CORRELATION BETWEEN ADHERENCE TO CHEMOPROPHYLAXIS AND MORBIDITY AMONG PATIENTS WITH SICKLE CELL DISEASE IN WEBUYE COUNTY HOSPITAL, KENYA

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This thesis is submitted in partial fulfillment of the requirement for the award of Degree of Master of Medicine in Family Medicine of Moi University

DECLARATION

Declaration by Student

This thesis is my original work and has not been presented to any other university or institution as a research paper for the award of any academic degree. No part of this thesis should be reproduced without prior written permission of the author and/or Moi University.

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DEDICATION

This work is dedicated to my beloved wife Evelyne, my daughter Mowadah and my son Raanan for the great support during the postgraduate period.

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ABBREVIATIONS

BMQ -	Brief Medication Questionnaire
HSCT -	Hematopoietic Stem Cell Transplant
IREC -	Institutional Research and Ethics Committee
MEMS -	Medication Event Monitoring System
MOPC -	Medical Outpatient Clinic
POPC -	Pediatric Outpatient Clinic
SCA -	Sickle Cell Anemia
SCD -	Sickle Cell Disease
VOC -	Vaso-occlusive Crisis
WHO -	World Health Organization

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DEFINITION OF TERMS

Sickle Cell Disease – This is a hereditary disorder in which the red blood cells have haemoglobin S (HbS), which is a deviant form of the protein that carries oxygen. The people who inherit sickle-cell genes from both parents are homozygotes (HbSS) and develop SCD and also have lifelong symptoms, whereas those who inherit the gene from one parent have the sickle-cell trait (SCT) or heterozygotes (HbAS) and generally lead normal lives. (Al-busaidi, 2010).

Chemoprophylaxis – This is the administration of medication to prevent the development of a disease (Mcbride, 2010). In this study chemoprophylaxis referred to proguanil, folic acid and the monthly benzathine penicillin injection.

Medication Adherence – This is defined by the World Health Organization as "the degree to which the person's behavior corresponds with the agreed recommendations from a health care provider." (Osterberg & Blaschke, 2005)

Morbidity – The Center for Disease Control defines morbidity as “any departure, subjective or objective, from a state of physiological or psychological well-being, in practice this encompasses disease, injury, and disability.” In this study this definition included hospitalizations, acute painful crises, acute febrile illnesses and blood transfusions.

ABSTRACT

Background: According to the 2014 World Health Organization (WHO) estimate, 240,000 babies are born with SCD yearly in sub-Saharan Africa with most of them dying in early childhood. In Kenya, more than 80% of patients living with SCD are in the Western counties, where it is a major contributor to morbidity and mortality. Although SCD has been widely studied in Kenya, there is paucity of data on medication adherence and associated morbidity.
Objective: To determine the relationship between adherence to chemoprophylaxis and morbidity among patients with SCD in Webuye County Hospital.
Methods: A prospective observational study of 137 participants was done at the outpatient clinic in Webuye County Hospital. Participants who met the inclusion criteria were consecutively sampled. Sociodemographics were documented using interviewer-administered questionnaires. All participants were on proguanil and folic acid, those ≤ 5 years were on penicillin. Febrile illnesses, hospitalizations and blood transfusions were recorded over 6 months. Adherence was assessed using Brief Medication Questionnaire (BMQ) and participants dichotomized into adherent (n=97) and non-adherent (n=33). Data was analyzed using STATA version 14. Categorical variables were summarized as frequencies and percentages and continuous variables as means and median. Incidence risk ratios and Poisson regression compared clinical outcomes and adherence. A p value ≤0.05 was considered significant.
Results: Participants' median age was 5 years with (69)50.4% being male. Adherence to proguanil, folic acid and benzathine penicillin injection was 75.4%, 85.4% and 100% respectively. Non-adherence to folic acid increased the rate of hospitalizations (2.05 IRR; 95% CI 1.085 - 3.880, p = 0.027). Non-adherence to folic acid and proguanil increased the rate of blood transfusions (4.21 IRR; 95% CI 1.974 - 9.018, p < 0.001) and (4.24 IRR; 95% CI 1.913 - 9.397, p < 0.001) respectively. Non-adherence to folic acid and proguanil increased the rate of painful episodes (1.86 IRR; 95% CI 1.202 – 2.894, p = 0.005) and (1.52 IRR; 95% CI 1.011 – 2.290, p = 0.44) respectively. Non-adherence to folic acid and proguanil increased the rate of febrile illnesses (1.44 IRR; 95% CI 0.948 - 2.208, p = 0.086) and (1.33 IRR; 95% CI 0.907 - 1.976, p = 0.142) respectively.
Conclusions: Adherence to benzathine penicillin**,** proguanil and folic acid was comparable to other studies. The non-adherent had a statistically significant increased rate of hospitalizations, blood transfusions and painful episodes.
Recommendations: Adherence evaluation of all patients with SCD during routine care. Studies to identify causes and remedy of non-adherence to proguanil and folic acid.

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CHAPTER ONE

1.0 INTRODUCTION

1.1 Background

Sickle cell disease is common throughout much of Africa affecting up to 3% of births in some parts of the continent (Ndila et al., 2014). It is estimated that 240,000 children are born with SCD in sub-Saharan Africa (Julie Makani et al., 2015). Scott D. Grosse et al concluded that if untreated African children born with HbSS have early mortality of between 50% and 90% (Grosse et al., 2011). In Africa SCD contributes the equivalent of 25% of deaths among children below five years (George and Opara, 2011).

The overall global pooled estimate of mortality among patients with SCD is 0.64 per 100 years of child observation with the highest rate seen in Africa being 7.3 (Wastnedge et al., 2018). This constitutes an important public health burden in sub-Saharan Africa which has the highest prevalence of SCD in the world.

Newborn screening and the administration of preventive interventions to children with SCD is known to be cost-effective for many of the countries in SSA including Kenya (Kuznik et al., 2016). The former is not widely implemented in these countries while the doable preventive medications are shrouded with the challenges of non-adherence.

The levels of medication adherence are moderate in patients on management for chronic diseases including SCD because of the various barriers (Lam & Fresco, 2015). The WHO reported that medication adherence among patients on care for chronic diseases including SCD averages only 50% in developed countries (Lo, 2003). The scale of impact of this is presumed to be worse in low-resource income countries like Kenya given the scarcity of health resources with inequities and inaccessibility to quality health care (Awad et al., 2017).

The medication adherence among patients on care for chronic diseases like SCD from clinical trials range from 43 to 78 percent (Kaleva, 2015) even though it is expected to be higher in these studies owing to the attention and strict follow-up schedules for the participants. This directly underscores the weight of the problem of non-adherence in a normal uncontrolled setting. A Nigerian cross-sectional study reported 50.9% adherence to prescribed medication among patients on follow-up in an outpatient setting of a tertiary health facility (Salaudeen et al., 2018).

Adherence to the various prescribed therapeutic modalities is a major determinant of outcomes of the entire treatment plan (Svarstad, 1999). Poor medication adherence affects the patient, the whole system of health delivery and the financial burden because it leads to increased morbidity and deterioration of the disease under treatment (Jimmy & Jose, 2011). The WHO recommends that patients get between 1.6 and 1.8 as the number of medicines per prescription (Adebisi et al., 2014) but a Nigerian study found that on average every patient with SCD got 4.5 which is more than twice the recommended standard (Atif et al., 2016). This is because in addition to the treatment of acute illness the management of SCD includes malaria prophylaxis, penicillin-based prophylaxis and folic acid which increase the number of drugs per prescription. This in turn could contribute to the levels of non-optimal adherence to medication.

Generally, the levels of medication adherence among patients with SCD using reported adherence measurement techniques ranges from 48% to 89% according to a systematic review paper done by researchers in a high resource setting (Walsh & Sarah, 2017). The level of adherence to folic acid and oral penicillin among patients with SCD was 61% and 55% respectively by the mean medication possession ratio (Walsh et al., 2014). The adherence level to penicillin was high above

90% when given as an injectable, which is far better than oral administration which gives adherence levels of 40% to 44% by urine test (Walsh et al., 2014).

A cross-sectional survey in the USA found that health care providers report that medication non-adherence and lack of monitoring are impediments to treatment in patients with SCD (Giudicessi et al., 2011). A study in the Middle East documented that there is significant improvement in the WHO-health related quality of life for patients with SCD who regard treatment adherence (Al Jaouni et al., 2013).

A 2018 systematic review showed that regular administration of antimalarial prophylaxis decreases the occurrence of symptomatic malaria among children living with SCD (Frimpong et al., 2018) even though it demonstrated that there is no difference in the risk of hospital admissions, painful episodes and blood transfusions between the treatment and placebo groups.

The number of painful episodes among patients with SCD significantly increases with lower ages of the child and decreases with the regular use of anti-malaria prophylaxis (Amoran et al., 2017). The annual frequency of hospitalizations among patients with SCD range from one to eight, with a mean of two with more than half of the patients having one hospital admission and about a quarter having more than three admissions (Adegoke et al., 2014).

Oniyangi et al found that malaria chemoprophylaxis in a study of 97 children living with SCD decreases the number of painful episodes and the number of blood transfusions. He also reported that the number of hospitalizations is greatly reduced in patients on malaria chemoprophylaxis (O Oniyangi & Aaa, 2009). Malaria prophylaxis in patients with SCD results in a significant drop in

the complains by the patients and the need for blood transfusions. There is no effect on the number of hospitalizations and episodes of vaso-occlusive crises (Diop et al., 2011).

