year and a standard deviation of cluster sizes of 0.58. Hence the coefficient of variation of cluster sizes (CV) is 0.58/3 = 0.19 and $CV^2 = 0.036$. Assuming an intra-cluster correlation coefficient (ICC) of 0.1 and allowing for 10% loss-to-follow-up, a sample size of 25 clusters (villages) of an average of 3 children per village (75 children per arm, $N = 375$ overall (for 125 clusters for the 5 arms)) has 80% power to detect a 25% absolute increase in uptake from an estimated 50% in the OPD and delivery at home groups to 75% in the arms supported by SMS reminders ($\alpha = 0.05$). The ICC of 0.1 is slightly more conservative than the ICC in a previous trial of delivery approaches for IPTc in the Gambia.

Data management and statistical analysis

Data is collected and recorded by one of the trained study staff at the point of contact. Data is entered directly into computer tablets that will be pre-programmed and uploaded with electronic case report forms (eCRFs). The eCRFs have crosschecks for verification, validation and comply with Good Clinical Practices (GCP). These gadgets are connected to a desktop allowing data to be directly uploaded into a database.

The percentage of children receiving PMC according to schedule in each arm will be obtained and compared between arms using relative risks (RR) and the 95% CI for the RR will be reported. The estimates of the RR will be adjusted for prognostic factors and potential confounding factors at baseline using log binomial or Poisson regression

with adjustment for cluster effects. Using Cox regression, hazard ratios will be calculated for morbidity endpoints such as incidence of severe anaemia, severe malaria and all cause hospital re-admissions, for repeated events with robust standard error estimation methods to account for correlation between episodes within children. Incidence rates per child-year and absolute rate reductions will also be calculated.

Discussion

This protocol describes a study in which we will determine the optimum PMC delivery mechanism in a Malawian context by comparing community versus health facility based strategies. Presently in African health systems and particularly in Malawi, post-discharge health management systems are not in place, and there is need to assess a number of relevant strategies for effective delivery of PMC in a largely rural community that would typically benefit from this intervention.

We postulate that this post-discharge care in the form of PMC may be delivered either in the community or at a health facility. The most likely scenario where the health care provider is least involved would be where mothers are given all the PMC drugs on discharge from hospital and allowed to administer the drugs on her own to the child (Arm 1). In recent years there has been successful disease control programs operationalizing more decentralized drug delivery programs in the community in low-income countries, making it a viable option for PMC. However as we postulate that the mother could forget to administer the PMC, we would like to test two different reminder systems. The first is through the use of SMS technology, which has been shown to be user-friendly and acceptable from our own pilot work (unpublished pilot study) and other current programs in Malawi (Arm 2 and 5).

An alternate reminder system is the use of Health Surveillance Assistants (HSA). HSA are Ministry of Health (MoH) employees who are responsible for basic health promotion activities in the community. Ideally MoH strives to have one HSA for every 1000 people, but in reality they often cater for much larger populations and are usually over-burdened with many disease control programs. In some areas in rural Malawi there are Village Health committees, which are made up of voluntary members of the community. They work hand in hand with the HSA. We postulate that HSAs and where available village health volunteers (VHVs) are an option for reminding mothers to give PMC to their child (Arm 3).

Another option for delivery of PMC is to request the mother or caretaker to return to the health care facility to collect the drugs for each treatment course (Arms 4 and 5). This is a plausible strategy as it is consistent with the management of chronic illness such as TB and HIV where drugs are routinely collected from a health facility by the patients. This would be an alternative strategy as part of EPI or management of other chronic illnesses e.g. chest follow up clinic.

Abbreviations

ACTs: Artemisin based combination therapies; AL: Artemether-Lumefantrine; CRF: Case Report Form; DHP: Dihydro-Artemesinin-Piperaquine; EC: Ethics Committee; EPI: Expanded programme for immunizations; GCP: Good Clinical Practice; Hb: Haemoglobin concentration; HSA: Health surveillance assistant; ICC: Intra-Cluster Correlation; IPT: Intermittent Preventive Therapy; PMC: Post discharge malaria chemoprevention; SMS: Short message service; SP: Sulfadoxine-Pyrimethamine; WHO: World Health Organization

Author contributions

The authors include all professionals/co-investigators that have participated in the trial for a minimum of one year and these include BR, KP, MM, SL, BB and TG. BR, KP, BB and TG contributed to the design of the trial and clinical methods. BR contributed the economic evaluation methods and analysis plan. MM contributed to the randomization procedures, statistical analysis plan and other areas of methodology. SL contributed the qualitative methods and analysis. TG coordinated the implementation of the trial. TG wrote the first draft of the manuscript and all authors have approved the final version.

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Ethics approval and consent to participate

The protocol and related documents (informed consent and participant information sheets) were submitted for review to the Institutional Review Boards (IRB) and Research Ethics Committees at the Malawi College of Medicine and the Regional Ethics Committee of Norway. The study was approved by the College Of Medicine research ethics committee (COMREC), approval number P.02/15/1679, and the Regional Ethics Committee of Norway, approval number 2015/537/REK vest. Written consent was obtained from legal guardians of the study participants prior to enrolment.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Publisher's Note

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Screening number. ☐☐☐☐

PMC Study **Enrolment Visit**

Form completed by ☐☐☐*(Staff ID)*

Client's Initials ☐☐☐*(initials)*

Date of Visit ☐☐/ ☐☐☐/ ☐☐☐☐*(dd/mmm/yyyy)*

No.	Questions	Categories	Skip pattern
	A. CHILD DEMOGRAPHIC CHARACTERISTICS		
1	Child's date of birth	☐☐/ ☐☐☐/ ☐☐☐☐ *(dd/mmm/yyyy)*	
2	How old is the child	☐☐*Months*	
3	What is the sex of the child	☐*1=Male, 2=Female*	
4	Number of siblings of the child in the household. (By "household", we mean all the people usually living together in this house and sharing meals, expenses and living arrangements.)	☐☐*Alive*☐☐*dead*	
5	Number of people in the household	Adults (>15 Years) Children (<=15 years)	
6	Are you the main care taker of the child? (caretaker should be one who lives with the child in the same household)	☐*1=Yes, 2=No*	If no go to section H Reminder to follow up.
	B. PREVIOUS MEDICAL HISTORY		
7	How many times has your child suffered from malaria in the past year?	☐☐*Times*	
8	Has your child been admitted to a hospital for malaria in the past year?	☐*1=Yes, 2=No, 3=Not Sure*	***If No, go to Q27***
9	If Yes, how many times has your child been admitted due to malaria before the current admission?	☐☐*times*	
10	Date for admission 1	☐☐/ ☐☐☐/ ☐☐☐☐ *(dd/mmm/yyyy)*	
11	Date for admission 2	☐☐/ ☐☐☐/ ☐☐☐☐ *(dd/mmm/yyyy)*	
12	Date for admission 3	☐☐/ ☐☐☐/ ☐☐☐☐ *(dd/mmm/yyyy)*	
13	Date for admission 4	☐☐/ ☐☐☐/ ☐☐☐☐ *(dd/mmm/yyyy)*	
14	Date for admission 5	☐☐/ ☐☐☐/ ☐☐☐☐ *(dd/mmm/yyyy)*	
15	Has your child been admitted to a hospital for any other illness in the last three months?	☐*1=Yes, 2=No, 3=Not Sure*	***If No, go to Section C***

Severe Anaemia Study *Recruitment Form*

First name _____ **Study Number** _____

Surname _____

Study group ☐ **1** = Severe anaemia case, **2** = Hospital controls, **3** = Community controls

Consent ☐ **1** = Full consent, **2** = No consent, **3** = Only for BM, **4** = Only for HIV test

HIV counsel ☐ **1** = Yes HIV results, **2** = No HIV results, **8** = Not applicable, **9** = Missing

Study Centre ☐ **1** = QECH, **2** = CDH

Recruitment date ☐☐/☐☐/☐☐

Discharge date ☐☐/☐☐/☐☐

DEMOGRAPHIC DATA

Date of birth ☐☐/☐☐/☐☐

Age _____ *months* (only if DOB is not known)

