HEALTH-RELATED QUALITY OF LIFE AND DRUG THERAPY PROBLEMS IN PATIENTS WITH SICKLE CELL DISEASE ON HYDROXYUREA AT KENYATTA NATIONAL HOSPITAL

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A research dissertation submitted in partial fulfillment of the requirements for the award of the Degree of Master of Pharmacy in Clinical Pharmacy, in the School of Pharmacy of the University of Nairobi.

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DEDICATION

This work is a dedication for all those who have died or suffer due to sickle cell disease.

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LIST OF ABBREVIATIONS AND ACRONYMS

ACS	Acute chest syndrome
ANC	Absolute neutrophil count
ALT	Alanine transaminase
ALP	Alkaline phosphatase
AST	Aspartate transaminase
BPI	Brief Pain Inventory
BUN	Blood Urea Nitrogen
CRF	Case report form
dL	Deciliter
DMC	Drug monitoring committee
FDA	Food and Drug Administration
fL	Femtolitre
GGT	Gamma glutamyl transferase
Hb	Haemoglobin
HbA	Adult haemoglobin
HbF	Fetal haemoglobin
HbS	Sickle haemoglobin
HLA	Human leukocyte antigen
HU	Hydroxyurea
IRR	Incidence risk ratio
ISC	Irreversibly sickled cells

ITT	Intent-to-treat
L	Litre
LDH	Lactate dehydrogenase
MCV	Mean corpuscular volume
mg	Milligram
mITT	Modified intent to treat
NO	Nitric oxide
NSAIDs	Non-steroidal anti-inflammatory drugs
pg	Picogram
PP	Per protocol
RCT	Randomized controlled trial
RBC	Red blood cells
SCA	Sickle cell anaemia
SCD	Sickle cell disease
SCLD	Sickle cell chronic lung disease
SCPC	Sickle cell pain crisis
SCr	Serum Creatinine
SF-36v2	Short form-36 version 2
SpO2	Peripheral capillary oxygen saturation
umol	Micromol
VOC	Vaso-occlusive event
WHO	World Health Organization

OPERATIONAL DEFINITIONS

Acute chest syndrome: An acute episode with x-ray findings of lung infiltrates, and the patient also presents with at least one of the following: fever (>38.5^{0}C) cough, tachypnea, chest pain or wheezing.

Alanine transaminase (ALT): An enzyme used to assess for liver disease. The normal levels are between 20-60 IU/L.

Aspartate transaminase (AST): An enzyme used to assess for liver disease. The reference range in males is 6-34 IU/L and females is 8-40 IU/L.

Blood, urea, nitrogen (BUN): It is a test that forms part of the basic metabolic panel that is a surrogate marker for the kidney and liver function. The reference range is 10-20 mg/dl or 3.6-7.1 mmol/L.

Bodyweight: This is the weight that is read on a weighing scale. It is given in kilograms (kgs).

Hematocrit: This is a percentage of the volume of erythrocytes to the volume of blood in a sample. The standard reference range is 33.5-54.0%.

Haemoglobin: An iron-based molecule that binds and transports oxygen and carbon dioxide. The reference range in men is 14-18 g/dL, and in women is 12-16 g/dL.

Hepatic sequestration: this presents clinically as an enlarged liver, right upper quadrant pain, and acute fall in Hb by approximately 2g/dl.

Mean corpuscular haemoglobin: This is the average weight of haemoglobin in an erythrocyte. The reference value is 25-38 pg.

Mean corpuscular volume (MCV): This is the average volume of erythrocytes in a blood sample. The normal range is 80-110fL.

Neutrophil: A type of white blood cells. Neutrophils make the largest component of white blood cells. The reference range is 1.5-7.0 x 10^9/L.

Platelets: Blood cells responsible for clotting. The reference range is 150-450 x 10^9/L.

Priapism: a sustained, purposeless penile erection requiring a visit to a medical facility.

Red blood cell count: this is the number of red blood cells present in a blood sample. The reference range is 3.90-5.50 $x10^9$/L.

Reticulocytes: these are red blood cell precursors. They indicate how effective erythropoiesis is. The reference range for reticulocyte count is 0.5% -1.5%.

Serum creatinine (Scr): gives an estimate of renal function. The reference range is 60-130 umol/L.

Sickle cell disease/anaemia: A genetically acquired disease that occurs due to mutations in the haemoglobin chains leading to the haemoglobin S variant.

Sickle cell-related pain crisis (SCPC): An acute painful episode requiring a visit to a medical facility, use of parenteral non-steroidal anti-inflammatory drugs, or oral/ parenteral opioids

Transfusion: Process of transferring blood or blood components to a patient through an intravenous route.