In a Nigerian RCT of 270 patients with SCD, medication adherence levels to intermittent preventive treatment (IPT) with a fixed-dose combination of mefloquine-artesunate (MQAS) or sulfadoxine-pyrimethamine plus amodiaquine (SPAQ) were by far more excellent than daily doses of proguanil, with only 43% of patients taking more than 75% of the prescribed daily doses with resultant less acute illness episodes in the outpatient in children who received IPT than those who received proguanil. This study also reported that older children above 10 years have poorer medication adherence levels (Olaosebikan et al., 2015).

Though there is widespread use of folic acid in SCD, there is ongoing controversy about its impact on the disease morbidity. Some studies have demonstrated its undetermined effect on infections and painful episodes in these patients while others show an increased risk of repeat painful episodes in those patients not on supplementation (R Dixit et al., 2016).

Hospitalizations among patients with SCD has various determinants including increasing age, status of personal health insurance, being in third world countries, not being on the scheduled specialized outpatient follow-up, concomitant diseases like asthma and having no principal caregiver (Cronin et al., 2019).

1.2 Research Problem Statement

The prevalence of HbAS and HbSS among children in Western Kenya is reported to be 17.6% and 1.6% respectively with a similar prevalence reported by Foote EM et al among children in in a similar study in Nyando (Foote et al., 2013). Approximately 362 patients living with SCD had been enrolled for follow-up in the Webuye County Hospital outpatient clinic according to the 2016

hospital records. These findings draw attention to the extent of sickle cell disease as a public health problem in Western Kenya. In Kenya 80% of the patients with SCD are of the Luhya and Luo ethnic groups predominantly in the Western part of the country (Aluoch, 1993). Most of the Webuye County Hospital (WCH) catchment population consists of the Luhya.

A study in WCH in 2016 found that the median age of patients with SCD was 5 years. There was only one patient at 18 years while 57% were below seven-and-a-half years. This emphasizes that SCD in WCH is still associated with early mortality.

A majority of patients enrolled in the pediatric outpatient clinic of this facility have SCD and are on preventive medications for the same. Despite the care given in the scheduled follow-up these patients are often readmitted due to associated morbidities. Since medication non-adherence is a major adjustable factor that impacts therapy outcomes in the care of patients with chronic diseases, its evaluation among patients with SCD may provide information for decisive intervention and hence result in positive outcomes in therapy (Niti et al., 2013).

The use of chemoprophylaxis among patients with SCD is expected to result in reduced frequency of infection, hospitalizations and episodes of acute crises (Loiselle et al., 2017). My literature search on the level of adherence to penicillin, proguanil and folic acid and its effects on morbidity in East Africa including Kenya yielded limited data. This study sought to bridge this gap of knowledge in Webuye County Hospital, a semi-rural health facility in Western Kenya.

1.3 Study Justification

This study was conducted to fill the gap of knowledge of the level of adherence to proguanil, folic acid and penicillin in patients with SCD and its correlation to morbidity in Webuye County Hospital. The findings of the study will be shared with other health care providers through scientific conferences and publications in peer reviewed journals.

The study findings will also be shared with the staff at Webuye County Hospital and Western Kenya at large in order to inform the care of patients with SCD. This will bring to awareness to these health providers the effects of medication non-adherence and emphasize the need for patient education, including adherence counselling in the continued care of patients with SCD. This will help in improving care to the patients and improve health outcomes. The findings of this study will also aid the policy makers and financiers in Webuye, Bungoma and Kenya in strategies to enhance adherence to chemoprophylaxis in the care of patients with SCD.

1.4 Research Question

What is the relationship between adherence to chemoprophylaxis and morbidity in patients with SCD attending the outpatient clinic in Webuye County Hospital?

1.5 Objectives

1.5.1 Broad Objective

To determine the relationship between adherence to chemoprophylaxis and morbidity among patients with SCD in Webuye County Hospital.

1.5.2 Specific Objectives

1. To determine the level of adherence to penicillin, proguanil and folic acid in patients with SCD in Webuye County Hospital.
2. To determine the frequency of hospitalizations, acute febrile illness, acute painful episodes and blood transfusions among patients with SCD in Webuye County Hospital.
3. To determine the relationship between the level of adherence to chemoprophylaxis and the frequency of hospitalizations, acute febrile illness, acute painful episodes and blood transfusions among patients with SCD in Webuye County Hospital.

CHAPTER TWO

LITERATURE REVIEW

2.0 Definition and Classification

Sickle Cell Disease (SCD) is a common inherited disorder of the hemoglobin that is multi-systemic and often presents with recurrent episodes of acute illness and progress to irreversible organ failure (Weatherall et al., 2004). SCD was initially defined in the early 18th century by James Herrick (Sergeant GR, 2001) and it refers to all genotype forms of the illness that contain one or more sickle gene and with more than 50% of the hemoglobin being hemoglobin S (HbS) (Geoge & Opara, 2011). Apart from the homozygous SS genotype there exists more than five others that are related to this condition (George & Opara, 2011).

2.1 Pathophysiology

SCD is an inherited autosomal recessive hemoglobinopathy (Ware et al., 2017) that has an abnormal peptide resulting from the substitution of valine for glutamic acid at position 6 of the beta globin chain (Hunt & Ingram, 1958). Whenever patients with SCD get into circumstances that subject the red blood cells to persistent deoxygenation, they develop a sickle or crescent shape, become inflexible, increase blood viscosity, and block or limit blood flow within limbs or organs (Connes et al., 2014) resulting in acute and chronic complications.

2.2 Epidemiology

Globally, more than 300,000 babies are born with SCD yearly with a projected increase of up to 400,000 by 2050 (Piel et al., 2013). More than 75% of these patients live in sub-Saharan Africa

(Sadarangani et al., 2009a) where a majority of them do not live passed their childhood (Williams & Obaro, 2011).

More than 70% of the people of African descent who have SCD have Hemoglobin SS (HbSS) genotype with a likelihood that it is the only form found in East Africa (Mpalampa et al., 2012). A survey done in Uganda concluded that the overall prevalence of sickle cell disease is 0·7% (Ndeezi et al., 2016).

2.3 Diagnosis

The diagnosis of SCD is achieved by initially employing the sickling test as a screening modality (Okwi et al., 2010) then confirmed by hemoglobin electrophoresis (Rees et al., 2018). There are also other tests like high performance liquid chromatography (HPLC) available in some centers. Point-of-care (POC) diagnostic testing for SCD (Bond et al., 2017) is still under development, this may be especially useful in areas where it is not possible or convenient to transfer blood samples to a centralized laboratory (Grosse et al., 2005).

Early diagnosis of SCD improves survival due to early enrollment into management. Although newborn screening to identify affected individuals before the development of complications is ideal, most individuals in sub-Saharan Africa are diagnosed at a mean age of two years when they present with symptoms of the disease (Tshilolo et al., 2008).

2.4 Morbidity and Mortality

The presentation of SCD is varied over a wide spectrum ranging from acute pain syndromes to early onset stroke, leg ulcers with resultant increased risk of early deaths due to multiple organ

dysfunction. The onset of these manifestations is often delayed to till after infancy when the predominant fetal hemoglobin (HbF) is substituted by the adult hemoglobin (Piel et al., 2017).

The high morbidity and mortality in patients with SCD results in a huge socio-economic burden especially because of frequent hospitalizations following episodes of sickle cell crises (Mpalampa et al., 2012). Most of the hospitalizations are due to uncontrolled acute painful episodes (Jerrell et al., 2011). They are also hospitalized usually due to fever and need for blood transfusion (Cronin et al., 2019). The main types of crises in SCD include vaso-occlusive crises, aplastic crises, acute sequestration and hemolytic crises (Juwah et al., 2004).

In tropical Africa, malaria is the most common cause of anemic and vaso-occlusive crises (Diop et al., 2011). A Nigerian study reported that the comorbidities related to SCD include malaria 34.3%, dactylitis 25.4%, pneumonia 10.7% and osteomyelitis 7.1% (Geoge & Opara, 2011). In patients with SCD in African populations there is increased incidence of bacterial infections including bacteremia, pneumonia and meningitis (Ramakrishnan et al., 2010).

2.5 Management

Currently, the main therapeutic modalities with noteworthy outcomes for patients with SCD are transfusion with erythrocytes, bone marrow transplant and hematopoietic stem cell transplant (Bolan et al., 2009), nevertheless, these therapeutic modalities are costly and hence are rarely performed especially in low resource settings (Bolan et al., 2009). Treatment modalities that target vascular dysfunction in order to prevent major organ damage are still under evaluation and may have the greatest effects in patients with SCD (Benjamin M. Davis, Glen F. Rall, 2017). Most of

the management of patients with SCD is supportive entailing proper hydration, pain relief, blood transfusion and psychosocial support (Davies & Oni, 1997).

Patients living with SCD require sufficient hydration, including increased oral fluids at home and parenteral fluids during hospitalization for the management of vaso-occlusive episodes. Many of the health facilities in sub-Saharan Africa have only nonsteroidal anti-inflammatory drugs (NSAIDs) and some non-opioid analgesics leading to sub-optimal pain management (J. Makani et al., 2013).

Chemo-preventive medicines are generally used as adjuncts in the long-term follow-up of patients with SCD. These include penicillin prophylaxis (Patel, et al 2010), pneumococcal vaccine, folic acid and malaria prophylaxis (Davies & Oni, 1997). The WHO African Regional strategy recommends that malaria chemoprophylaxis to be given to all children living with SCD (Al-busaidi, 2010). A Nigerian study reported that although most patients with SCD have unexpectedly high frequency of crises within a month, chemoprophylaxis is likely to have more positive outcomes than other lifestyle approaches in the prevention of VOC (Amoran et al., 2017).