Sex ☐ **1** = Male, **2** = Female

Ethnic origin ☐ **1** = Chewa, **2** = Yao, **3** = Sena, **4** = Tumbuka, **5** = Lomwe, **6** = Ngoni
7 = Tonga, **8** = Other *Specify*_____ , **9** = Missing/Unknown

Religion ☐ **1** = Catholic, **2** = Prot-major, **3** = Prot-Adventist, **4** = Prot-Jehovah,
5 = Traditional, **6** = Muslim, 7 = others, **9** = Missing

Age mother ☐ **Estimated Age** (if unknown) ☐

Education **Mother** ☐ **1 =** Non / minimal (alliterate), **2 =** Primary
Father ☐ **3** = Secondary, **4** = Tertiary, **9** = Missing

Job **Mother** ☐ **1 =** Unemployed, **2** = Self employed, **3** = Wage employed
Father ☐ **4** = White collar job, **9 =** Missing

Health **Mother** ☐ **1** = healthy, **2** = died, **3** = sick, specify_____

Property no ☐ Record no of categories: Cattle, Land, Car/Motorbike, bicycle, TV, Radio/CD, **9**=missing

Number of siblings ALIVE ☐ **DIED** ☐ (*excluding patient* & *same mother and father*)

PREVIOUS MEDICAL HISTORY

Chronic illness ☐ **1** = No, **2** = Haematologic, **3** = Cardiac, **4** = Nephrotic, **5** = Developmental **6** = Multiple, **7** = Other *Specify* _____ , **9** =Missing

	Y / N	
Previous Admissions	☐	*If yes Specify* _____
Previous Transfusion	☐	If *yes Specify* _____
Previous Ant malarial	☐	*In last 2 months, if yes Specify* _____
Previous Antibiotics	☐	*In last 2 months, if yes Specify* _____
Previous Haematinics	☐	*In last 2 months, if yes Specify* _____
Previous Multivitamins	☐	*In last 2 months, if yes Specify* _____

Weight loss or Failure to Thrive ☐ 1 = yes; 2 = no; 3 = less than three points on curve

CURRENT MEDICAL STATUS

Presenting problem 1 ☐ code and *Specify* _____

Presenting problem 2 ☐ code and *Specify* _____

Fever _____ *days*

Cough _____ *days*

Vomit _____ *days*

Diarrhoea _____ *days*

Last fluid intake _____ *hrs*

Diet details:

	Y / N			
Bloody stool	☐	**Meals with meat per <u>month</u>**	☐	Concerning last month
Bloody urine	☐	**Meals with fish per <u>month</u>**	☐	More meals/day is possible
Jaundice history	☐	**Poor appetite in last month**	☐	**1** = Yes **2** = No
Respiratory distress	☐	**Breastfeeding**	☐	**1** = Yes only BF, **2** = No
Fitting	☐			**3** = Yes & additional feeds
Coma	☐			

History details:

CLINICAL EXAMINATION

Weight _____ *kg* **Pulse rate** _____ *bpm*

Length _____ *cm* **Blood pressure** _____ */ mmhg*

Temperature _____ *^{o}C* (if axillary add 0.5) **O2 saturation** _____ *%*

Respiratory rate _____ */ min*

Respiratory rhythm ☐ **1** = Regular, **2** = Irregular, **9** = Missing

Respiratory amplitude ☐ **1** = Normal, **2** = Irregular, **3** = Deep, **9** = Missing

	Y / N		Y / N
Grunting	☐	**Cold periphery**	☐
Nasal flaring	☐	**Fitting on admission**	☐
Chest recessions	☐	**Neck stiffness**	☐
Anaemia	☐	**Skin changes**	☐
Jaundice	☐	**ENT/mouth abnormalities**	☐
Oedema	☐	**Chest signs**	☐
Xeropthalmia	☐	**Bleeding**	☐
Skeletal deformities	☐	**Koilonychia**	☐
Angular stomatitis	☐	**Glossitis**	☐

NB if any of these is confirmed please describe Abnormalities in <u>Clinical Examination</u>

General feeding condition ☐ **1** = good, **2** = fair, **3** = poor (describe in Clinical Examination)

Lymphadenopathy ☐ **1** = absent, **2** = regional, **3** = general

Pallor: **Conjunctiva** ☐ **1** = absent, **2** = mild/moderate, **3** = severe **NB Asses before Hb!**

Palmar ☐ **1** = absent, **2** = mild/moderate, **3** = severe **NB Asses before Hb!**

Dehydration ☐ **1** = Mild, **2** = Moderate, **3** = Severe, **4** = No, **9** = Missing

Coma score ☐ **(0-5)**

Spleen _____ *cm* **Hb** _____ *g/dl*

Liver _____ *cm* **Malaria slide** _____ parasites/200 WBCs

Presenting diagnose 1 ☐ code and *Specify* _____

Presenting diagnose 2 ☐ code and *Specify* _____

Clinical examination details:

Severe Anaemia Study *Active Follow- Up Visit*

Initials _____ **Study Number** _____

FU visit ☐ **1** Month, **3** = 3 Months, **6** = 6 Months, **12** =12 Months, **18** =18 Months

Date of visit ☐

Iron prophylaxis taken ☐ **1** = Yes, **2** = No, **7** = Partial, **8** = Not applicable

History of Severe illness ☐ **1 =** Yes, **2** = No

History of hospital admission ☐ **1 =** Yes, **2** = No

Presenting problem ☐ code and *Specify* _____

Temperature _____ ^{o}c (if axillary add 0.5)

Length _____ cm

Weight _____ Kg

Spleen _____ cm

Hb _____

Malaria slide _____ parasites/200 WBCs

Presenting diagnose ☐ code and *Specify* _____

Action taken ☐ **1** = Admission, **2** = Rx + extra FU, **3** = Rx +no FU, **4** = No action

Details

Severe Anaemia Study *Passive Follow- Up Visit*

Initials _____ **Study Number** _____

Date of visit [ ]

Presenting problem 1 [ ] code and *Specify* _____

Presenting problem 2 [ ] code and *Specify* _____

History details [ ]

Temperature _____ *°c* (if axillary add 0.5 *°c*)

Weight _____ *Kg*

Spleen _____ *cm*

Details on examination [ ]

Hb _____ g/dl

Malaria slide _____ parasites/200 WBCs

Presenting diagnose 1 [ ] code and *Specify* _____

Presenting diagnose 2 [ ] code and *Specify* _____

Action taken [ ] **1** = Admission, **2** = Rx + extra FU, **3** = Rx +no FU, **4** = No action, **9** = Missing

Severe Anaemia Study *Location*

First name _____ **Study Number** _____

Surname _____

Father name _____

Mother name _____

Village _____

Compound head _____

GPS Position _____

Route description

Transport money _____ (one way)

Screening number. ☐☐☐☐

16	If yes, how many times has your child been admitted for any other illness in the last three months?	☐☐*Times*	
17	Date of Admission 1	☐☐/ ☐☐☐/ ☐☐☐☐ *(dd/mmm/yyyy)*	***Check in the health passport or hospital records***
18	What was the reason for admission 1? (Tick all that apply)	☐*Malaria,* ☐*Anaemia,* ☐*Pneumonia,* ☐*Diarrhoea,* ☐*Sepsis,* ☐*Injury,* ☐*Other specify*_____	
19	Date of Admission 2	☐☐/ ☐☐☐/ ☐☐☐☐ *(dd/mmm/yyyy)*	
20	What was the reason for admission 2? (Tick all that apply)	☐*Malaria,* ☐*Anaemia,* ☐*Pneumonia,* ☐*Diarrhoea,* ☐*Sepsis,* ☐*Injury,* ☐*Other specify*_____	
21	Date of Admission 3	☐☐/ ☐☐☐/ ☐☐☐☐ *(dd/mmm/yyyy)*	
22	What was the reason for admission 3? (Tick all that apply)	☐*Malaria,* ☐*Anaemia,* ☐*Pneumonia,* ☐*Diarrhoea,* ☐*Sepsis,* ☐*Injury,* ☐*Other specify*_____	
23	Date of Admission 4	☐☐/ ☐☐☐/ ☐☐☐☐ *(dd/mmm/yyyy)*	
24	What was the reason for admission 3? (Tick all that apply)	☐*Malaria,* ☐*Anaemia,* ☐*Pneumonia,* ☐*Diarrhoea,* ☐*Sepsis,* ☐*Injury,* ☐*Other specify*_____	
25	Date of Admission 5	☐☐/ ☐☐☐/ ☐☐☐☐ *(dd/mmm/yyyy)*	
26	What was the reason for admission 3? (Tick all that apply)	☐*Malaria,* ☐*Anaemia,* ☐*Pneumonia,*	