White blood cells: These are components of whole blood that mediate immunity and are markers of infection. The reference range is 4.0-11.0 x 10^9/L.

ABSTRACT

Background: Sickle cell disease is an inherited genetic disorder caused by presence of a mutated form of hemoglobin. It is estimated that 312,000 babies are born with sickle cell disease every year, with 90% of these births occurring in Africa. It has a high mortality rate with 50-90% of babies born with the disease dying before the age of five. Multi-organ involvement and painful crises are the hallmarks of sickle cell disease. Studies have revealed that patients with sickle cell disease have a lower quality of life compared to the general population. Hydroxyurea is the standard therapy for the management of sickle cell disease.

Objective: To determine the health-related quality of life and drug therapy problems with hydroxyurea use in patients with sickle cell disease at Kenyatta National Hospital.

Methods: A cross-sectional study was conducted at the Kenyatta National hospital hemato-oncology clinic. Sixty-seven participants were eligible. Enrolled participants answered questionnaires designed to collect information on the socio-demographic and medical characteristics. The World health organization Quality of Life (QoL) tool was used to determine the health-related quality of life score.

Data was entered into Epi-info version 7, and STATA version 13 was used for data analysis. Descriptive data analysis was employed to summarize key variables. Linear regression analysis was done on pooled data to identify the most important determinants of quality of life and to control for confounding.

Results: Participants had a median age of 20.7 (±7.2) years, 52% were male and had experienced several sickle cell disease-related complications with acute chest syndrome (65.7%) being the most prevalent. The most frequently reported clinical symptoms included headache (44%) and painful crisis (38.8%). Non-compliance (86.6%) was the most prevalent drug therapy problem. In the quality of life assessment, psychological health had the highest score of 68.2%. Positive family history (p=0.030) (6.58 CI 0.66, 12.50) was significantly associated with better overall quality of life scores. Vomiting (p=0.099) (4.77 CI -10.46, 0.93) and chest pain (p=0.697) (1.71 CI -10.43, 7.02) were associated with lower overall quality of life scores.

Conclusion: The main drug therapy problem was non-compliance. Health-related quality of life among sickle cell patients was suboptimal across all domains. Strategies to contain drug therapy problems such as non-compliance should be encompassed in the management of patients. Effective management of pain and complications associated with sickle cell disease will improve the health-related quality of life of patients.

CHAPTER ONE: INTRODUCTION

1.1 Background

Sickle cell disease (SCD) is a genetically acquired haemoglobinopathy which occurs due to mutations in the human β-globulin locus gene located on chromosome 11 leading to defective beta haemoglobin. The sickled haemoglobin, HbS has a high propensity to polymerize. Under hypoxic conditions, red blood cells (RBC) change from the biconcave shape and assume a 'sickle' shape. They aggregate and occlude blood vessels (1). Patients usually develop painful episodes known as sickling crises that occur due to obstruction of blood vessels by sickled cells. There is multi-organ involvement affecting the cardiovascular, gastrointestinal, renal, pulmonary, nervous, ocular and skeletal systems. On average, patients with SCD suffer about eight crises events annually, together with a myriad of health conditions and complications.

The highest burden of sickle cell disease is found in Sub-Saharan Africa (2). There is a high death rate in children under five years, with 50-90% of infants born with sickle cell disease dying before the age of 5 years. World Health Organization (WHO) estimates that sickle cell disease is responsible for 5-15% of under-five mortality (3). In an epidemiological study on pediatric patients with SCD, the patients had growth retardation and lower body weight compared to other children. There was also a delay in achieving sexual and skeletal maturity. The median survival age was 14.3 years. One-fifth of patients died before their third birthday, a third before their fifth birthday, and a half between the ages of 5 and 30 years (2).

To date, no drug can alter the HbS chemically and thus cure SCD. Available treatment modalities prevent the sickling of red cells, thus reducing vaso-occlusion, organ damage and painful episodes (4). Currently, only hydroxyurea (HU) and crizanlizumab (ADAKVEO®) have been approved for use in SCD by the U.S. Food and Drug Association (FDA) (5). Hydroxyurea, an analogue of urea, is used as an anticancer agent, has demonstrated efficacy in reducing painful crisis, blood transfusions and acute chest syndrome. Hydroxyurea was approved by the FDA for use in adults with sickle cell disease in 1998 and in 2017; it was approved for use in pediatric patients. Hydroxyurea causes an increase in fetal haemoglobin (HbF) which ameliorates the disease process. It is associated with reduced morbidity and possibly

mortality (6). Hydroxyurea is associated with myelosuppresion and potential teratogenic effects on long term use (4). Crizanlizumab was approved by the FDA for use in sickle cell disease in 2019. It effective in preventing vaso-occlusive crisis in patients with SCD (7).