A number of microbes including *Streptococcus pneumoniae, Hemophilus influenzae*, and non-typhi Salmonella species are among the key causes of infection in SCD. In both developed and developing countries, there has been substantial reduction in adverse sequelae of these infections due to penicillin chemoprophylaxis and vaccines against *Streptococcus pneumoniae* and *Hemophilus influenzae* (Rees et al., 2018). Penicillin prophylaxis is highly effective in preventing bacterial infection, monthly intramuscular penicillin prophylaxis is preferred over daily oral penicillin because of the better adherence level of 88.5% (King et al., 2011) compared to that of oral penicillin that ranges from 50% to 60% (Patel et al., 2010).

Many of these patients get blood transfusions occasionally whenever there is symptomatic anemia, aplastic crisis, splenic or hepatic sequestration, acute chest syndrome or acute multi-organ dysfunction with severe anemia and in cases of preparation of these patients for a major surgery (Chukwuemeka et al., 2015). The use of hydroxyurea in patients with SCD reduces the frequency of sickle cell-related pain, the incidence of acute chest syndrome and blood transfusions by about 50% (Kumar et al., 2014) majorly by inducing fetal hemoglobin.

Studies show that proguanil is effective, affordable, and safe for long-term use as chemoprophylaxis in patients with SCD in sub-Sahara Africa where the prevalence of malaria is still high (Sadarangani et al., 2009a) and hence most clinicians in this region routinely prescribe proguanil during the follow-up of children with SCD.

Patients with SCD have higher rates of erythropoiesis and hence it is postulated that they are likely to develop folate deficiency hence, these patients need at least 1 mg of oral folic acid daily as supplement for the reducing folic acid stores and also to reduce the effects of anemia (Dixit et al., 2016) even though a Cochrane review of 2016 concluded that there was inadequate evidence to support the effects of folic acid supplementation on anemia and its associated presentation in patients with SCD and could possibility result in high blood levels of folate (Dixit et al., 2016).

Patients with SCD are to undergo yearly primary prevention of stroke by screening all those aged between 2 to 16 years using a transcranial doppler ultrasound in order to identify those at greatest risk for administration of chronic transfusions and disease modifying therapies like hydroxyurea (Russo et al., 2019).

To minimize the effects of chronic anemia in the patients with SCD, there is often a requirement of chronic transfusions, which is usually monthly in order to decrease the percentage of HbS in the blood. This effectively prevents complications of the disease like stroke and greatly leads to improved patient health-related quality of life (Yawn & John-Sowah, 2015). Due to the frequent blood transfusions the patients with SCD are to be on iron chelation therapy to effectively remove excess iron (Ballas et al., 2018).

All patients with SCD who are aged nine months and older should be started on hydroxyurea, which works primarily by increasing the level of fetal hemoglobin (HbF), a hemoglobin type that does not sickle. Hydroxyurea reduces the frequency of VOCs and acute chest syndrome, it also reduces mortality, and decreasing the need for RBC transfusions and hospitalizations (Charache et al., 1995).

2.6 Complications

Acute chest syndrome (ACS) is one of the life-threatening vaso-occlusive complications in SCD and in low in-come countries it carries a high mortality rate. The diagnosis by most clinicians is based on fever, pain, increased respiratory effort, low pulse oximetry values and new lung infiltrate on chest radiograph. In sub-Saharan Africa, it is typically treated with a broad-spectrum antibiotic to cover encapsulated organisms and a macrolide antibiotic to cover mycoplasma and chlamydia, pain control and hydration, oxygen and/or blood transfusion, if needed and available (Ansong et al., 2013).

A study of 2047 patients with SCD in sub-Saharan Africa evaluating the association between steady-state hemolysis and vascular complications (Dubert et al., 2017) found supporting data as

in high-income countries that anemia was associated with elevated tricuspid regurgitant jet (TRJ) velocity, microalbuminuria (Drawz et al., 2016), and leg ulcers (Minniti et al., 2011). However, the researchers of this study underscored that in Africa, the major etiologies of relative anemia in SCD may be different from high-income countries because of other key determinants such as malnutrition and infectious diseases.

One of the leading causes of mortality in patients with SCD are the cardiopulmonary complications that include asthma, chronic lung disease and pulmonary hypertension (Parent et al., 2011).

Avascular necrosis of the femoral head is one of the long-term orthopedic complications in adults with SCD. The required treatment for these patients should include physical therapy and surgical interventions. However in sub-Saharan Africa, few tertiary health facilities are able to provide surgical interventions (Ansong et al., 2013).

There is a recommended routine urinalysis on every scheduled visit and screening for hematuria and proteinuria every six months because renal complications are common in patients living with SCD. Early referral to nephrologist should be sought in cases of persistent proteinuria or other nephropathy to slow the risk of progression of sickle nephropathy (Drawz et al., 2016).

2.7 Medication Adherence Measurement Techniques

The precise determination of adherence to any treatment protocol directly affects the measurement of its effectiveness and further informs planning of treatment (Lo, 2003). There are two approaches to medication adherence measurement.

Subjectively, the caregivers and patients could be asked to measure their adherence behavior in an approach called self-report (Osterberg & Blaschke, 2005). In this adherence measurement strategy,

if it is done by health care professionals there is the tendency of overstating the level of adherence for their patients whereas if it is by the patients, the reports could skew to extremes of great precision if they are truthful and great inaccuracy if they deny non-adherence (Farmer, 1999). Subjective medication adherence measurement is done using patient or investigator administered questionnaires. These are designed to assess the determinants of human behavior as relates to medical adherence.

The other approaches are objective, these are generally viewed as a build-up of the subjective methods (Osterberg & Blaschke, 2005), although they have challenges in evaluating the effects of human behavior on medication adherence and are costly (Jimmy & Jose, 2011). Pill counts is one of the main objective method of measuring medication adherence. This method is easy and widely used. The pills that remain can be counted at the scheduled follow-up appointments though there can be discrepancies in counting resulting in mal estimation of adherence. This may also give some details including when the medicines are taken and the trends of missing pills (Osterberg & Blaschke, 2005).

The Medication Event Monitoring System (MEMS) is another objective approach. It is a technology-based approach which keeps memory of the specific pattern of the dates and times in which the vessel containing the medicines was opened. Though it gives a more precise detailing on the way the patient takes the medicine it is expensive and hence less widely used (Lam & Fresco, 2015).

The use of computer databases in the pharmacies where the patients get their medicines could be a good record of prescriptions, the issuing and subsequent refilling of the medicines. This system assumes that the medicines taken are used which is not always so. In addition, patients are also likely to get the supplies to their prescriptions from chemists or other pharmacies (Jimmy & Jose, 2011).

The use of biomarkers is a biochemical strategy for measuring medication adherence. In this method, the biomarkers are incorporated to medicines and tracking done in the body fluids (usually urine and blood). The disadvantage of this approach is that it is invasive and also directly impacted by individual variations of absorption and excretion of the medicine.

It is important to note that there is definitely no "gold standard tool" for measuring medication adherence and its determinants and hence there is documented application of mixed approaches (Lam & Fresco, 2015) and therefore the selected approach should have adequate validity and reliability (Farmer, 1999). Recently, a caucus of medication adherence research experts from a wide spectrum of diseases advocated for the use of self-report adherence measurement techniques due to their high specificity (Stirratt et al., 2015).

In this study we employed the use of the hospital injection records and Brief Medication Questionnaire, a subjective strategy which explores medication-taking behavior and barriers to adherence. This tool has three components that screen for three aspects of medication adherence - the medication regime, the participant's belief and the recall. This tool is preferred in clinical

settings because it caters for multiple drug regimens, ability for self-administration, and reduced need for health workers training as demonstrated by Svarstad et al (Lam & Fresco, 2015).

A systematic review in 2014 reported that several factors affected medication adherence in patients with SCD including drug factors (e.g. preventive antibiotic adherence was higher when given parentally than orally), wrong doses, dread for adverse effects, and forgetting to take medications. This study also documented that medication non-adherence caused increased episodes of vaso-occlusive crises and hospital admissions (Walsh & Sarah, 2017).

CHAPTER THREE

3.0 METHODOLOGY

3.1 Study Setting

The study was conducted at Webuye County Hospital. The hospital is located in Bungoma County in Western Kenya. It stands on a 37-acre piece of land along the Eldoret-Bungoma highway, just below the Chetambe Hills. The hospital has an immediate catchment population of 98,494 people. It is a high capacity level 4 hospital serving as a referral for other peripheral facilities. It has a bed capacity of 217 beds. It offers both out-patient and in-patient services. The facility is also used by Moi University in the training of the registrars in Family Medicine.

3.2 Study Design

This was a prospective observational study. Patients with SCD who were registered and scheduled for outpatient clinic follow-up with prescribed preventive medicines were followed up for six months with a two-monthly frequency to document the cumulated number of clinical outcomes. The study period was between 1st April 2018 and 31st December 2018. Recruitment took place from April 2018 to May 2018 while follow-up was from May 2018 to December 2018.

3.3 Target Population

The patients on care for SCD at Webuye County Hospital. As per the hospital records in 2016, 362 patients were registered for follow-up at the outpatient clinic.

3.4 Study Population

Those patients with SCD who were registered for follow-up at the outpatient clinic and met the eligibility criteria.