Screening number. ☐☐☐☐

		☐*Diarrhoea,* ☐*Sepsis,* ☐*Injury,* ☐*Other specify*_____	
27	Did your child have a blood transfusion in the past four weeks?	☐*1=Yes, 2=No, 3=Not Sure*	***If No, go to Section C***
28	If yes, what was the reason for blood transfusion	☐*1=severe anaemia,* *2=blood loss due to injury,* *3=leukemia,* *4=sickle cell disease,* *5=other* specify_____	
C. MALARIA CONTROL MEASURES			
29	Do you have mosquito nets in your household?	☐*1=Yes, 2=No*	***If No, go to section D***
30	How many sleeping spaces are in your household?	☐☐	
31	How many sleeping spaces in your household are covered by ITN?	☐☐	
32	Did the child sleep under an ITN the night before admission?	☐*1=Yes, 2=No, 3=Not Sure*	***If yes, go to Q34***
33	If no, what was the reason? (Tick all that apply)	☐*Forgot,* ☐*Travelled away,* ☐*Child allergic to the net,* ☐*Net was being used by others,* ☐*Others, specify*_____	
34	At any time in the past 12 months, has your house been intermittently residual sprayed against mosquitoes?	☐*1=Yes, 2=No, 3=Not Sure*	***If no, go to Section D***
35	If yes, when was your house sprayed?	☐☐☐/ ☐☐☐☐*(mmm/yyyy)*	
D. TREATMENT ADHERENCE			
36	Has your child been prescribed treatment to take at home before?	☐*1=Yes, 2=No, 3=Not Sure*	***If No, go to section E***
37	If Yes, what measures did you put in place to make sure your child took all the prescribed doses? (Tick all that apply)	☐*Schedule drugs at meal times,* ☐*Schedule drugs at bathing time,* ☐*Put written reminders on the wall,* ☐*Share information with family members to remind you,* ☐*Others, specify*_____	
38	Did your child vomit any of the	☐*1=Yes, 2=No, 3=Not Sure*	If no ,go to

	drugs that you gave him/her at home?		40.
39	If yes, what did you do if your child vomited immediately after taking drugs?(Tick all that apply)	☐ *Administered another dose,* ☐*Did not do anything,* ☐*Reported to the HSA,* ☐*Others, specify*_____	
40	What measures do you put in place to make sure your child does not vomit medications?(Tick all that apply)	☐*Give drugs with sweetened water/drink,* ☐*Give drugs with meals,* ☐*Breastfeed immediately after giving drug,* ☐*Do nothing,* ☐ *Others, specify*_____	
E. CURRENT MEDICAL HISTORY			
41	Which of the following symptoms was your child experiencing on admission?(Tick all that apply)	☐*Fever, (**duration in days)*** ☐*Cough, (**duration in days)*** ☐*Vomiting, (**duration in days)*** ☐*Diarrhoea, (**duration in days)*** ☐*Other specify _____, (**duration in days)***	
42	What is the diagnosis for this admission? (Tick all that apply)	☐*1=malaria,* *2=anaemia,* *3=Pneumonia,* *4=Other specify*_____	
F. GUARDIAN DEMOGRAPHIC CHARACTERISTICS			
43	How old are you?	☐☐*years*	
44	Is this estimated or your actual age?	☐*1= Actual, 2=Estimated*	
45	Sex	☐*1=Male, 2=Female*	
46	Current marital Status	☐*1=Single,* *2=Married,* *3=Widowed,* *4=Divorced/Separated,* *5=Others, specify*_____	
47	What religion do you practice?	☐*1=Catholic,* *2=CCAP,* *3=Anglican,* *4=Seventh Day Adventist,* *5=Muslim,* *6 =No religion,* *7=Other religion,* *specify*_____	
48	What is your tribe or ethnic background?	☐*1=Chewa,* *2=Yao,*	

Screening number. ☐☐☐☐

		3=Sena, *4=Lomwe,* *5=Tumbuka,* *6=Ngonde,* *7=Tonga,* *8= Ngoni* *9=Others, specify_____*	
49	What is your relation with the child?	☐*1= Son/daughter* *2=niece/nephew* *3=grandson/granddaughter* *4=brother/sister* *5=other, specify_____*	
50	Highest level of education completed by you?	☐*1=None,* *2=Lower primary school (1-4),* *3=Upper primary school (5-8),* *4=Lower secondary school(Form 1-2)* *5=Upper secondary school (Form 3-6)* *6=Tertiary level,* *7=Other, specify_____*	
51	What is main source of income of your household?	☐*1= Subsistence farming* *2=Government work* *3=Business* *4=Large scale farming,* *5=Private formal work* *6=Casual work for wages,* *7=None,* *8=Other; specify_____*	
52	Are you able to read?	☐*1=yes, 2=no, 3=not sure*	
53	Are you able to write?	☐*1=yes, 2=no, 3=not sure*	
54	Who makes important decisions in your home?	☐*1=Me* *2=Someone else*	If me, go to Q62.
55	How is the decision maker related to the child?	*1 = Sister/ Brother* *2 = Mother/ Father* *3 = Mother in law / Father in law* *4= Grandmother / grandfather* *5 = Aunt / uncle* *6 = Cousin* *17 = Does not wish to disclos* *8 = Other_____*	
56	What religion does the decision maker practice?	☐*1=Catholic,* *2=CCAP,* *3=Anglican,* *4=Seventh Day Adventist,* *5=Muslim,*	

Screening number. | | | | |

		6 =No religion, *7=Other, specify_____*	
57	What is the tribe or ethnic background of the decisionmaker?	☐*1=Chewa,* *2=Yao,* *3=Sena,* *4=Lomwe,* *5=Tumbuka,* *6=Ngonde,* *7=Tonga,* *8= Ngoni* *9=Others, specify_____*	
58	Highest level of education completed by the decision maker?	☐*1=None,* *2=Lower primary school (1-4),* *3=Upper primary school (5-8),* *4=Lower secondary school(Form 1-2)* *5=Upper secondary school(Form 3-6)* *6=Tertiary level,* *7=Other, specify_____*	
59	What is the main source of income of the decision maker?	☐*1= Subsistence farmer* *2=Government worker* *3=Business* *4=Large scale farmer,* *5=Private formal worker,* *6=At school/university,* *7=Casual worker for wages,* *8=None,* *9=Other; specify_____*	
60	Is the decisionmaker able to read?	☐*1=yes, 2=no, 3=not sure*	
61	Is the decisionmaker able to write?	☐*1=yes, 2=no, 3=not sure*	
62	Who is the main breadwinner?	☐*1 = Me* *2 = Decision Maker* *3 = Someone else*	If 1 or 2, go to Q65.
63	What is the main source of income of the main breadwinner?	☐*1= Subsistence farmer* *2=Government worker* *3=Business* *4=Large scale farmer,* *5=Private formal worker,* *6=At school/university,* *7=Casual worker for wages,* *8=None,* *9=Other; specify_____*	
64			
G. Household assets			
65	What is your main source of	☐*1=Piped in dwelling*	