Studies conducted to assess the health-related quality of life (HRQol) among sickle cell patients have shown that the patients' quality of life (QoL) is severely compromised and the scores are equivalent to patients undergoing hemodialysis (8). The goal of therapy is focused on reducing the mortality rates of patients, but these studies have demonstrated a need for exemplary care to improve the quality of life for these patients. Studying the QoL among patients with sickle cell disease on hydroxyurea and the related drug therapy problems is required for the identification of recommendations to improve therapy and optimize treatment and overall QoL.

1.2 Problem Statement

The cornerstone of management in sickle cell disease involves infection prevention and supportive management of vaso-occlusive crises. Hydroxyurea has demonstrated improvement in the clinical outcomes in sickle cell disease with patients experiencing fewer vaso-occlusive crises and complications (9). Its use is limited to prophylaxis in patients with moderate to severe crises. There has been no proven benefit of hydroxyurea in the treatment of the crises. This drug has proven to be useful in primary prevention of stroke in SCD (10). Hydroxyurea is a cytotoxic agent and causes bone marrow suppression with a potential risk of developing secondary neoplasms such as leukaemia. Other side effects include gastrointestinal disturbances; nausea, vomiting and diarrhoea and dermatological side effects such as pruritus and macular-papular rash (11). Other studies have demonstrated that not all patients are responsive to hydroxyurea therapy (12). Due to these shortcomings, the management of SCD is sub-optimal.

Studies conducted have assessed the impact of hydroxyurea on hospitalization, frequency of blood transfusions and haematological profile of patients with sickle cell anaemia. There are few studies on the quality of life and drug therapy problems among this cohort of patients. HRQoL assessment in sickle cell disease is feasible, and there is a need to identify the drug therapy problems that may be barriers to effective HU therapy. This study will contribute to the literature on hydroxyurea use

and HRQoL among patients with SCD. Sickle cell disease has detrimental effects on the psychological and mental health of patients with patients more likely to suffer from anxiety, depression and even suicidal tendency. It is of utmost importance that these aspects of a patient's life be considered when treating the patient and when developing policy and treatment guidelines.

It is prudent to identify the drug therapy problems (DTPs) faced by these patients. Studies to identify barriers to hydroxyurea treatment have shown that those patients with fewer barriers to treatment have better clinical and economic outcomes compared to those who face many barriers with hydroxyurea therapy (13). The findings can be used to inform policy, funding and provision of hydroxyurea to patients. Challenges such as cost, accessibility, side effects faced by the patients need to be clearly outlined, and this study sought to report on these barriers to treatment.

Many sicklers are generally from a low social class and cannot afford consistent drug therapy and may suffer from adverse drug reactions impacting QoL (2). The impact of DTPs on HRQoL has never been evaluated in both Kenya and other studies. Suboptimal therapy and lack of psychosocial support critically affect QoL. Without evidence on the prevalence of DTPs and subsequent effects on HRQoL clinicians and pharmacists remain indifferent to problems potentially posed by hydroxyurea therapy. This study, therefore, sought to identify DTPs and its potential impact on HRQoL.

1.3 Research Questions

1. What is the health-related quality of life (HRQoL) of patients with sickle cell disease on hydroxyurea at Kenyatta National Hospital (KNH)?
2. What are the drug therapy problems (DTPs) associated with hydroxyurea use in patients with sickle cell disease at KNH?
3. What is the association between HRQoL and drug therapy problems in patients on hydroxyurea?

1.4 Objectives

1.4.1 Main objective

To evaluate the health-related quality of life and drug therapy problems among patients with sickle cell disease using hydroxyurea at KNH.

1.4.2 Primary specific objectives

The specific objectives were to:

i. Determine the health-related quality of life in patients with sickle cell disease on hydroxyurea at KNH.

ii. Measure the prevalence of drug therapy problems associated with hydroxyurea use in patients with sickle cell disease at KNH.

iii. Determine the association between health-related quality of life and drug therapy problems among patients on hydroxyurea.

1.6 Study Justification

Hydroxyurea use reduces hospitalizations, transfusions and pain-related episodes. This subsequently lowers the number of hospital visits, admissions, use of opioids and concomitant medication. Hydroxyurea improves the HRQol among patients and also lowers costs of treatment (11). Despite the beneficial effects of hydroxyurea, treatment remains suboptimal, and adherence among patients varies from 35-75% (14).

Identification of DTPs will possibly lead to prescriber and pharmaceutical interventions to optimize care if findings are shared with relevant stakeholders. This will inform the national policy on the management of SCD with hydroxyurea if study findings show that dosing is suboptimal, and patients may require additional psychosocial support. Given that suboptimal care increases the economic cost of disease management, mortality and morbidity.