3.5 Eligibility Criteria

3.5.1 Inclusion Criteria

All patients with SCD aged between 6 months and 18 years and already on follow up at the outpatient clinics were enrolled for the study. The age bracket is based on a study in the same hospital in 2016 that documented that out of the patients studied only one patient had been above 18 years. The six months was because by the time of the study proposal writing and its implementation there was no neonatal screening program and hence there was a general delay in the diagnosis of SCD. The available screening tests also are used for those 6 months and above. It is also worth noting that SCD symptomatology is often delayed to towards the end of infancy when the fetal hemoglobin is replaced by adult hemoglobin.

3.6 Sample Size

In this study, the main exposure was adherence to chemoprophylactic medicines. This study aimed to compare the number of hospitalizations per unit time of 6 months between patients with SCD who adhere to and those who do not adhere to proguanil, folic acid and penicillin. It was anticipated that rate ratios were to be used to compare the two sub-populations. The sample size for the study was determined using the Signorini formula for Poisson regression (Signorini, 1991).

Here is the formula for the minimum sample size calculation:

$$N = \emptyset \frac{\left(Z_{1-\alpha/2}\sqrt{V(b_1|\beta_1 = 0)} + Z_{1-\rho}\sqrt{V(b_1|\beta_1 = B1)}\right)^2}{\mu_T e^{\beta_o} B1^2 (1 - R^2)}$$

Where

$$V(b_1|\beta_1 = 0) = \frac{1}{Var(X1)}$$

$$V(b_1|\beta_1 = B1) = \frac{1}{1 - \pi_{x1}} + \frac{1}{\pi_{x1} e^{\beta 1}}$$

$$V(X1) = \pi_{x1}(1 - \pi_{x1})$$

$\emptyset$ = 1 - assuming no over dispersion

e^{β_o} = 0.33 - there was to be an approximated average number of two hospitalizations within six months (Adegoke et al., 2014)

μ_T = 1 - there was to be cumulation of the number of hospitalizations once at the end of six months

π_{x1} = 0.5 - the estimated prevalence of level of medication adherence was 50% (Lo, 2003)

$e^{\beta 1}$ = 1.5 - there was an estimated 70% increase in the number of hospitalizations among the non-adherent participants (Cronin et al., 2019)

R^2 = 0.1

Using the above formula and estimates, the supposed minimum sample size of 137 was to be sufficient to estimate for at least three outpatient visits in 6 months at 95% confidence level with a power of 80%.

3.7 Sampling Technique

A consecutive sampling technique was employed in the recruitment of the study participants. This is because we anticipated to have a minimum sample size of 137 out of the expected approximately 180 out of 362 registered patients with SCD in the first 6 months. Criteria for recruitment was prepared at the beginning of the study for patients who had been on follow-up in the outpatient clinic. All the patients with SCD who met the eligibility criteria were enrolled and a tag with the study number put on their files. Recruiting went on for the subsequent clinic days until the required sample size of 137 was attained. A day prior to the clinic days, the research assistant with the help of the hospital records staff would go through all the files of those participants already enrolled and were due for the visit to confirm the unique identifiers and due dates. This was done until all the participants were followed-up for six months.

3.8 Study Procedure

The Webuye County Hospital protocol for the management of patients on scheduled outpatient visit for SCD are that patients below 5 years were scheduled for monthly visits whereas those above 5 years were scheduled for every 2 months. Participants were also asked to seek treatment in case of acute illness in between the scheduled clinics. In this study, participants were seen after every two months (3 times in the six months of follow-up) to document the frequency of clinical outcomes.

All the participants like the other patients with SCD had prescriptions of:

Folic acid, which was prescribed at a dose of 2.5mg/day

Proguanil, which was prescribed as shown below:

Age	**Weight**	**100mg tablet**
Under 8 months	5 - 8 kg	¼ tab/day
8 months to 3 years	9 - 16 kg	½ tab/day
4 to 7 years	17 - 24 kg	¾ tab/day
8 to 10 years	25 - 35 kg	1 tab/day
11 to 13 years	36 – 50 kg	1 ½ tab/day
14 years and over	50 kg and over	2 tab/day

Figure 1: Proguanil age-based dosages for patients with SCD

A monthly parenteral benzathine penicillin was prescribed for those under five years as follows: 300,000 IU dose for children below 10kg, 600,000 IU for those with weights between 10 and 27kg and 1,200,000 IU for those over 27kg.

The pneumococcal vaccine was indicated but at the time of the study it was out of stock in the hospital pharmacy. Hydroxyurea was also prescribed according to the local protocols, but its supplies and affordability was very variable at the time of the study.

In the study, a targeted baseline history and physical examination of all the participants was done. There was confirmation of the prescription of proguanil, folic acid and penicillin prophylaxis as required. The prophylaxis response was evaluated during the scheduled follow-up visits by recording the frequency of hospitalizations, acute febrile illnesses, blood transfusions and acute painful crises.

Study interviews were done prior to receiving the recommended routine care on their scheduled visit day every 2 months. All the study participants were attended to by the clinicians assigned to the outpatient clinics just like all the other patients with SCD. They all received medical education and counseling about their condition, the importance of adequate hydration, consistent use of treated mosquito nets, the requirement and importance of adherence to prescribed medication and scheduled outpatient visits as part of their routine care.

Patients with other comorbidities like infections, anemia, and malnutrition were treated as per set guidelines and protocols. Hospital admission was done as per the hospital protocols.

3.9 Data Collection

Data was collected by the principal investigator assisted by an on-site research assistant that was trained beforehand by the principal investigator. All the participants that met the inclusion criteria filled an investigator administered questionnaire. The questionnaire was translated into Kiswahili and subjected to a process of forward and backward translation. The accuracy and meaning of the translated versions both forward and backward were checked, and recommended amendments where necessary were discussed before being finalized.

The questionnaire was pretested on 20 patients with SCD and their guardians at the Webuye County Hospital child health outpatient triage for content, design, readability and comprehension, and necessary modifications made to make it simple to understand and answer to ensure accurate data capture and validity. The final version of the pre-tested questionnaire was composed of four sections, containing both open-ended and closed questions to collect socio-demographic characteristics of the participants including age, gender, and the parent's/guardian's marital status, educational level, family monthly income and health insurance cover.

Confirmation of the diagnosis of SCD was done by reviewing evidence of laboratory documentation in the patient records. The prescription of penicillin injection, proguanil and folic acid was also confirmed in the patients' files.

The participant's history and physical examination were done at the initial visit. Data about the clinical variables of the study population including number of hospital admissions, blood transfusions, acute febrile episodes and acute febrile illnesses was recorded at the end of the 6 months by accumulating the recordings on a standard follow-up proforma.

The evaluation of adherence to proguanil and folic acid was done by filling the interviewer administered Brief Medication Questionnaire (BMQ) at the last visit of follow-up. The hospital injection register was inspected for the participants who were on the penicillin injection to prove receipt of the same on the scheduled follow-up days.

The data collected from the participants was used to evaluate the level of adherence to proguanil, folic acid and benzathine penicillin injection. It was also used to assess associations of hospitalizations, blood transfusions, febrile illnesses and painful episodes in the adherent and the non-adherent groups.

3.10 The Brief Medication Questionnaire (BMQ)

This is a self-report medication adherence measurement tool that has nine items including the initial five items that evaluate the regimen, the next two items assessing belief and the last two items evaluating the recall. The instrument's total score consists of the sum of the scores of its three sections. Participants receive a score of 1 if their response indicates potential non-adherence and 0 if it indicates adherence. The score for the regimen screen ranges from 0 - 7, and the belief and recall screens both range from 0 - 2. Thus, the maximum total BMQ score is 11 and any score greater than 0 for any one of the sections indicates potential non-adherence to prescribed treatment.

The BMQ classifies participants into the following categories:

1) Adherence (no positive response in any domain)
2) Probable adherence (positive response in one domain)
3) Probable low adherence (positive responses in two domains)
4) Low adherence (positive responses in all three domains)

In this study participants were defined as adherent if they scored for adherence and probable adherence and non-adherent if they scored for low adherence and probable low adherence. Overall

drug adherence was for all participants who met the criterion of adherence for both proguanil and folic acid.

The BMQ is a tool that was validated using Medication Events Monitoring System (MEMS) in twenty patients and its sensitivity varied from 80% to 100% and specificity from 90% to 100% and hence making it superior to other existing tools that are used in determining adherence to medications (Svarstad et al, 1999). The BMQ has also been validated and used to evaluate adherence in patients with SCD in Kenya (Badawy et al., 2017).

3.11 Data Management and Statistical Analysis

The questionnaires were checked for completeness by the researcher. Data was entered in an excel database and exported to STATA version 14 where data coding, cleaning and analysis was done.

Descriptive statistics such as measures of central tendency and measures of spread were used for continuous variables while frequency and proportions were tabulated for categorical variables.

Total BMQ score was classified into two categories, adherence and non-adherence to measure adherence to proguanil and folic acid. The rate of hospitalizations, blood transfusions, febrile illness and painful episodes were compared between the two groups using poison regression where incidence rate ratios were reported. Statistic and corresponding confidence interval were reported at 0.05 alpha level of significance.

3.12 Study Limitations

The use of the BMQ, a self-report measure of adherence to proguanil and folic acid, is subjective and may be limited by recall bias and social desirability. Nonetheless, this technique has been used in earlier studies of chronic illnesses including SCD and even the locally. It also has hight sensitivity and specificity in previous studies. Additionally, self-report adherence measures correlate with other objective biomarkers of other medicines used in SCD.

Even though hospitalizations, blood transfusions, episodes of fever and pain are key distractions in a patients' life, there is still the likelihood of inaccurate recall of these events. Future studies to evaluate the accuracy of participant reported frequency of these events could help to support our findings.