	drinking water?	*2=Communal stand piped* *3= Hand pump/ borehole* *4=Tanker service* *5=Private well* *6=Public well* *7=Spring* *8=River/stream* *9=Pond/dam/lake* *10=Rainwater* *11= Bottled water* *12= Other, specify* ……	
66	Where is that water source located?	☐*1=In own dwelling,* *2= In own yard/plot,* *3=Elsewhere*	
67	How long does it take to go there, to get water and come back?	☐☐.☐hours/*minutes*	
68	Who usually fetches water?	☐*1=Female >15 years,* *2=male >15 years* *3=Female <=15 years* *4=male <=15 years*	
69	Do you do anything to the water to make it safer to drink?	☐*1=yes, 2=no, 3=don't know*	*If No, go to Q71.*
70	If yes, what do you do to make the water safer to drink?	☐*1=Boil,* *2=Add Bleach /Chlorine/Alloy* *3=Strain through a cloth,* *4= Use water filter,* *5= Solar disinfection,* *6= Let it stand and settle,* *7=Other_____*	
71	What type of toilet do members of household usually use?	☐*1=Flush toilet* *2=Pit latrine* *3=Dug-out pit with roof* *4=Dug-out pit without roof* *5=None* *6=Does not wish to disclose* *7=No facility, bush, outdoor* *8= Other, specify_____*	
72	Do you share this toilet with other households?	☐*1=yes, 2=No*	***If no, go to Q74***
73	How many households use this	☐☐☐*households*	

	toilet facility, including your own?		
74	Please indicate if your household owns any of the following (tick those that apply):	☐ *Electricity* ☐ *Clock/ watch* ☐ *Radio* ☐ *Black and white TV* ☐ *Colour TV* ☐ *Mobile phone* ☐ *Non-mobile Phone* ☐ *Refrigerator* ☐ *Freezer* ☐ *Generator/Inverter* ☐ *Washing machine* ☐ *Computer* ☐ *Digital camera* ☐ *Non-digital camera* ☐ *Video deck* ☐ *VCR/ DVD* ☐ *Torch* ☐ *Sewing machine* ☐ *Bed* ☐ *Table* ☐ *Cabinet/cupboard* ☐ *Fan* ☐ *Battery operated Cassette player* ☐ *Plow* ☐ *Grain grinder* ☐ *Hammer mill* ☐ *Candles* ☐ *Kerosine lamps* ☐ *Solar panel*	
75	What type of fuel does your household mainly use for cooking?	☐ *1=Electricity,* *2=LPG/ natural gas,* *3=Biogas,* *4=Kerosene,* *5=Coal, lignite* *6=Charcoal,* *7= Wood/firewood,* *8=Straws/Shrubs/grass,* *9=Agricultural crop residue,* *10=Animal Dung,* *11=No food cooked in household*	

Screening number. ☐☐☐☐

		12=Other, specify_____	
76	Where is the cooking usually done?	☐*1=Inside the house,* *2=In separate building,* *3=Outdoors,* *4=Other,specify_____*	
77	Do you have a separate room that is used as a kitchen?	☐*1=yes, 2=No*	
78	What is the main material the roof in your house is made of?	☐*1=Grass,* *2= Iron sheets* *3= Clay* *4= Tiles* *5= Concrete* *6= Plastic Sheeting* *7= Does not wish to disclose* *8= Does not know* *9= Other, specify_____*	
79	What is the main material the main walls of yours house are made of?	☐☐*1=Grass* *2=Mud (Yomata)* *3=Compacted Earth (Yamdindo)* *4=Mud bricks (unfired)* *5=Burnt bricks* *6=Concrete* *7=Wood* *8=Iron sheets* *9=Does not wish to disclose* *10=Does not know* *11=Other,* *specify_____*	
80	What is the main material the floor in your house is made of?	☐*1=Earth/sand,* *2=Smoother Mud* *3=Smooth cement* *4=Wood* *5=Tile* *6=Does not wish to disclose* *7=Does not know* *8=Other, specify_____*	
81	How many rooms are there in your house?	☐☐*number of rooms*	
82	How many rooms in your house are used for sleeping?	☐☐*number of rooms*	

Screening number. ☐☐☐☐

83	Does any member of this household own (tick those that apply):	☐*Bicycle* ☐*Motorcycle/scooter* ☐*Animal drawn cart* ☐*Car or Truck* ☐*Boat with motor* ☐*Tractor* ☐*Boat*	
84	The structure you live in (house, flat, shack), does your household:	☐*1= Own the structure* *2=Pay rent/Lease* *3=No rent, with consent of owner* *4=No rent, without consent, squatting* *5=Other, specify*	
85	The land your structure (house, flat, shack) sits on, does your household?	☐*1=Own the structure,* *2=Pay rent/ Lease* *3=No rent, with consent of owner* *4=No rent, without consent, squatting* *5=Other, specify* _____	
86	Does any member of this household own any agricultural land?	☐*1=yes, 2=no*	If no, go to Q89
87	Do you know the size of the land?	☐*1=yes, 2=no*	If no, go to Q89
88	How many Acres of land (altogether) are owned by the members of the household?	☐.☐☐*Acres*	
89	Does this household own any livestock, herds, other farm animals, or poultry?	☐*1=yes, 2=no*	If no, go to Q91
90	How many of the following animals does this household own?	☐☐*Milk cow/ bull* ☐☐*Sheep* ☐☐*Horse/donkey/mule* ☐☐*Chicken* ☐☐*Goats* ☐☐ *Pigs* ☐☐ *Others*	
91	Does any member of this household have a bank account?	☐*1=yes, 2=No, 3= Don't Know*	
92	What is your contact number?		
93	What is your alternative contact number		
H. CLINICAL EXAMINATION			
94	Anthropometric Measurements	**Weight** ☐☐.☐*kg* **Height** ☐☐.☐*cm*	
95	Vital Signs	**Pulse rate** ☐☐☐*beats/min*	

Screening number. ☐☐☐☐

		Temperature ☐☐.☐*ºC* **Respiratory rate** ☐☐☐*/min*	
96	Other Signs (Tick all that apply)	☐*Chest signs,* ☐*Chest recessions,* ☐*Oedema,* ☐*Loss of appetite,* ☐*Lymphadenopathy,* ☐*Dehydrated* ☐*Jaundice* ☐*Bleeding tendencies* ☐*Other* *specify*_____	
97	**Lab Investigations**	Hb Level: ☐☐.☐*g/dl* *DBS* *MRDT: Positive*☐*1=Yes, 2=No*	

Randomisation

Is the client eligible for randomisation? ☐*1=Yes, 2=No*
If no, what was the reason for not being eligible? _____

Village _____

TA

1. Mwambo
2. Chikowi
3. Malemia
4. Mlumbe
5. Kuntumanji
6. Sub T/A Ntholowa
7. Sub T/A Nkagula
8. Sub T/A Ngwelero
9. Sub T/A Mbiza
10. Sub T/A Nkapita

Study ARM 1. **Arm 1** 2. **Arm 2** 3. **Arm 3** 4. **Arm 4** 5. **Arm 5**

Client Identification Number (ARM 1) ☐☐☐
Client Identification Number (ARM 2) ☐☐☐
Client Identification Number (ARM 3) ☐☐☐
Client Identification Number (ARM 4) ☐☐☐
Client Identification Number (ARM 5) ☐☐☐

Client Identification Number ☐☐☐☐☐☐

PMC study **Drug Collection Form**

Form completed by ☐☐☐*(Staff ID)*
Client's Initials ☐☐☐*(initials)*
Visit Number ☐*1=First, 2=Second, 3=Third*
Study Arm ☐*1=Arm 1, 2= Arm 2, 3= Arm 3, 4=Arm 4, 5=Arm 5*
Date of visit ☐☐ / ☐☐☐ / ☐☐☐☐*(dd/mmm/yyyy)*

General information to trial staff:

If the mother/guardian combines the trip to the health facility with a sick visit, the *Sick Visit Form* should also be filled out.