Determining the QoL among patients will help inform health care practitioners on the gaps in management and with a focus on improving the well being of the patients. Patients with sickle cell disease will benefit from the findings of this study because steps can be taken to ensure not just the physical health but also their psychological, mental, social and economic well being are considered during therapy.

1.7 Delimitations of the study

The study was conducted at the haematology department in Kenyatta National Hospital. The sickle cell patients enrolled at KNH are a small sample in comparison to the sickle cell patients in the region and Kenya as a whole. The study enrolled patients attending KNH and did not include patients from other facilities. Patients enrolled were those who had been taking hydroxyurea for at least 6 months.

CHAPTER TWO: LITERATURE REVIEW

2.1 Introduction

Sickle cell disease is associated with a myriad of clinical syndromes due to vaso-occlusion and hemolysis of red blood cells. This chapter summarizes the findings of studies done on drug therapy problems and health-related quality of life of patients and treatment modalities used in the management of sickle cell disease.

2.2 Epidemiology of Sickle cell disease

Sickle cell anaemia is a hemoglobinopathy that is genetically acquired. Its inheritance pattern is autosomal recessive. Individuals who carry only one defective gene are heterozygous and bear the sickle cell trait, HbAS. People who are homozygous with the HbSS sequence have the sickle cell disease. Five percent of the world's population carry the sickle cell trait (3,15).

Approximately 312,000 infants are born with SCD. An estimated 75% of these births are in Sub-Saharan Africa, where unfortunately the disease has been neglected (2). Approximately 2% of the children born in Sub-Saharan Africa have sickle cell disease. Nigeria has the highest burden of disease with over 150,000 children with SCD (3). More than 100,000 Americans are affected with a prevalence of 1 in 365 in African-Americans and 1 in every 16,300 Hispanic Americans (15). Regions with the highest malaria density have the highest SCD incidence due to a conferred resistance to *Plasmodium falciparum* malaria in people with the sickle cell trait. This is referred to as balanced polymorphism (16). In Kenya, a retrospective five-year cohort study conducted in Kilifi County Hospital, children with SCD accounted for 3.1% of the total admissions (2). In Kenya, over 80% of sickle cell patients are of Luo (58.4%) or Luhya (23.9%) ethnicity. The sickle cell trait was found to be highest (35%) in Kambes, of the Mijikenda group in the coastal region in an epidemiological study (17).

2.3 Clinical syndromes of Sickle cell disease

Sickled cells have increased adhesive properties causing them to stick together and cause vaso-occlusion, impeding oxygen transport to tissues. Repeated episodes of ischemia and reperfusion injury create a chronic inflammatory state with elevated levels of white blood cell count, platelets and serum acute phase reactants (4). In SCD erythrocytes undergo extensive intravascular and extravascular hemolysis. The

spleens' ability to detect minimal defects in RBC causes increased destruction of sickled cells in the reticuloendothelial system. The sickled cells have increased fragility causing intravascular hemolysis (18).

General vaso-occlusive crisis (VOC) is a sudden onset of painful episodes often triggered by cold weather, stress, dehydration, infection and overexertion. Painful crisis is the hallmark of sickle cell disease (19). Chronic pain is due to tissue damage which occurs due to infarcts; this is the aetiology in avascular necrosis and leg ulcers. There is also intractable pain with no identifiable cause (4).

Acute chest syndrome (ACS) is a sudden onset of pneumonia-like symptoms and chest x-rays reveal infiltrations. Microbial infiltration by *Streptococcus pneumonia*, *Haemophilus influenza*, *Chlamydia, Mycoplasma* or *Legionella* is an initiating factor. If not adequately managed the associated mortality rates are high, 4-10% (19). Sickle cell chronic lung disease (SCLD) is caused by irreversible remodelling and pulmonary scarring that leads to interstitial fibrosis. Eventually, this can progress to restrictive lung disease, hypoxemia, pulmonary hypertension and cor-pulmonale (20).

Gastrointestinal sequelae occur due to vaso-occlusion, infarcts and hepatic or splenic sequestration (18). Hemolysis causes raised bilirubin levels which can cause cholelithiasis. Splenic sequestration is a common crisis in pediatric patients under seven years (18). In adolescents and adults, the spleen is fibrotic and has undergone autosplenectomy and therefore cannot enlarge, making the incidence of splenic sequestration low. Peptic ulcers are a common occurrence (1,4).