In this study participants were consecutively recruited, this may have introduced a selection bias, nonetheless, the participants were not included basing on the disease severity, social determinants nor age hence greatly mitigating for this bias.

3.13 Ethical Considerations

Approval was granted by Moi University IREC before the study was commenced. The approval number is IREC Approval Number 0003066 as attached in the appendix. Permission for the study was also granted by Webuye County Hospital management.

A written informed consent was obtained from all participants by having the consent form administered by the principal investigator to the participant's caregiver and verbal assent obtained for all children above seven years.

The purpose, objectives and design of the study was fully explained to the hospital administration and participants. The participants were assured of the voluntary nature of participation and their right to opt out at any stage of the study.

The subjects were clearly informed that there were neither incentives nor any form of payment for participation. Confidentiality was maintained and participants assured that there was no victimization in any way as a result of their response. Anonymity was maintained partly by ensuring that the participants were not compelled to use their real names.

There were no invasive procedures to the participants of the study. The investigators also ensured that the participants were comfortable through the entire data collection period.

The questionnaires were secured under lock and key and was accessible only to the primary researcher. The participants were assured that the data was to be used for research purposes only.

The participants, the hospital and Moi University will benefit from the study in form of the continuous professional development and feedback on the research findings, conclusion and recommendations.

CHAPTER FOUR

4.0 RESULTS

4.1 Introduction

The results herein are based on 137 patients with SCD on follow-up at Webuye County Hospital outpatient clinics.

4.2 Socio-demographic Characteristics

The age of the participants at recruitment ranged from 6 months to 17.5 years with a median age of 5 years (IQR 3.5, 9). Males were 69 (50.4%) compared to females 68 (49.6%). There was no significant difference (p = 0.420) in the average age between females (median 5.4 years, IQR 3.3, 9) and males (median 5 years, IQR 3.5, 8). The age of patients at diagnosis of SCD ranged from 1 month to 17 years with an average of 2.4 years (IQR 1, 4.9). There was no significant difference (p = 0.326) between the average age of diagnosis between females (Median 2.5 years, IQR 1, 5.6) and males (median 2.3 years, IQR 1, 4).

4.3 Medication Adherence Level Based on the BMQ Scores

Variable	**Category**	**Frequency**	**Percentage**
Proguanil adherence	Adherence	98	75.38
	Non-adherence	32	24.62
Folic acid adherence	Adherence	111	85.38
	Non-adherence	19	14.62
Overall drugs adherence	Adherence	97	74.62
	Non-adherence	33	25.38

Table 1: Summaries of the adherence levels of proguanil and folic acid based on the BMQ scores
All the study participants had complete adherence to the monthly benzathine penicillin injection as recorded in the hospital outpatient injection book. Proguanil and folic acid adherence scores were 75.4% and 85.4% respectively. The overall adherence to both proguanil and folic acid was 74.6%.

4.4 Sickle Cell Disease Details at Recruitment of Participants

Variable	Category	Adherent Frequency (%) (n=97)	Non-adherent Frequency (%) (n=33)	Total (%) (n=130)
Confirmed diagnosis	Yes	97(74.6)	33(25.4)	130
Medication	Penicillin	49(81.7)	11(18.3)	60
	Folic acid	97(74.6)	33(25.4)	130
	Proguanil	97(74.6)	33(25.4)	130

Table 2: Details of SCD in the participants

The diagnosis of SCD was done to all participants through clinical and sickling test methods, a peripheral blood film and confirmatory hemoglobin electrophoresis was done for 31(24%) and 21(16%) of the participants respectively. All participants were on proguanil and folic acid while those scheduled for the monthly benzathine penicillin injection were 60 (46.2%).

4.5 Participant's Caregiver Details

Variable	Category	Adherent Frequency (%) (n=97)	Non-Adherent Frequency (%) (n=33)	Total (n=130)
Caregivers relationship with participant	Mother	74(75.5)	24(24.5)	98
	Grandmother	13(68.4)	6(31.6)	19
	Father	5(71.4)	2(28.6)	7
	Others	5(80.0)	1(20.0)	6
Education level of the caregiver	No	8(72.7)	3(27.3)	11
	Primary	48(73.8)	17(26.2)	65
	Secondary	26(72.2)	10(27.8)	36
	Tertiary	15(83.3)	13(16.7)	18
Caregiver marital status	Married	87(77.7)	25(22.3)	112
	Separated	6(60.0)	4(40.0)	10
	Single	4(57.1)	3(42.9)	7
	Widow	0(0)	1(100)	1
Monthly income	≤ 2500	26(68.4)	12(31.6)	38
	2501 - 4000	19(73.1)	7(26.9)	26
	4001 - 7000	26(74.3)	9(25.7)	35
	≥ 7001	26(83.9)	5(16.1)	31
NHIF	No	71(71.7)	28(28.3)	99
	Yes	26(83.9)	5(16.1)	31

Table 3: Participants' caregiver's details

Three-quarters of the participants were under the care of mothers. About 54% of the caregivers had attained secondary and tertiary education level. The caregivers' monthly income ranged from Kshs. 500 to 43,000 with only 23% having the NHIF insurance cover.

4.6 Abnormal Clinical Signs at Recruitment of Participants

Variable	Adherence Frequency (%) (n=97)	Non-adherence Frequency (%) (n=33)	Total (n=130)
Pallor	62(73.8)	22(26.2)	84
Respiratory rate	27(71.1)	11(28.9)	38
Heart rate	9(75.0)	3(25.0)	12
Jaundice	91(75.2)	30(24.8)	121
Abnormal temperatures	26(66.7)	13(33.3)	39
Skeletal findings	9(56.3)	7(43.7)	16
Cardiac findings	22(73.3)	8(26.7)	30
Other findings	52(72.2)	20(27.8)	72
Hepatomegaly	80(72.7)	30(27.3)	110
Splenomegaly	26(72.2)	10(27.8)	36

Table 4: Summary of the abnormal clinical signs of the participants at recruitment

Approximately 65% of the patients had a degree of pallor. Abnormal respiratory rates were found in 29% of the participants. About 9% of the participants had deranged heart rates. Scleral jaundice was in 92% of the participants. Deranged axillary body temperatures were found in 31% of the participants. Abnormal skeletal findings including swelling, deformities or features of osteomyelitis were recorded in 12% of the participants. Hepatomegaly and splenomegaly were found in 85% and 29% of the participants respectively. Other clinical abnormalities including tonsillar hypertrophy, stroke sequelae, features suggestive of fungal infections of the skin were found in 55%.

4.7 The Outcomes Within 6 Months of Follow-up

Variable	Category	Adherent Frequency (%) (n=97)	Non-Adherent Frequency (%) (n=33)	Total (n=130)
Hospitalizations	0	59(77.6)	17(22.4)	76
	1	20(76.9)	6(23.1)	26
	2	13(86.7)	2(13.3)	15
	>2	5(38.5)	8(61.5)	13
Blood transfusions	0	87(82.1)	19(17.9)	106
	1	9(47.4)	10(52.6)	19
	2	0(0)	3(100)	3
	>2	1(50)	1(50)	2
Acute febrile illnesses	0	8(88.9)	1(11.1)	9
	1	4(80)	1(20)	5
	2	24(85.7)	4(14.3)	28
	>2	61(69.3)	27(30.7))	88
Acute painful episodes	0	11(68.7)	5(31.3)	16
	1	11(78.6)	3(21.4)	14
	2	18(85.7)	3(14.3)	21
	>2	57(72.2)	22(27.8)	79
Use of mosquito net	Yes	90(77.6)	26(22.4)	116
	No	7(50)	7(50)	14

Table 5: Frequency of the clinical outcomes within six months of follow-up

Within the six months of follow-up, six participants were lost to follow up while one had died at home of an unidentified cause, hence the analysis on the table above involved 130 participants (n=130). Participants who were hospitalized during the period were 54. Out of this 54, 26 had one hospitalization, 15 had two hospitalizations, 13 had more than three hospitalizations. Blood transfusion was administered to 8% of the participants.

Over the six months period, 93% had acute febrile illnesses that ranged from 1 to 32 episodes with 68% of these having more than three episodes. Acute painful episodes were recorded in 88% of the participants with the frequency ranging from 1 to 28 and a majority of 61% having more than three episodes. Over that period, 89% of the participants reported as having used mosquito nets.

4.8 Association Between Adherence to Proguanil and Folic acid and the Frequency Hospitalizations, Acute Febrile Illnesses, Blood Transfusions

4.8.1 Association Between Adherence to Proguanil and Folic Acid and the Frequency of Hospitalizations

		Hospitalizations within 6 months		
Factor	Category	IRR	p-value	[95% CI]
Folic acid adherence	Adherence	1		
	Non-adherence	2.05	0.027	[1.085 – 3.880]
Proguanil adherence	Adherence	1		
	Non-adherence	1.72	0.056	[0.986 – 3.009]

Table 6: The association between adherence to proguanil and folic acid and hospitalizations

The rate of hospitalizations increased 2.05 times among those who have low adherence to folic acid as compared to those who were adherence (IRR=2.05, p=0.027, 95% CI 1.08 – 3.88).