No.	Questions	Categories	Skip pattern
	A. DRUG COLLECTION INFORMATION		
1	Is the child alive?	☐*1=Yes, 2=No*	If No, complete the verbal autopsy, STOP, end of form
2	Has mother/guardian collected participants study drugs?	☐*1=Yes, 2=No*	If no, STOP, end of form
3	Is the child sick today?	☐*1=Yes, 2=No*	If yes, fill the sick visit form
	B. PROVIDERS TIME INFORMATION FOR THE OPD VISIT		
4	Total time broken down by personnel/activity: - Total time spent seeing the nurse - Total time spent seeing the clinician - Total time spent in registration - Total time spent in pharmacy	 ☐☐☐*minutes* ☐☐☐*minutes* ☐☐☐*minutes* ☐☐☐*minutes*	
C	**C. PATIENT COSTS AND TIME INFORMATION FOR THIS OPD VISIT**		
5	Did anyone travel with you to the OPD today?	☐*1=Yes, 2=No*	If no, skip to Q7
6	What is his/her occupation?	☐*1= Subsistence farmer* *2=Government worker* *3=Business* *4=Large scale farmer,* *5=Private formal worker,* *6=At school/university,* *7=Casual worker for wages,* *8=None,* *9=Other;* *specify*_____	

Client Identification Number ☐☐☐☐☐☐

7	How much time have you spent at the OPD today?	☐☐☐*minutes*	
8	Did the person accompanying you spend the same amount of time?	☐***1** = Yes, **2** = No,*	If yes, go to Q9
	If no, how much time?	☐☐☐*minutes*	
9	Did you use any money at the health facility today or because of today's OPD visit (this includes the person accompanying)?	☐***1** = Yes, **2** = No, 3=Don't know*	If no, go to Q12
10	How much money did you spend on each of the following:	☐☐☐☐☐*Enrolment and health passport .* ☐☐☐☐☐*Registration* ☐☐☐☐☐*Consultation* ☐☐☐☐☐*Haemoglobin/Hb test* ☐☐☐☐☐*Malaria test* ☐☐☐☐☐*Other laboratory tests* ☐☐☐☐☐*Mosquito net* ☐☐☐☐☐*Medicines* ☐☐☐☐☐*Food/drink (related to OPDvisit)* ☐☐☐☐☐*Gift for health worker* ☐☐☐☐☐*Under-the-table payment* ☐☐☐☐☐ *Other* _____ ☐☐☐☐☐ *Total*	
11	How much money did you spend at today's visit in total? If she doesn't know details, ask her to give her best estimate.	☐☐☐☐.☐☐*Kwacha*	If there is a discrepancy please probe.
12	Was there anything you should have spent money on, but you did not?	☐***1** = Yes, **2** = No*	If no, go to Q15
13	If yes, specify		
14	The reason for not spending the money	☐ *1=Didn't want to,* *2=Didn't bring enough,* *3=Couldn't afford it,* *4= Other*_____	
15	Did you have travel costs to the OPD today (this includes child and person	☐***1** = Yes, **2** = No*	If no, skip next question

Client Identification Number ☐☐☐☐☐☐

	accompanying)?		
16	How much money did you spend in total on travel to the health facility today- on the way here only (this includes child and person accompanying)?	☐☐☐☐☐☐*Kwacha*	
17	What mode of transport did you use to the health facility today?	☐*Walking* ☐ *Own bicycle* ☐ *Bicycle taxi* ☐ *Minibus* ☐ *Pick up* ☐*Other, specify*_____	
18	How much time did you spend travelling to the health facility today – on the way there only?	☐☐☐*minutes*	
19	How many days are you unable to work due to the drug collection?	☐☐days	

Form Checked by (initials):	☐☐☐	Date: ☐☐/☐☐/ ☐☐
Data Entered by (initials):	☐☐☐	Date: ☐☐/☐☐/ ☐☐
Double entered by (initials):	☐☐☐	Date: ☐☐/☐☐/ ☐☐

Client Identification Number ☐☐☐☐☐☐

PMC study — Sick Visit Form

Form completed by ☐☐☐ *(Staff ID)*

Client's Initials ☐☐☐

Date of visit ☐☐ / ☐☐☐ / ☐☐☐☐ *(dd/mmm/yyyy)*

No.	Questions	Categories	Skip pattern
	A. MEDICAL HISTORY		
1	Is the child alive?	☐ *1=Yes, 2=No*	If No, complete the verbal autopsy, STOP, end of form
2	Is your child having any of the following symptoms (Tick all that apply)	☐ *Fever,* ***(duration in days)*** ☐ *Skin problems/rashes* ***(duration in days)*** ☐ *Sleep disturbance* ***(duration in days)*** ☐ *Headache,* ***(duration in days)*** ☐ *Dizziness,* ***(duration in days)*** ☐ *Diarrhoea,* ***(duration in days)*** ☐ *Abdominal pain,* ***(duration in days)*** ☐ *Vomiting,* ***(duration in days)*** ☐ *Nausea,* ***(Duration in days)*** ☐ *Other, specify* ***(Duration in days)*** _____	
3	Has your child visited any health facility with an illness since the last study contact	☐ *Yes* ☐ *No* ☐ *Not sure*	*If yes, complete the missed sick visit form as well*
4	Has your child been admitted to a health facility with any other illness since the last study contact?	☐ *Yes* ☐ *No* ☐ *Not sure*	If no, go to Q6
5	If yes, what was the reason for admission? (Tick all that apply)	☐ *Malaria,* ☐ *Anaemia,* ☐ *Pneumonia,* ☐ *Diarrhoea,* ☐ *Sepsis,* ☐ *Injury,* ☐ *Other specify* _____	
6	Has your child received blood since the last study follow up	☐ *Yes* ☐ *No* ☐ *Not sure*	
7	Time spent by nurse:	☐☐☐ *minutes*	
	PHYSICAL EXAMINATION		
8	Anthropometric measurements	**Weight** ☐☐.☐ *kg* **Height** ☐☐.☐ *cm*	
9	Vital Signs	**Temperature** ☐☐.☐ ˚C *(if axillary add 0.5 ˚C)* **Respiratory rate** ☐☐☐ *breaths/min* **Pulse Rate** ☐☐☐ *beats/min*	
10	Time spent by nurse:	☐☐☐ *minutes*	
11	Other signs (Tick all that apply)	☐ *Pallor* ☐ *Jaundice* ☐ *Chest signs* ☐ *Dehydration*	

		☐*Enlarged spleen* ☐*Enlarged liver* ☐*Enlarged lymph nodes* ☐*Mouth ulcers* ☐*Skin rash* ☐*Fungal infection* ☐*Others, specify*	
12	Time spent by clinician:	☐☐☐*minutes*	
13	Are the laboratory Investigations done?	1. Yes 2. No 3. N/A	If no, go to Q15
14	**Laboratory Investigations**	**HemoCue Hb check** ☐☐**.** ☐*g/d* **Malaria Microscopy**☐ 1=*Positive, 2=Negative* **MRDT**☐ 1=*positive, 2=negative* ***DBS Collected 1. Yes 2. No*** **Additional blood tests needed?** ☐***1** = Yes, **2** = No* **If yes, which tests?** *(Please tick)*☐**FBC** ☐**Blood culture** ☐**Urinalysis** ☐**Other (***please*	
15	Time spent by nurse: Time spent by lab technician:	☐☐☐*minutes* ☐☐☐*minutes*	
16	Presenting diagnosis 1	☐☐☐☐☐ insert diagnosis code	
17	Presenting diagnosis 2	☐☐☐☐☐ insert diagnosis code	
18 19	Time spent by clinician: Time spent by nurse:	☐☐☐*minutes* ☐☐☐*minutes*	
20	How many types of drugs was the child given?	☐	

21 Drug details (anti-malarials and other non-study drugs given)

Drug	***Dose***	***Units****(ml,g,mg,tablets and iu)*	***Duration (days)***

22 *Was the child prescribed any drugs but the drugs were not given ? 1 yes 2. No If yes fill the table below*

Drug	***Dose***	***Units****(ml,g,mg,tablets and iu)*	***Duration (days)***

23 24	Time spent by nurse: Time spent by clinician:	☐☐☐*minutes* ☐☐☐*minutes*	
25	Has the child been admitted to the hospital today?	☐***1** = Yes, **2** = No*	If yes ,Complete SAE form