In infancy, thickening of the periosteum of the hands and feet causes demineralization of the bone. Swelling over the affected areas occurs, causing a painful condition called dactylitis (4,18). Bone infarcts can be secondarily infected by microorganisms such as *Salmonella* spp, *Escherichia coli* and *Staphylococcus* species causing osteomyelitis (4). Chronic hypoxia compromises the growth plate causing early closure of the epiphyseal plate, causing patients to have a shorter stature compared to the general population (21). Sickle cell leg ulcers occur due to compromised blood flow, recurrent vaso-occlusive episodes, trauma, prolonged periods of standing and iron overload. They cause intense and chronic pain, secondary infections, social isolation and lower the quality of life (22).

In periods of physiological stress such as infections and vasoocclusive crises, hematopoietic demands increase, and this can trigger an aplastic crisis in the bone marrow in an attempt to meet the oxygen demands. It is more common in patients under 16 years. Parvovirus B-19 has been associated with aplastic crisis in SCD (4).

The lifespan of RBC in SCD is significantly reduced from 120 days in normal subjects to 16-20 days (23). The baseline laboratory values of haemoglobin levels in SCD are generally between 6 and 9g/dL (24). Bone marrow activity is increased in order to compensate for anaemia. Acute anaemia is a common complication of splenic sequestration crises (25). Chronic anaemia precipitates cardiac disease. Pulmonary hypertension, with a pulmonary arterial pressure greater than 25mmHg, subsequently causes cor-pulmonale. Other cardiovascular conditions in SCD are dilated cardiomyopathy, cardiac iron overload, dysrhythmia and myocardial infarction which can cause sudden death (4,18).

Vaso-occlusion in the arteries supplying the brain is responsible for the ischemic strokes. Hemorrhagic strokes are as a result of haemorrhage in the vessels in the circle of willis (4). Occlusion of the central retinal artery may cause sudden vision changes (4). Sickle cell disease predisposes patients to ocular abnormalities such as neovascularization and retinal anomalies (18).

Vasoocclusive events, coupled with reduced nitric oxide (NO) can cause priapism. Ischemic (low flow) priapism is prevalent in SCD. This can cause permanent damage if not promptly treated (4).

Infants born with SCD have average weight at birth, but by the end of the first year, the weight will be lower than the non-SCD counterparts. Children with SCA are less nourished and score lower in the weight for age Z-score. There is a delay in the pubertal growth spurt and age of menarche (2,4).

Infarcts and splenic sequestration crises lead to scarring and loss of function. This predisposes the SCD patients to infections by encapsulated bacteria. *Pneumococcus* spp is the leading cause of infection. Patients with SCD are 30-600 times more likely to get pneumococcal infections caused by *Hemophilus influenza*, *Klebsiella* spp, *Escherichia coli, Staphylococcus* and other pathogenic species (4,18). Kidney infarcts and injury impair the kidneys' ability to concentrate urine. Hemolysis of RBS leads to

hyperuricemia which predisposes the patients to gout and urate nephropathy (18). The nature of sickle cell disease has detrimental psychological effects on patients. Patients are predisposed to stigmatization, social withdrawal, poor performance, depression and even suicidal tendencies. They also face rejection and stigmatization due to the disease (22).

2.4 Management of sickle cell disease

Therapy is aimed towards adequate supportive measures to prevent crises, alleviate painful episodes and support erythropoiesis. There are disease-modifying therapies which include transfusions and transplant and pharmaceuticals. Hydroxyurea and crizanlizumab are the only two drugs with FDA approval for use in sickle cell disease (5).

Oxygen supplementation is used in sickle cell crisis and especially in acute chest syndrome. There is no clear evidence of oxygen improving outcomes in sickle cell crisis. However, hypoxic patients with oxygen saturation (SpO2) less than 92%, supplemental oxygen should be initiated. Dehydration increases the viscosity of the intravascular fluid and can initiate or propagate sickling. It is therefore recommended that fluids should be given to hypovolemic patients with a goal of euvolemia. Aggressive hydration, especially with isotonic crystalloid, is not recommended (11).

Pain management should follow the recommended WHO stepwise approach. Moderate painful episodes require analgesics such as paracetamol (acetaminophen). Non-steroid anti-inflammatory drug (NSAID) use, however, remains controversial in SCD due to the risk of renal injury despite their effectiveness in pain management, NSAIDs can be used in acute cases, but long term use is not recommended. There is a strong recommendation for prompt initiation of opioids in severe painful crises (11). A single intravenous (IV) dose equal to the patients' total daily requirements should be given at first. The dose should be escalated by 25% until pain relief is achieved. Patient-controlled analgesia is recommended in severe painful crises. Parenteral corticosteroids have been shown to speed up pain resolution but carry a risk of pain reactivation. Further studies are required to prove their effectiveness in pain management (26).