4.8.2 Association Between Adherence to Proguanil and Folic acid and the Frequency of Acute Febrile Illnesses

		Acute febrile illness within 6 months		
Factor	Category	IRR	p-value	[95% CI]
Folic acid adherence	Adherence	1		
	Non-adherence	1.44	0.086	[0.948 – 2.208]
Proguanil adherence	Adherence	1		
	Non-adherence	1.33	0.142	[0.907 – 1.976]

Table 7: The association between adherence to proguanil and folic acid and acute febrile illnesses

The rate of acute febrile illnesses within six months for the non-adherent to folic is 1.44 times higher than the rate among the adherent (IRR=1.44, p=0.086, 95% CI 0.948 – 2.208). The rate of acute febrile illnesses within six months for the non-adherent to proguanil is 1.33 times higher than the rate among the adherent (IRR=1.33, p=0.142, 95% CI 0.907 – 1.976).

4.8.3 Association Between Adherence to Proguanil and Folic Acid and the Frequency of Blood Transfusions

		Blood transfusions within 6 months		
Factor	Category	IRR	p-value	[95% CI]
Folic acid adherence	Adherence	1		
	Non-adherence	4.21	<0.001	[1.974 – 9.018]
Proguanil adherence	Adherence	1		
	Non-adherence	4.24	<0.001	[1.913 – 9.397]

Table 8: The association between adherence to proguanil and folic acid and the blood transfusions

The number of blood transfusions within six months for the non-adherent to folic acid is 4.21 times higher than the rate for the adherent (IRR=4.21, $p<0.001$, 95% CI 1.974 – 9.018). The number of blood transfusions within six months for the non-adherent to proguanil is 4.21 times higher than the rate for the adherent (IRR=4.24, $p<0.001$, 95% CI 1.913 – 9.397).

4.8.4 Association Between Adherence to Proguanil and Folic acid and the Frequency of Painful Episodes

		Painful episodes within 6 months		
Factor	Category	IRR	p-value	[95% CI]
Folic acid adherence	Adherence	1		
	Non-adherence	1.86	0.005	[1.202 – 2.894]
Proguanil adherence	Adherence	1		
	Non-adherence	1.52	0.044	[1.011 – 2.290]

Table 9: The association between adherence to proguanil and folic acid and painful episodes

The frequency of painful episodes within six months is 1.86 times more in the non-adherent to folic acid as compared to the adherent participants (IRR=1.86, p=0.005, 95% CI 1.202 – 2.894). The frequency of painful episodes within six months is 1.52 times more in the non-adherent to proguanil as compared to the adherent participants (IRR=1.52, p=0.044, 95% CI 1.011 – 2.290).

4.8.5 The Association Between Adherence and Participant Caregiver Characteristics

Variable	Category	Adherent (n=97)	Non-Adherent (n=33)	p-value
Caregivers relationship with participant	Parent	79	26	0.738[c]
	Relative	18	7	
Education level of the caregiver	Illiterate/primary	56	20	0.219 [c]
	Secondary/tertiary	41	23	
Marital status of the caregiver	Married	87	25	0.045 [c]
	Not married	10	8	
Monthly income	≤ 2500	26	12	0.531 [c]
	2501 - 4000	19	7	
	4001 - 7000	26	9	
	≥ 7001	26	5	
NHIF	Don't have	71	28	0.175 [c]
	Have	26	5	

[c] Chi Square test

Table 10: The association between adherence and participant caregiver characteristics

None of the caregiver's characteristics had statistically significant associations with overall medication adherence.

4.8.6 The Association Between Adherence to Folic Acid and the Participants' Clinical Characteristics

Variable	Category	Adherence to folic acid		p-value
		Adherent	Non-adherent	
Pallor	None	25	21	0.018[c]
	Mild/moderate	28	56	
Respiratory rate	Normal	42	50	0.078[c]
	Abnormal	11	27	
Heart rate	Normal	49	69	0.761[f]
	Abnormal	4	8	
Jaundice	No	6	3	-
	Yes	47	74	
Fever	No	38	53	0.726[c]
	Yes	15	24	
Skeletal findings	Normal	50	64	0.056[c]
	Abnormal	3	13	
Cardiac findings	Normal	39	61	0.454[c]
	Abnormal	14	16	
Other findings	Normal	27	31	0.229[c]
	Abnormal	26	46	
Hepatomegaly	0 (normal)	14	6	0.004[c]
	1-14 (abnormal)	39	71	
Splenomegaly	0 (normal)	45	49	0.008[c]

	1-10 (abnormal)	8	28

[c] Chi Square; [f] Fisher Exact Test

Table 11: The association between adherence to folic acid and the participants' clinical characteristics

Pallor, hepatomegaly and splenomegaly were statistically associated with adherence to folic acid.

4.8.7 The Association Between Adherence to Proguanil and the Participants' Clinical Characteristics

Variable	Category	Adherence to proguanil		P-value
		Adherent	Non-adherent	
Pallor	None	18	28	0.051[c]
	Mild	16	43	
	Moderate	3	22	
Respiratory rate	Normal	29	63	0.229[c]
	Abnormal	8	30	
Heart rate	Normal	36	82	0.177[f]
	Abnormal	1	11	
Jaundice	No	5	4	-
	Yes	32	89	
Temperatures	Normal	29	62	0.189[c]
	Abnormal	8	31	
Skeletal findings	Normal	36	78	0.039[f]
	Abnormal	1	15	
Cardiac findings	Normal	31	69	0.242[c]
	Abnormal	6	24	
Other findings	Normal	21	37	0.079[c]
	Abnormal	16	56	
Hepatomegaly	0 (normal)	12	8	0.001[c]

	1-14 (abnormal)	25	85	
Splenomegaly	0 (normal)	32	62	0.023[c]
	1-10 (abnormal)	5	31	

[c] Chi Square; [f] Fisher Exact Test

Table 12: The association between adherence to proguanil and the participants' clinical characteristics

Abnormal skeletal findings, hepatomegaly and splenomegaly were statistically associated with adherence to proguanil.

CHAPTER FIVE

5.0 DISCUSSION

5.1 Introduction

Among patients with SCD below the age of 18 years, this study evaluated the level of adherence to the monthly benzathine penicillin injection, proguanil and folic acid. The effect of this level of adherence was correlated with morbidity in these patients.

Clinical Findings

Approximately 65% of the patients had a degree of pallor. The participants who had deranged respiratory rate were 29%. About 9% of the participants had deranged heart rates. Scleral jaundice was in 92% of the participants. Deranged axillary body temperature was recorded in 31% of the participants. Abnormal skeletal findings were in12% of the participants. This study found that 85% and 29% of the participants had hepatomegaly and splenomegaly respectively, these findings are unlike what was found in a cohort study in Kilifi, Kenya which found that 20% and 33% had clinically detectable hepatomegaly and splenomegaly respectively (Sadarangani et al., 2009).

Tachycardia or irregular heart rate was recorded in 22% of the participants. Other findings including tonsillar hypertrophy and fungal infections of the skin was listed in 55% of the participants.

5.2 The Level of Adherence to Medicines

In this study we found that the level of adherence to proguanil and folic acid according to the BMQ scores was 75.4% and 85.4% respectively. All the studied participants who were on

benzathine penicillin injection had 100% adherence. Walsh et al in their 2014 systematic review found the adherence to penicillin injectables in patients with SCD to be 90%, which was slightly lower than this study but by far better than the documented adherence of between 40% to 71.2% for oral penicillin. Another systematic review of 2016 documented similar results of the adherence rates of penicillin prophylaxis in patients with SCD to range from 12% to 100% (Loiselle et al., 2016).

The level of adherence to proguanil was at 75.4% which was way higher than 43% (Olaosebikan et al., 2015) that was found in a Nigerian study. Unlike this study, the Nigerian study was a randomized controlled trial and the researchers defined adherence as use of more than three-quarters of the prescribed pills. They also used pill count as the technique of assessing adherence. A cross-sectional study of 100 participants in Nigeria found a higher adherence to proguanil as reported by caregivers of children living with SCD with a mean adherence rate of 88.2% unlike what was found in this study (Fowora, 2017).

The adherence level of folic acid was 85.4%, which was higher than what was found in a 2014 systemic review by K. E. Walsh et al., 2014 that reported it at 61%. A Nigerian study reported a higher adherence rate of 95.7% to folic acid unlike the 85.4% found in this study. This result was somewhat expected as folic acid is the least expensive and easiest to use of all the medications in sickle cell disease (Fowora, 2017). In 2010, a USA retrospective cohort study of 93 participants reported that folic acid had the highest adherence rates among all the medications that he studied even though he reported an adherence rate of 61.3% which was lower than the 85.4% in this study (Patel G. et al., 2013).

The overall medication adherence score for both proguanil and folic acid was 74.6%, which was lower compared to the 92% found in a study in Kilifi, Kenya (Sadarangani et al., 2009). This is likely because in that study the adherence was just a report of the patient's caregiver without using a validated technique to evaluate adherence.

In a study of 64 participants in the USA state of Philadelphia on the effect of medication adherence to the quality of life among patients living with SCD, overall adherence was 84.2% unlike the 74.6% recorded in our study (Barakat et al., 2005). The high adherence score in that study could have been because it was a self-report using a non-validated questionnaire.

5.3 Frequency of the Clinical Outcomes

The number of participants who had hospitalizations within the 6 months of follow-up was 54 out of 130, this represents 42% of the participants. Out of those who were hospitalized, 48% had one hospitalization, 27% had two hospitalizations, 24% had more than three hospitalizations. This is lower than what was reported by a retrospective study in Ibadan, Nigeria that had 161 children aged between 9 months and 18 years and 85.6% had one admission each, 12.6% had two admissions each and 1.7% had three admissions each. The higher rate of hospitalizations in the Nigerian study could have been because of the high cost of proguanil, causing inconsistencies in its use and the participants did not routinely receive the penicillin prophylaxis in their clinic (Brown et al., 2012). A Tanzanian cross-sectional study found that in the 12 months preceding the study, 69.4% had been hospitalized once and 27.4% had been hospitalized twice or more times. In

the participants' lifetimes, 40.3% had been hospitalized ≥ 5 times and 0.8% had been hospitalized > 10 times (Saidi et al., 2016).