	C. PROVIDER'S TIME INFORMATION		
26	Time spent overall giving treatment to the patient (related to this disease incidence only).	☐☐☐*minutes*	
27	Total time broken down by personnel/activity: - Total time spent by the nurse - Total time spent by the clinician -Total time spent by the lab technician -Total time spent by the registration (this does not include waiting by the patient, *strictly* the time spentby the administration).	☐☐☐*minutes* ☐☐☐*minutes* ☐☐☐*minutes* ☐☐☐*/minutes*	
	D. PATIENTS REFERRAL COSTS		
28	Were you referred here from another health facility?	☐***1*** *= Yes,* ***2*** *= No, 3 = Don't know*	*If no, go to the next section*
29	If yes, how much time did you spend traveling to that health facility	☐☐☐*minutes*	
30	How much time did you spend at that health facility?	☐☐☐*minutes*	
31	How much money did you spend travelling to that health facility?	☐☐☐☐☐*Kwacha*	
32	How much money did you spend at that health facility?	☐☐☐☐☐*Kwacha*	
	E. PATIENT COSTS AND TIME SPENT AT THE OPD		
33	Did anyone travel with you /visit you at the OPD?	☐*1=Yes, 2=No*	If no, skip next question + question 36 and 37
34	What is his/her occupation?	☐*1= Subsistence farmer* *2=Government worker* *3=Business* *4=Large scale farmer,* *5=Private formal worker,* *6=At school/university,* *7=Casual worker for wages,* *8=None,* *9=Other;specify*_____	
35	How much time did the patient spend at the OPD?	☐☐☐*minutes*	
36	Did the person accompanying you spend the entire time with you?	☐***1*** *= Yes,* ***2*** *= No,*	If yes, go to Q38
37	If no, how much time?	☐☐☐*minutes*	
38	How many days were you unable to work due to your child's illness (this includes time before coming to the OPD)?	☐☐*days*	
39	Did you use any money at the OPD or due to the OPD	☐*1=Yes, 2=No, 3=Don't know*	If no, go to Q42

	visit (this includes her, the person accompanying/visiting etc, but *not* travel costs)?		
40	How much money did you spend on each of the following:	☐☐☐☐☐*Enrolment and under-five care book.* ☐☐☐☐☐*Registration* ☐☐☐☐☐*Consultation* ☐☐☐☐☐*Haemoglobin/Hb test* ☐☐☐☐☐*Malaria test*SEP 1 ☐☐☐☐☐*Other laboratory tests* ☐☐☐☐☐*Mosquito net* ☐☐☐☐☐*Medicines* ☐☐☐☐☐*Food/drink (related to OPD visit)* ☐☐☐☐☐*Gift for health worker* ☐☐☐☐☐*Under-the-table payment* ☐☐☐☐☐*Other*_____ Total ☐☐☐☐☐	
41	If she doesn't know details, ask her to give her best estimate of the total she spent at today's visit:	☐☐☐☐☐Kwacha	If there is a discrepancy probe
42	Did you have travel costs to the OPD?	☐***1*** *= Yes,* ***2*** *= No*	If no, go to Q44
43	How much money did you spend in total on travel to the health facility - on the way here only (this includes person accompanying and child)?	☐☐☐☐☐ Kwacha	
44	What mode of transport did you use to the health facility?	☐*Walking* ☐ *Own bicycle* ☐ *Bicycle taxi* ☐ *Minibus* ☐ *Pick up* ☐*Other,specify*_____	
45	How much money will you spend on travelling back home?	☐☐☐☐☐ Kwacha	
46	How much time did you spend travelling to the health facility – on the way here only?	☐☐☐*minutes*	
47	How much time will you spend going back home?	☐☐☐*minutes*	
	F. COSTS AS A BARRIER TO CARE		

Client Identification Number ☐☐☐☐☐☐

48	When seeking treatment for your child, was there something you should have spent money on, but did not?	☐*1=Yes, 2=No, 3=Don't know*	If no, skip next two questions
49	If yes, please specify the items:	_____	
50	The reason for not spending the money	☐*1=Didn't want to,* *2=Didn't bring enough money,* *3=Couldn't afford it,* *4= Other, specify* _____	
51	Did you have to borrow money to seek care?	☐*1=Yes, 2=No, 3=Don't know*	
52	Did you have to sell any assets to seek care?	☐*1=Yes, 2=No, 3=Don't know*	
53	Since last contact with study staff, did you ever wish to seek treatment for your child, but could not afford to do so?	☐*1=Yes, 2=No, 3=Don't know*	
	G. VISIT OUTCOME		
54	Is the child admitted today	☐*1=Yes, 2=No*	If no , end of form if yes, complete post admission form on discharge
55	If yes, what is the diagnosis	☐*Malaria,* ☐*Anaemia,* ☐*Pneumonia,* ☐*Diarrhoea,* ☐*Sepsis,* ☐*Injury,* ☐*Other specify*_____	

Form Checked by (initials):	☐☐☐	Date: ☐☐/☐☐/ ☐☐
Data Entered by (initials):	☐☐☐	Date: ☐☐/☐☐/ ☐☐
Double entered by (initials):	☐☐☐	Date: ☐☐/☐☐/ ☐☐

Client Identification Number ☐☐☐☐☐☐

PMC study Missed Sick Visit Form

Form completed by ☐☐☐*(initials)*
Client's initials ☐☐☐*(initials)*
Date of Visit ☐☐ / ☐☐☐ / ☐☐☐☐ *(dd/mmm/yyyy)*

	Question	Categories	Skip Pattern
A. MEDICAL HISTORY			
1	Is the child alive?	☐*1=Yes, 2=No*	If No, complete the verbal autopsy, STOP, end of form
2	When was the last time your child visited another health facility with an illness	☐☐/☐☐☐/☐☐☐☐*dd/mmm/yyyy (insert date)*	
3	Has your child been admitted to a health facility with any other illness since the last study contact?	☐ *Yes* ☐ *No* ☐ *Not sure*	If no, go to Q5
4	If yes, what was the reason for admission? (Tick all that apply)	☐*Malaria,* ☐*Anaemia,* ☐*Pneumonia,* ☐*Diarrhoea,* ☐*Sepsis,* ☐*Injury,* ☐*Other specify*_____	
5	What type of facility did you go to seek treatment?	☐*Another hospital* SEP ☐*Private clinic* SEP ☐*Health Centre* ☐*Dispensary* SEP ☐*Drug store/pharmacy/drug peddler* ☐*Private laboratory for diagnosis only* ☐*Didn't go anywhere/waited till it was over* ☐*Traditional healer/Village doctor* ☐*Other, specify*_____	
6	The last time your child visited another health facility with an illness, were laboratory investigations carried out?	☐ *1=Yes, 2= No, 3=Not sure*	If no, skip to Q5 Check with health passport.
7	Was the HB done?	☐ 1=Yes, 2= No HbLevel ☐.☐☐ g/dl	If no, go to next test

Client Identification Number ☐☐☐☐☐☐

	Was malaria slide done? Was MRDT done?	☐ 1=Yes, 2= No Malaria slide: Positive ☐ 1=Yes, 2= No ☐ 1=Yes, 2= No MRDT: Positive ☐ 1=Yes, 2= No	If no, go to next test If no, skip the test
8	What was the diagnosis the last time your child visited another health facility?	Diagnosis 1☐☐☐☐☐☐ Insert code Diagnosis 2☐☐☐☐☐☐ insert code Diagnosis 3☐☐☐☐☐☐ insert code Other, specify_____	
9	Was your child given any of the following malaria treatment	☐*1=ArtemetherLumefantrine 2=Quinine sulphate 3=Amodiaquineartesunate 4=Other, specify*_____	Please check in the health passport book
10	How many types of other treatment was the child given	☐☐	
11	**Other treatment given**		

	Drug	***Dose (mgs/tablets)***	***Units 1. ml 2. g 3. mg 4. iu 5. tablets***	***Duration (days)***	

12	*Was the child prescribed any drugs but the drugs were not given ? 1 yes 2. No If yes fill the table*				
	Drug	***Dose (mgs/tablets)***	***Units 1. ml 2. g 3. mg 4. iu 5. tablets***	***Duration (days)***	