Patients with SCD are predisposed to infections by encapsulated organisms such as *Streptococcus pneumoniae* due to a non-functioning spleen. Penicillin prophylaxis

reduces mortality rates from 25% to 4%. Prophylactic penicillin use until five years of age is therefore recommended to reduce mortality in children (11,27). Malaria prophylaxis is recommended in patients who live in malaria-endemic regions (28). Folic acid supplementation is required to support the increased bone marrow activity. Deficiency of folic acid and vitamin B12 can trigger an aplastic crisis (11).

Transfusion is a lifesaving treatment option that is recommended in symptomatic anaemia, aplastic crises, ACS, splenic crisis, severe disease, primary and secondary prevention of stroke and complicated pregnancy (4,27). There are three available modalities, simple transfusion, exchange transfusions or chronic blood transfusions (4). Simple transfusion is sufficient if the patient is stable. In all transfusions, the goal is to get the Hb level at 10g/dl since if Hb levels are higher; then there is an increased risk of vaso-occlusion occurring due to the increased viscosity. Transfusion has been shown to lower the incidence of stroke in SCD (27). Chronic blood transfusions should be initiated in children with a transcranial doppler ultrasound velocity >200cm/s for primary stroke prevention (11).

Stem cell transplant involves transplanting healthy bone marrow from a matched person, usually a sibling, to replace the patients' bone marrow. If successful, the new bone marrow makes healthy red blood cells, making stem cell transplant a potential cure for SCD. Patients have a mean increase in haemoglobin to normal levels and improved quality of life (29). Stem cell transplant remains underused due to the associated mortality risk, with 5 out of 8 HLA matched siblings refusing the process due to fear of mortality. Other challenges involved include the high cost, lack of a matching sibling and graft versus host disease that requires immunosuppressants (30).

2.4.1 Hydroxyurea

Hydroxyurea (HU) is an antineoplastic agent that is used for the treatment of certain cancers such as myelodysplastic syndrome and chronic myelogenous leukaemia (5). Its mechanism of action is postulated to be due to inhibition of ribonucleotide reductase, causing an intermittent cytotoxic suppression of erythroid progenitors and cell stress signaling. This affects erythropoiesis kinetics with recruitment of early erythroid progenitor cells with an increased level of fetal hemoglobin (HbF) (31). Hydroxyurea therefore, increases the amount of HbF, which lacks the beta chains; the red blood cells cannot sickle or polymerize. Increased levels of HbF have been shown

to reduce morbidity and mortality. It also reduces the production of white blood cells, causing a total reduction in inflammatory mediators, adhesion and destruction of RBCs. Hydroxyurea also reduces platelet numbers and consequently causes a reduction in thrombotic and vasoocclusive events. Hydroxyurea increases the amount of nitric oxide by stimulating its production, which is a potent vasodilator. Overall hydroxyurea therapy reduces the incidence of vasoocclusive events, painful crisis, acute chest syndrome, transfusions and hospitalizations (12). The primary endpoints of hydroxyurea therapy include; the number of painful episodes, blood transfusions, acute chest syndrome crisis, hospitalizations and improved quality of life assessment.

In the MSH trial, 299 patients were randomized to receive hydroxyurea or placebo and followed up for two years. Hydroxyurea reduced the number of episodes of pain crisis experienced in SCD. The number of crisis requiring hospitalization was significantly reduced. Patients on HU therapy stayed for more extended periods without experiencing painful crisis upon initiation of HU therapy. In the placebo group, the median time to first, second and third crisis was 1.35, 4.13 and 7.04 months respectively compared to hydroxyurea arm of 2.76, 6.58 and 11.9 months, respectively (32). In an Indian double-blind, randomized, placebo-controlled trial, conducted on young children and young adults between the ages of 5-18 years for 18 months, HU caused a significant reduction in the number of VOC events after 18 months of HU therapy (33). A multicentre two year, randomized clinical trial on infants between 9-18 months, the BABY HUG trial, revealed that patients on HU therapy were 0.68 times less likely to experience pain. Patients on placebo had twice the incidence of pain episodes, and dactylitis was five times more in this arm (31).