Eight percent of the participants had blood transfusion within the six months of follow-up. This was lower than what was reported in a recent cohort study in Kilifi that found that the most common reason for hospitalization among patients with sickle cell disease was severe anemia requiring blood transfusion (Uyoga et al., 2019). This is also unlike a Nigerian study that reported that 39.1% of all the patients got blood transfusion during hospitalization (Brown et al., 2012).

Over the six months of follow-up 93% of the participants had episodes of acute febrile illnesses that ranged from 1 to 32 with 68% of these having more than 3 episodes. This agrees with most studies in developing countries having malaria endemicity and inconsistent availability and use of the pneumococcal and influenzae vaccines by patients living with SCD.

Acute painful episodes were found in 88% of the participants, episodes ranged from 1 to 28 with 61% of these having more that 3 episodes within the six months of follow-up. Our findings compare with what Shapiro et al documented based on pain diaries among school-going children with SCD that on average they experience two pain episodes a month lasting about 4 days, miss school on 41% of pain days, and are hospitalized for 16% of their pain episodes. A US emergency department study that found that the main complain at the casualty among patients with SCD was pain in 67% of the cases (Daniel et al., 2017). The lower episodes reported in study could be attributed to the other interventions like hydroxyurea and routine chronic blood transfusion regimens that the patients with SCD in the US are subjected to.

5.4 Relationship Between Adherence and Clinical Outcomes

5.4.1 Non-adherence to Folic Acid

In this study the incidence of hospitalizations, blood transfusions, acute febrile illnesses and painful episodes increased 2.05, 4.21, 1.44, 1.86 times in the non-adherent to folic acid. This is in contrast to the none effect on disease morbidity concluded in a systematic review of the effectiveness of consistent folic acid supplementation (Ruchita Dixit et al., 2018). Other previous studies have had conflicting results on the effect of folic acid supplementation in patients living with SCD with some suggesting improved outcomes in reduction in the frequency of dactylitis while others even citing adverse events with its use. These conflicting results may be due to genetic polymorphisms in folic acid/homocysteine metabolism between patients, inconsistent supplementation doses and various ethnic group representations in the different studies.

5.4.2 Non-adherence to Proguanil

The incidence of painful episodes within six months was 1.52 times more in the non-adherent to proguanil as compared to the adherent participants (IRR=1.52, p=0.044, 95% CI 1.011 – 2.290)

The incidence of blood transfusions and acute febrile illnesses in the non-adherent to proguanil was increased 4.24 and 1.33 respectively (IRR=4.24, p<0.001, 95% CI 1.913 – 9.397). This can be explained because malaria causes increased hemolysis and severe anemia. An RCT of 97 children in Nigeria confirmed that consistent use of malaria chemoprophylaxis using proguanil or pyrimethamine may be more effective than placebo at reducing sickle cell crises and hospital admissions in children with sickle cell disease in an area of malaria endemicity (Oluseyi Oniyangi & Omari, 2019). The increased febrile episodes are likely to have been due to the increased

episodes of symptomatic malaria infections since there was 100% documented adherence to the benzathine penicillin injections that is likely to have reduced the bacterial infections.

This study found that there are worse outcomes among patients who had poor adherence to proguanil and folic acid which agrees with the findings of a cross-sectional study of 115 patients in Cairo, Egypt that concluded that patients who had poor adherence and late initiation of treatment had low WHO-quality of life scores (Al Jaouni et al., 2013).

CHAPTER SIX

6.0 CONCLUSION AND RECOMMENDATIONS

6.1 Conclusion

The adherence level of proguanil, folic acid and monthly benzathine penicillin injection was 75.4%, 85.4% and 100% respectively. This agrees to a great degree with other studies on the subject.

Non-adherence to proguanil was associated with an increased rate of incidence of blood transfusions and painful episodes.

Non-adherence to folic acid was associated with increased rate of incidence of hospitalizations, blood transfusions and acute painful episodes.

Non-adherence to both proguanil and folic acid was not associated with increased rate of incidence of acute febrile illnesses.

6.2 Recommendations

1. All patients with SCD should have medication adherence evaluation during their routine clinic visits.
2. Further studies to identify causes and ways to address non-adherence to proguanil and folic acid in patients living with SCD.

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APPENDIX 1

Informed Consent

Study Number ……

Study title: Relationship between adherence to chemoprophylaxis and morbidity among patients with sickle cell disease in Webuye County Hospital

Invitation to participate

You are invited to participate in this study on Relationship between adherence to chemoprophylaxis and morbidity among patients with sickle cell disease in Webuye County Hospital

Basis for selection

You are eligible to participate in this study since you are on the follow up at the outpatient clinic for sickle cell disease.

Purpose of the study

To determine the relationship between the level of adherence to chemoprophylaxis and morbidity among patients with SCD

Procedures

You will be asked some questions about your personal details and those of the patient and specific questions about your therapy. A prick will be taken for laboratory tests. The patient may be referred for further evaluation if need be.

Potential benefits

There is no financial reward for participation in this study. Knowing the level of adherence to chemoprophylaxis will help to improve care for the patients in the clinic and inform policy.

Potential risks

There are no risks in this study as no invasive procedures will be used. The malaria tests will be done under sterile procedures.

Guarantee of confidentiality

To ensure confidentiality, your name will not appear on any materials or reports of the research findings (including web site postings of the results, conference presentations or publications). Materials associated with this study will be kept under lock and key in a cabinet. The signed consent form will be stored separately from your data to ensure complete confidentiality.

Withdrawal from participation

Participation in this study is voluntary and your decision to or not to participate will not affect your care at Webuye County Hospital. If you decide not to participate, you are free to withdraw your consent and to discontinue your participation at any time.

Offer to answer any questions

If you have any questions about the procedures at any time, please do not hesitate to ask. All questions about the procedures and the study in general will be answered. However, some questions may not be answered until after you have completed the procedures to ensure that the answers will not affect your responses.

Participant's statement

I am voluntarily making the decision to participate and my signature certifies that I have heard and understand the aforementioned information. In addition,my questions have all been answered to my satisfaction and signing this document doesn't mean I waive any legal rights.

Participant's signature …… Date…….

Researcher's statement

In my judgment, the aforementioned participant is voluntarily and knowingly giving informed consent and possesses the legal capacity to do so.

Researcher's name…….

Researcher's signature …… Date……...…….

0725424215

zacheuswere@gmail.com

APPENDIX 2

Fomu ya Idhini

Nambari ya utafiti ……

Ulinganishaji wa kiwango cha kuzingatia matumizi ya dawa za kinga na magonjwa kati ya wagonjwa walio na ugonjwa wa seli-mundu kwenye hospitali ya Webuye

Mwaliko wa Kushiriki

Wewe unaalikwa kushiriki katika utafiti huu 'Ulinganishaji wa kiwango cha kuzingatia matumizi ya dawa za kinga na magonjwa kati ya wagonjwa walio na ugonjwa wa seli-mundu kwenye hospitali ya Webuye'

Msingi wa kuteuliwa

Unafuzu kuwa mshiriki katika utafiti huu kwa sababu unatibiwa ugonjwa wa Seli Mundu katika kliniki ya hospitali

Sababu ya utafiti

Kuamua uhusiano kati ya kiwango cha kuzingatia matumizi ya kinga na matukio ya malaria kati ya wagonjwa walio na ugonjwa wa seli mundu

Utaratibu

Utaulizwa maswali fulani kuhusu maelezo yako binafsi halafu damu itatolewa ili ipelekwe kwenye mahabara kufanyiwa vipimo vya malaria. Unaweza kutumwa kwa tathmini zaidi ikiwa ni lazima kwa gharama yako.

Uwezekano wa faida

Hakuna zawadi ya fedha kwa ajili ya kushiriki katika utafiti huu. Kujua kiwango cha damu itasaidia katika utambuzi wa mapema ili matibabu sahihi na rufaa inapohitajika.

Uwezekano wa hatari

Hakuna hatari katika utafiti huu na hakuna taratibu vamizi zitatumika. Vipimo vya damu vitafanyika chini ya taratibu salama.

Dhamana ya usiri

Kuhakikisha usiri, jina lako halitaonekana kwenye vifaa vyovyote au ripoti ya matokeo ya utafiti (ikiwa ni pamoja na kuweka matokeo kwa mtandao, maonyesho mkutano au machapisho). Vifaa husika na utafiti huu vitawekwa chini ya kufuli na ufunguo. Fomu uliyotia saini ya idhini itahifadhiwa tofauti na takwimu zako ili kuhakikisha usiri kamili.

Kujiondoa kwa ushiriki

Kushiriki katika utafiti huu ni wa hiari na uamuzi wako wakutoshiriki hautaathiri kuhudumiwa kwako katika hosipitali ya Webuye. Unaweza kuondoa ruhusa yako na kusitisha ushiriki wako wakati wowote.

Kujibu maswali

Ikiwa una maswali yoyote kuhusu taratibu wakati wowote, tafadhali usisite kuuliza. Maswali yote kuhusu taratibu na utafiti kwa ujumla yatajibiwa. Katika hali chache yawezekana baadhi ya

maswali yasijibiwe mpaka baada ya kumaliza taratibu ili kuhakikisha kwamba majibu si ya kuathiri majibu yako.