13	Was your child admitted during this visit?	☐ *1=Yes, 2= No, 3= Not sure*	If no, skip to section C

Client Identification Number ☐☐☐☐☐☐

B. PATIENT COSTS AND TIME SPENT for those admitted			
14	What facility was your child admitted to?	☐*Another hospital* SEP ☐*Private clinic* SEP ☐*Health Centre* ☐*Traditional healer/Village doctor* ☐*Other, specify*_____	
15	Was your child admitted with a diagnosis of severe malarial anaemia?	☐ 1=*Yes, 2=No, 3=Not Sure*	If no, go to 13
16	If Yes, what medication was given to your child for severe malarial anaemia?	☐*1=ArtemetherLumefantrine* *2=Quinine sulphate,* *3=Amodiaquineartesunate,* *4=Other, specify*_____	
16	Did your child have a blood transfusion during this time?	☐ 1=*Yes, 2= No, 3=Not sure*	
17	Did anyone travel with you to the health facility?	☐*1=Yes, 2=No*	If no, go to 16
18	What was his/her occupation?	☐*1= Subsistence farmer* *2=Government worker* *3=Business* *4=Large scale farmer,* *5=Private formal worker,* *6=At school/university,* *7=Casual worker for wages,* *8=None,* *9=Other; specify*_____	
19	How much time did you spend at the health facility?	☐☐☐minutes	
20	Did the person accompanying you spend the same amount of time?	☐***1*** *= Yes,* ***2*** *= No,*	If yes, go to 19
21	If no, how much time?	☐☐☐*minutes*	
22	What mode of transport did you use to the health facility?	☐*Walking* ☐ *Own bicycle* ☐ *Bicycle taxi* ☐ *Minibus* ☐ *Pick up* ☐ *Other, specify*_____	
23	How time did you spend travelling to the health facility?	☐☐☐*minutes*	

Client Identification Number ☐☐☐☐☐☐

24	How much time did you spend going back home?	☐☐☐*minutes*	
25	How many days were you unable to work due to your childs illness (this includes time before and after seeking treatment)?	☐☐days	
26	Did you use any money at the health facility or because of the visit (this includes her and anyone accompanying, does NOT include travel)?	☐***1*** *= Yes,* ***2*** *= No,*	If no, skip next two questions.
27	How much money did you spend on each of the following:	☐☐☐☐☐*Enrolment and health passport* ☐☐☐☐☐*Registration* ☐☐☐☐☐*Consultation* ☐☐☐☐☐*Haemoglobin/Hb test* ☐☐☐☐☐*Malaria test* ☐☐☐☐☐*Other laboratory tests* ☐☐☐☐☐*Mosquito net* ☐☐☐☐☐*Medicines* ☐☐☐☐☐*Food/drink (related to OPD visit)* ☐☐☐☐☐*Gift for health worker* ☐☐☐☐☐*Under-the-table payment* ☐☐☐☐☐*Other*_____ ☐☐☐☐☐ *Total*	
28	If she doesn't know/remember the details, ask her to give her best estimate of the total she spent at the health facility:	☐☐☐☐☐☐Kwacha	If there is a discrepancy probe
29	How much money did you spend in total on travel to the health facility- on the way there only (this includes the person	☐☐☐☐☐☐Kwacha	

	accompanying and the child)?		
30	How much time did you spend travelling to the health facility?	☐☐Hours	
C. **PATIENT COSTS AND TIME SPENT FOR those not admitted**			
31	Did anyone travel with you /visit you at the health facility?	☐*1=Yes, 2=No*	If no, go to 28
32	What is his/her occupation?	☐*1= Subsistence farmer* *2=Government worker* *3=Business* *4=Large scale farmer,* *5=Private formal worker,* *6=At school/university,* *7=Casual worker for wages,* *8=None,* *9=Other; specify*_____	
33	How much time did you spend at the health facility?	☐☐☐*minutes*	
34	Did the person accompanying you spend the same amount of time?	☐***1*** *= Yes,* ***2*** *= No,*	If yes, go to 31
35	If no, how much time?	☐☐☐*minutes*	
36	How much time did you spend travelling to the health facility – on the way here only?	☐☐☐minutes	
37	How much time did you spend travelling back home?	☐☐☐minutes	
38	How many days were you unable to work due to your childs	☐☐*days*	

	illness (this includes time before and after seeking treatment)?		
39	Did you use any money at the health facility or because of the visit (this includes her and anyone accompanying, does NOT include travel)?	☐*1=Yes, 2=No, 3=don't know*	
40	How much money did you spend on each of the following:	☐☐☐☐☐*Enrolment and health passport* ☐☐☐☐☐*Registration* ☐☐☐☐☐*Consultation* ☐☐☐☐☐*Haemoglobin/Hb test* ☐☐☐☐☐*Malaria test* ☐☐☐☐☐*Other laboratory tests* ☐☐☐☐☐*Mosquito net* ☐☐☐☐☐*Medicines* ☐☐☐☐☐*Food/drink (related to OPD visit)* ☐☐☐☐☐*Gift for health worker* ☐☐☐☐☐*Under-the-table payment* ☐☐☐☐☐*Other*_____ ☐☐☐☐☐ *Total*	
41	How much money did you spend on the visit in total.If she doesn't remember ask her to give her best estimate	☐☐☐☐☐☐Kwacha	
42	How much money did you spend in total on travel to the health facility - on the way there only (this includes person accompanying and child)?	☐☐☐☐☐☐ Kwacha	

Client Identification Number ☐☐☐☐☐☐

43	What mode of transport did you use to the health facility?	☐ *Walking* ☐ *Own bicycle* ☐ *Bicycle taxi* ☐ *Minibus* ☐ *Pick up* ☐ *Other, specify* _____	
44	How much money did you spend travelling back home?	☐☐☐☐☐☐ Kwacha	

D. COSTS AS A BARRIER TO CARE

45	When seeking treatment for your child, was there something you should have spent money on, but did not?	☐ *1=Yes, 2=No 3=don't know*	If no, go to 41
46	If yes, please specify the items:	_____	
47	The reason for not spending the money	☐ *1=Didn't want to,* *2=Didn't bring enough money,* *3=Couldn't afford it,* *4= Other, specify* _____	
48	Did you have to borrow money to seek care?	☐ *1=Yes, 2=No 3=don't know*	
49	Did you have to sell any assets to seek care?	☐ *1=Yes, 2=No 3=don't know*	

Form Checked by (initials):	☐☐☐	Date: ☐☐/☐☐/ ☐☐
Data Entered by (initials):	☐☐☐	Date: ☐☐/☐☐/ ☐☐
Double entered by (initials):	☐☐☐	Date: ☐☐/☐☐/ ☐☐

HOME VISIT FORM

SUBJECT ID:	VISIT DATE:
FIELD WORKER ID: [1]	

Please Tick the applicable course

PMC 1 (Week 2) ☐ **PMC 2 (Week 6)** ☐ **PMC 3 (Week 10)** ☐ **Unscheduled** ☐

NO	QUESTION	CATEGORIES	SKIP PATTERN
1	Is blister pack collected?	☐ *1=Yes, 2=No*	If yes go to Q3
2	If no, state the reason?		
3	Expected number of DHP tablets	☐☐	
4	Actual number of DHP tablets	☐☐	

Client Identification Number ☐☐☐☐☐☐

PMC STUDY **End of study visit form**

Form completed by ☐☐☐*(initials)*
Client's initials ☐☐☐*(initials)*
Date of Completion ☐☐ / ☐☐ / ☐☐ *(dd/mmm/yyyy)*
Study Arm ☐*1=Arm 1, 2= Arm 2, 3= Arm 3, 4=Arm 4, 5=Arm 5*
Cluster ☐☐☐