Hydroxyurea lowers the number of blood transfusions and hospitalizations. In a randomized clinical trial by Jain et al., the number of blood transfusions was lower in the HU arm in comparison to the placebo group (33). In a retrospective quasi-experimental study on children with SCD between the ages of 1-18 years in KNH and Gertrude's Children's Hospital, hydroxyurea was found to reduce the mean number of blood transfusions. A statistically significant mean decrease of 0.9 was reported. Hydroxyurea therapy was also shown to reduce the number of admissions (34). A Cochrane review revealed that patients on HU were less likely to be hospitalized for painful crisis, compared to patients receiving placebo. Patients on HU had shorter hospital stays (9). In a Cochrane review of 2 randomized controlled trials (BABY

HUG and MSH trials); patients on HU were less likely to develop an ACS event compared to patients on the placebo. HU also reduced the number of transfusions needed with a pooled risk reduction of 0.66 from the two trials. There was no proven statistically relevant reduction in hepatic and splenic sequestration crisis from use of HU (12,31,32).

In the SWiTCH study, the effectiveness of hydroxyurea and phlebotomy was compared to transfusion and chelation in secondary stroke prevention in 134 children who had suffered stroke episodes and had been receiving transfusions for at least 18 months. Ten percent of patients who were on HU and phlebotomy had recurrent strokes episodes compared to no episode experienced in the patients receiving blood transfusion, leading to early termination of the trial. This showed that HU was ineffective in the secondary prevention of strokes (35). In the TWiTCH study, however, HU was found to be equally effective as transfusion in preventing a primary stroke episode in children who had abnormal velocities in their transcranial doppler ultrasound and had no vasculopathy present in their magnetic resonance angiography (10,12).

Hydroxyurea raises HbF levels, and this is associated with reduced morbidity and mortality. In a Cochrane review of 3 clinical trials, hydroxyurea raised the HbF levels. Fetal haemoglobin levels were higher compared to patients in the placebo arm (12,31). It is postulated that levels of HbF less than 20% are associated with twice the odds of hospitalizations. Data from the HUSTLE study identified a preferred treatment target level of Hb F greater than 20% (36).

Hydroxyurea affects other haematological parameters such as haemoglobin, MCV, reticulocytes, bilirubin and WBC. Various studies conducted have shown a statistically significant increase in Hb and MCV levels. In the BABY HUG trial, haemoglobin was higher, with lower bilirubin and reticulocyte counts in patients on HU; demonstrating reduced hemolysis of RBCs (31). There was a statistically significant increase in Hb and MCV levels upon the use of hydroxyurea in the Jain trial and MSH trial, with a significant decline in bilirubin and reticulocyte count levels (12).

Patients on hydroxyurea reported a better general health perception at 18 months since starting treatment compared to patients on placebo as per the MSH clinical trial (32).

There was no significant reduction in leg ulcers and avascular necrosis of humerus and femur in patients using HU compared to those on placebo (12). The BABY HUG also demonstrated no significant decrease in renal function amongst patients not using HU.

Clinical studies in Africa have demonstrated the efficacy of hydroxyurea. In a cross over experimental study in Nigeria, HU significantly raised haemoglobin levels, hematocrit, MCV and body weight (28). In Malawi, HU reduced the frequency of hospitalizations, transfusions and annual school absenteeism within six months of treatment in children (37). A phase 1-2 open-label international trial conducted in Uganda, Kenya, Democratic Republic of Congo and Angola, HU use in children significantly raised the levels of Hb and HbF. Hydroxyurea also significantly reduced the incidence of sickle cell-related events such as vaso-occlusive pain, non-malarial infection, transfusion and malaria (38).

Studies conducted to determine the optimum dosage of hydroxyurea demonstrated dose escalation to a maximum tolerated dose (MTD) showed superiority compared to a standard fixed-dose. In a prospective study in Uganda, children randomized to receive HU by dose escalation to an MTD of 30 ± 2.5 mg/kg/day had significantly lower incidences of vaso-occlusive crisis, acute chest syndrome, hospitalizations and transfusions compared to those who received a fixed-dose (20 mg/kg/day) of HU. They also had better haematological parameters with higher Hb and HbF levels. Similar toxicities occurred in both treatment arms (39).

The primary dose-limiting side effect related to HU use is myelosuppression. Frequent monitoring is required to assess haematological function and dose adjustment in case of myelosuppression. In a comparative study of hydroxyurea and the placebo, the reported side effects included hair loss, fevers, skin rashes and gastrointestinal disturbances such as nausea. The side effects were reported in both arms with no statistically significant differences between the two groups. Seventy-nine percent of the patients on HU experienced hematologic toxicity compared to 37% of those on placebo (32). In a similar study, some of the minor reported adverse effects of HU were nausea, vomiting, diarrhea, gastric discomfort, changes in nail color and coughing (34).

Myelosuppression occurs with hydroxyurea use due to bone marrow suppression. In the BABY HUG study, hydroxyurea caused a decline in the absolute neutrophil count (ANC). Comparisons between patients on HU and placebo revealed a significant decrease in the neutrophil count, with the HU arm having lower ANC levels. Measurements taken at ten weeks and two years showed a statistically significant decline in ANC. Hematological toxicities were identified as a neutrophil count <2500 $x10^9$cells/L, platelet count <95,000 x 10^9 cell/L and Hb<5.3g/dL. No bleeding episodes were related to the low platelet count or infections due to the low neutrophil counts (12,31).