Kauli ya mshiriki

Mimi kwa hiari yangu nafanya uamuzi wa kushiriki na sahihi yangu ni thibitisho kwamba nimesikia na kuelewa maelezo. Pia maswali yangu yote yamejibiwa na nimeridhika. Kusaini hati hii haina maana mimi kuondoa haki yoyote ya kisheria.

Saini ya mshiriki….....Tarehe.....

Kauli ya mpelelezi

Katika hukumu yangu, mshiriki ni hiari na wanajua kutoa ridhaa na ana uwezo wa kisheria kufanya hivyo.

Jina la mpelelezi.....

Saini.....Tarehe.....

0725424215

zacheuswere@gmail.com

APPENDIX 3

Study Questionnaire A

Proforma to be filled at the start of the study

Patient study code …….

Date …….

Age …… Gender …… Current diagnosis……..……

Section A

Sickle cell disease details:

Age at diagnosis (years)	
Method of diagnosis (Tick where applicable)	Clinical……. Sickling test……. Haemoglobin electrophoresis……
Is the patient on scheduled visits?	Yes …… No ……
If yes above, on what medications is the patient using	Penicillin…… Folic acid…….. Proguanil…….. Others (Specify)……

Specific signs:

Pallor …… Respiratory rate …… Heart rate ……...

Jaundice …… Temperature ……

Skeletal findings…….

Hepatomegaly (*specify span in centimetres*)…….

Splenomegaly (*specify span in centimetres*)……..

Cardiac findings…….....

Section B

1) What is the relationship of the respondent to the patient? (*tick where applicable*)

Father	
Mother	
Guardian (Grandparent)	
Others (*specify*) ……	

2) What is the level of education of the respondent?

Illiterate	
Primary	
Secondary	
Tertiary	

3) What is the marital status of the respondent?

Married	
Single	
Divorced	

Separated	
Widowed	

4) What is the approximate level of income of the respondent?

Below Kshs. 2,500 per month	
Between Kshs. 2,501 and 4,000 per month	
Between Kshs. 4,001 and 7,000 per month	
Over Kshs. 7,000 per month	

5) Do you have NHIF cover?

Yes	
No	

APPENDIX 4

Participant's progress card

Proforma is in possession of the participant/investigator and it is to be filled by the attending clinician/investigator in case of any outpatient and/or inpatient care during and even outside of the scheduled visits during the period of study

Patient study code ……..

Date …….

Age …… Gender …… Current diagnosis…..……...

Specific signs:

Pallor ……..… Jaundice……. Respiratory rate……..

Heart rate……. Temperature…….

Management administered:

Slide for Microscopy/Malaria RDT (Specify laboratory results)	
Antimalarial (Specify the agent & duration)	
Antimicrobial (Specify agent & duration)	
Hospital Admission	Yes ……. No ……
Blood transfusion	Yes …….. No ……...

Is the patient febrile without malaria?

System	**Presentation**	**Remarks**
Respiratory	Cough? Fast breathing?	

	Features of respiratory distress?	
Ear infection	Ear discharge Ear drum changes?	
Throat infection	Inflamed tonsils?	
Other (specify)		

APPENDIX 5

Study Questionnaire B

To be filled at the last visit

Patient study code ……..

Date …….

1. How many times was the patient admitted in the last 6 months?

None	
1	
2	
3	
More than 3	

2 How many times did the patient have blood transfusion in the last 6 months?

None	
1	
2	
3	
More than 3	

3 How many times was the patient treated for having hotness of body or chills in the last 6 months?

None	
1	
2	
3	
More than 3	

4 Does the patient use a treated mosquito bed net? Yes …….…….. No ……

5 How many times have you had pain and or swelling of your limbs in the last 6 months?

None	
1	
2	
3	
More than 3	

APPENDIX 6

Brief Medication Questionnaire

Patient study code……

This form asks about the medications you currently take for management of sickle cell disease.

1. Did you bring your medications with you today? 1. No …….…….… 2. Yes ……..……...
2. How many medications do you currently take for sickle cell disease? ……
3. What medications do you currently take for sickle cell disease?

Medication name or description	Leave blank
Drug A:	
Drug B:	
Drug C:	

4. Did you stop taking any sickle cell disease medication in the past six months?

   1. No …….…….… 2. Yes ……..……... (Skip to next page)

5. What sickle cell disease medication was stopped? For what reason was it stopped?

a. Medication Stopped	b. Reason stopped
1.	
2.	
3.	
4.	

This questionnaire will be filled for every medicine on the patient's prescription

The following questions ask about your use of certain medications in the past week. For each question, please circle the number that best describes your experience. Answer the questions for each drug listed. Use extra pages if needed.

Drug: _____

6. How often does your doctor want you to take this drug?
    1. Every day
    2. As needed
    3. Don't know
7. How is this drug supposed to help you?

    _____

8. In the past week:
    a. Did you take any of this drug? 1. Yes ……. 2. No ……..
    b. How many days did you take this drug? I took it: 0 1 2 3 4 5 6 7 days
    c. How many times a day did you usually take it? I took it: 0 1 2 3 times a day
    d. How much did you usually take each time? I took: 0 pills, 1 pill, 2 pills, 3 pills each time
    e. How many times did you miss taking it? I missed it: 0 1 2 3 4 5 6 7 times

9. How well does this drug work for you?
    1. Not at all well
    2. Moderately well

3. Very well
4. Don’t know

10. How much does this drug bother you?
    1. Not at all
    2. Bothers a little
    3. Bothers a lot
    4. Don’t know

11. How much difficulty are you having in each area?

		0 None	**1 A little**	**2 A lot**
a.	It is hard to remember all the doses			
b.	It is hard to pay for this drug			
c.	It is hard to get my refill on time			
d.	I still get unwanted side effects from this drug			
e.	I worry about the long-term effects of this drug			
f.	This drug causes other concerns or problems			

APPENDIX 7

Scoring Procedures for BMQ Screens

Screen	Scoring	
Regimen Screen (Questions 1a-1e)		
Did R fail to list the prescribed drug in the initial (spontaneous) report?	1=yes	0=no
Did R stop or interrupt therapy due to a late refill or other reason?	1=yes	0=no
Did R report any missed days or doses?	1=yes	0=no
Did R reduce or cut down the prescribed amount per dose?	1=yes	0=no
Did R take any extra doses or more medication than prescribed?	1=yes	0=no
Did R report "don't know" in response to any questions?	1=yes	0=no
Did R refuse to answer any questions?	1=yes	0=no
NOTE: Score of ≥1 indicates positive screen for potential nonadherence		
Belief Screen (Questions 1g and 2-2a)		
Did R report "not well" or "don't know" in response to Q 1g?	1=yes	0=no
Did R name the prescribed drug as a drug that bothers him/her?	1=yes	0=no
NOTE: Score of ≥1 indicates positive screen for belief barriers		
Recall Screen (Question 1c and 3c)		
Did R receive a multiple dose regimen (2 or more times/day)?	1=yes	0=no
Did R report "very hard" or "somewhat hard" in response to Q 3c?	1=yes	0=no
NOTE: Score ≥1 indicates positive screen for recall barriers		
R = respondent		

The BMQ classifies participants into the following categories:

1. Adherence (no positive response in any domain)
2. Probable adherence (positive response in one domain)
3. Probable low adherence (positive responses in two domains)
4. Low adherence (positive responses in all three domains)

APPENDIX 8

The IREC Study Approval Letter

MU/MTRH-INSTITUTIONAL RESEARCH AND ETHICS COMMITTEE (IREC)

MOI TEACHING AND REFERRAL HOSPITAL
P.O. BOX 3
ELDORET
Tel: 33471//2/3

MOI UNIVERSITY
COLLEGE OF HEALTH SCIENCES
P.O. BOX 4606
ELDORET

Reference: IREC/2018/27
Approval Number: 0003066

26th July, 2018

INSTITUTIONAL RESEARCH & ETHICS COMMITTEE
25 JUL 2018
APPROVED
P. O. Box 3606 - 30100 ELDORET

Dr. Mbiri Zacheus Were,
Moi University,
School of Medicine,
P.O. Box 4606-30100,
ELDORET-KENYA.

Dear Dr. Were,

RE: FORMAL APPROVAL

The MU/MTRH- Institutional Research and Ethics Committee has reviewed your research proposal titled: -

"Relationship between Adherence to Chemoprophylaxis and Morbidity among Patients with Sickle Cell Disease in Webuye County Hospital".

Your proposal has been granted a Formal Approval Number: ***FAN: IREC 3066*** on 26th July, 2018. You are therefore permitted to begin your investigations.

Note that this approval is for 1 year; hence will expire on 25th July, 2019. If it is necessary to continue with this research beyond the expiry date, a request for continuation should be made in writing to IREC Secretariat two months prior to the expiry date. You will be required to submit progress report(s) on application for continuation, at the end of the study and any other times as may be recommended by the Committee.

Furthermore, you must notify the Committee of any proposal change (s) or amendment (s), serious or unexpected outcomes related to the conduct of the study, or study termination for any reason. You will also be required to seek further clearance from any other regulatory body/authority that may be appropriate and applicable to the conduct of this study.

Sincerely,

DR. S. NYABERA
DEPUTY-CHAIRMAN
INSTITUTIONAL RESEARCH AND ETHICS COMMITTEE

cc	CEO	-	MTRH	Dean	-	SOP	Dean	-	SOM
	Principal	-	CHS	Dean	-	SON	Dean	-	SOD