No.	**Questions**	Category	Skip pattern
A	**PREVIOUS MEDICAL HISTORY**		
1	Is the child alive?	☐*1=Yes, 2=No*	If No, complete the verbal autopsy, STOP, end of form
2	Did your child visit any health facility with an illness since last contact with study staff?	☐*1=Yes, 2=No, 3=Not Sure*	If yes, complete the missed sick visit form
B	**MALARIA CONTROL MEASURES**		
3	Do you have mosquito nets in your household?	☐*1=Yes, 2=No*	***If No, go to section C***
4	How many sleeping spaces are in your household?	☐☐	
5	How many sleeping spaces in your household are covered by ITN?	☐☐	
6	Did the child sleep under an ITN the night before admission?	☐*1=Yes, 2=No, 3=Not Sure*	***If yes, go to Q8***
7	If no, what was the reason? (Tick all that apply)	☐*Forgot,* ☐*Travelled away,* ☐*Child allergic to the net,* ☐*Net was being used by others,* ☐*Others,* *specify* _____	
8	At any time in the past 12 months, has your house been intermittently residual sprayed against mosquitoes?	☐*1=Yes, 2=No, 3=Not Sure*	***If no, go to Section C***
9	If yes, when was your house sprayed?	☐☐☐/ ☐☐☐☐*(mmm/yyyy)*	
C.	**PRESENT MEDICAL HISTORY**		
10	Is your child sick today?	☐*1=Yes, 2=No*	If no go to section D
11	Is your child having any of the following symptoms (tick any that apply)	☐*Fever* ***(Duration in days)*** ☐*Skin problems/rashes****(Duration in days)*** ☐*Sleep disturbance* ***(Duration in days)*** ☐ *Headache* ***(Duration in days)*** ☐ *Dizziness* ***(Duration in days)*** ☐ *Diarrhoea* ***(Duration in days)*** ☐ *Abdominal pain* ***(Duration in***	

		days) ☐*Vomiting**(Duration in days)*** ☐ *Nausea **(Duration in days)*** ☐ *Other, specify**(Duration in days)***	
D	**CLINICAL EXAMINATION**		
12	**Anthropometric Measurements**	**Weight** ☐☐.☐*kg* **Height** ☐☐.☐*cm*	
13	Vital Signs	**Pulse rate** ☐☐☐*beats/min* **Temperature** ☐☐.☐*°C* **Respiratory rate**☐☐☐*/min*	
14	Other Signs (Tick all that apply)	☐*Chest signs,* ☐*chest recessions,* ☐*oedema,* ☐*loss of appetite,* ☐*lymphadenopathy,* ☐*dehydrated* ☐*Jaundice* ☐*Bleeding tendencies* ☐*Other* *specify*_____	
15	LABORATORY INVESTIGATIONS		
	HB Malarial microscopy?	HbLevel ☐.☐☐ g/dl Malaria Microscopy: Positive ☐ 1=Yes, 2= No DBS	
16	What is the current diagnosis? (Tick all that apply)	☐*1=malaria, 2=anaemia,* *3=Pneumonia,4=No diagnosis* *5=Other* *specify*_____	
E	**GUARDIAN TIME AND TREATMENT COSTS**		
17	Has drug administration hindered you from conducting other activities?	☐1=Yes, 2=No, 3=Don't know	If no, skip next two questions.
18	How much time, on average, do you think each round of drug administration (all three days) prevented you from conducting other activities?	☐☐☐minutes	
19	What type of activities?	☐ Leisure time ☐ Household chores ☐ Working for wages ☐ Other, specify_____	
20	Did you have any additional costs due to the malaria treatment?	☐1=Yes, 2=No, 3=Don't know	If no, skip next question.
21	How much in total do you think these additional costs were?	☐☐☐☐☐Kwacha	

Client Identification Number ☐☐☐☐☐☐

E.	**COSTS AS A BARRIER TO CARE**		
22	Did you ever wish to come to a health facility for an unscheduled visit during this trial, but could not because of the costs?	☐ *1=Yes, 2=No*	
23	When treating your child with the trial drugs, there something you should have spent money on, but did not?	☐ *1=Yes, 2=No, 3=Don't know*	If no, skip next two questions
24	If yes, please specify:	_____	
25	The reason for not spending the money	☐ *1=Didn't want to,* *2=Didn't bring enough money,* *3=Couldn't afford it,* *4= Other, specify* _____	
26	Did you have to borrow money during the time of the trial to cover treatment costs?	☐ *1=Yes, 2=No, 3=Don't know*	
27	Did you have to sell any assets during the time of the trial to cover any treatment costs?	☐ *1=Yes, 2=No, 3=Don't know*	
F	**SMS REMINDER**		This only applies to those randomised into trial arm XX and XY.
28	Did you receive the SMS reminder to start a new dose of treatment for your child/collect the drug at the OPD?	☐ *1=Yes, 2=No, 3=Sometimes, 4=Not sure*	If yes, skip next question
29	If no, what was the reason? (Tick any that apply)	☐ Did not have access to a phone ☐ Did not always have access to a phone ☐ Did not have a charged phone ☐ Lost the phone that was registered with the study staff at enrolment. ☐ Was embarrassing to bother other people.	
30	If yes, did you find the reminder useful?	☐ 1= yes, 2=no, 3=not sure	If yes, skip the next question.
31	If no or not sure, why not?	☐ Did not need the reminder ☐ Was a struggle to keep phone charged ☐ The costs associated with keeping the phone charged outweighs the gains. ☐ Did not understand the SMS	
G.	**COSTS OF SMS REMINDER**		
32	How much money, on average, did you spend doing the following:	*Charging the phone:* ☐☐☐☐☐ *Kwacha* *Borrowing someone else's phone* ☐☐☐☐☐ *Kwacha*	

		Travel to phone charging place ☐☐☐☐☐ *Kwacha*	
33	How much time, on average, did you spend on the following:	*Charging the phone* ☐☐☐minutes *Borrowing someone else's phone* ☐☐☐minutes *Travel to phone charging place* ☐☐☐minutes	
H.	**HSA VISIT**		This only refers to trial arm XX.
34	Were you visited by the HSA?	1. yes 2. No	If no, go to section I
35	How many times did the HSA visit your home?	☐ 1= one, 2=two, 3=three, 4=not sure, 5=none	
36	How much time did you spend (on average) with the HSA?	☐☐☐minutes	
I.	**TREATMENT ADHERENCE**		Applies to all trial arms.
37	Of the doses that you collected at the OPD or had been given at discharge, did your child receive full doses of medication?	☐*1=Yes, 2=No, 3=Not Sure*	If yes, go to Q39
38	If no, why not?	☐*1=Forgot,* *2 = Lost the medication,* *3=Gave the medication to someone else,* *4 = Did not see the need as child was healthy, 5=Child vomited, 6=fear of side effects, 7=not sure how to administer drugs correctly* *8 = others, specify*_____	
39	If Yes, what measures did you put in place to make sure your child took all the prescribed doses? (Tick all that apply)	☐*Schedule drugs at meal times,* ☐*Schedule drugs at bathing time,* ☐*Put written reminders on the wall,* ☐*Share information with family members to remind you,* ☐*Others, specify*_____	
40	Did your child vomit any of the drugs that you gave him/her at home?	☐*1=Yes, 2=No, 3=Not Sure*	If no, go to Q42
41	If yes, what did you do if your child vomited immediately after taking drugs? (Tick all that apply)	☐ *Administered another dose,* ☐*Did not do anything,* ☐*Reported to the HSA,* ☐*Others, specify*_____	
42	What measures do you put in place to make sure your child does not vomit medications? (Tick all that apply)	☐*Give drugs with sweetened water/drink,* ☐*Give drugs with meals,* ☐*Breastfeed immediately after giving drug,* ☐*Do nothing,* ☐ *Others, specify*_____	

Form Checked by (initials):	☐☐☐	Date: ☐☐/☐☐/ ☐☐
Data Entered by (initials):	☐☐☐	Date: ☐☐/☐☐/ ☐☐
Double entered by (initials):	☐☐☐	Date: ☐☐/☐☐/ ☐☐

CERTIFICATE OF ETHICS APPROVAL

This is to certify that the College of Medicine Research and Ethics Committee (COMREC) has reviewed and approved a study entitled:

P.02/15/1679- Malaria chemoprevention with monthly treatment with dihydroartemisin-piperaquine for the post discharge management of severe anemia in children aged less than 5 years in Malawi: a 3 year, single site, parallel group, five arm cluster randomized trial of community versus health facility based delivery mechanisms by Prof. K. Phiri

On 15 July 2015

As you proceed with the implementation of your study, we would like you to adhere to international ethical guidelines, national guidelines and all requirements by COMREC as indicated on the next page

Approved by
College of Medicine
15 JUL 2015
(COMREC)
Research and Ethics Committee

Dr. C. Dzamalala- Chairperson (COMREC)

15th July 2015
Date

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