2.5 Drug therapy problems in patients using hydroxyurea

Hydroxyurea has been proven to be effective in the management of sickle cell disease. However, despite the beneficial effects, its use among sickle cell patients is not optimal. Many patients who could benefit from HU use are not on hydroxyurea (40). This is due to patient, caregiver and practitioner related factors. Patient barriers include lack of awareness about the drug, fear of adverse events, negative attitudes and financial challenges. Hydroxyurea is mostly given in specialists clinics with practitioners who have experience with it. This remains a challenge in lower-level facilities due to inadequate experience with HU, potential myelosuppression, fear of infertility and congenital disabilities (40).

Drug therapy problems assessment aims to evaluate the use of medicines in regards to the indication, effectiveness, safety and compliance to ensure treatment goals are met safely and cost-effectively. With regards to drug indication, DTPs include unnecessary drug therapy which encompasses lack of medical indication, drug abuse, duplicate treatment or inappropriate therapy where a more appropriate drug is available. Hydroxyurea is the standard therapy in sickle cell disease, and it is expected that it is used in patients above the ages of 9 months (6).

The need for additional therapy for synergistic effect, prevention or treating another condition is another DTP. Patients with sickle cell disease often require additional therapy such as analgesics and hematinics. Folic acid is usually prescribed alongside hydroxyurea to ensure bone marrow support. Patients usually require pneumonia prophylaxis, but this is commonly recommended for children under five years. Analgesics are given per the WHO ladder for pain management.

Agents that have been approved for SCD include Crizanlizumab and L-glutamine. Crizanlizumab a product from Novartis is available for intravenous use. In resource-limited countries, the monoclonal antibody agent is estimated to cost an estimated $85000-$130,000 per month. This high cost leaves only HU to be used in SCD in almost all patients (5).

The recommended dosage of hydroxyurea in adults at initiation is 15mg/kg/day and dose increments to a maximum of 35mg/kg/day. In pediatrics the starting dose is 20mg/kg/day to a maximum of 35mg/kg/day. In the BABYHUG trial, HU dose of 25-30mg/kg in children was recommended. In a study to establish optimum dosing of HU in children, low dose HU (10-15.9 mg/kg/day) was found to be as effective as high dose HU (16-26 mg/kg/day) in improving clinical outcomes in patients. Dose adjustments are made based on haematological parameters to avoid myelosuppression. Therefore DTPs can arise due to under dosing or dosage being too high. These are drug therapy problems. Olielo P, reports under dosing in 79.7% of the pediatric patients in a retrospective study on paediatrics (39,41).

Adverse drug reactions form part of drug therapy problems as they affect patient compliance and the quality of life of patients. The primary reported side effects with HU use are related to myelosuppression. This includes neutropenia and thrombocytopenia with incidences of 12.6% and 7.4% respectively. Associated with the myelosuppression are bacterial and viral infections and fever. The incidence of gastrointestinal disturbances is 13.1% include vomiting, nausea, constipation and diarrhea. Skin disturbances have been reported with an incidence of 3.2%; these manifest as skin and nail changes or rashes. Others include headaches, anaemia, mucositis, weight gain and respiratory disturbances. Side effects associated with long term use could be genetic mutations and secondary leukaemia through a direct causal relationship has not been proven (37). Overdose of HU is not a common occurrence with the highest dose taken being accidental ingestion of HU at 612mg/kg by an infant. The only adverse event that occurred was myelosuppresion (42).

Non-compliance is a patient-related DTP. In a retrospective study in Nairobi, there was good compliance in 78.1% of the patients. Challenges to adherence included the cost, availability, lack of a caregiver to administer the HU, forgetting to it and lack of prescriptions (34). Fear of effect on fertility was a barrier to adherence in a study

conducted on adults in Nigeria (28). In a cross-sectional study on adolescents and young adults, there was a significant relationship between adherence and HRQoL. Patients who experienced no difficulties in accessing HU had higher adherence rate and thus scoring better in HRQoL assessment (13).

2.6 Health-related quality of life in patients with sickle cell disease

In a longitudinal study called the PiSCES project, the HRQoL was determined in comparison to other patients with chronic conditions. Patients with SCD had worse HRQoL scores in most aspects, apart from mental health. The HRQoL in SCD is worse than the general population, patients with asthma and cystic fibrosis. The bodily pain scores were worse compared to the others. The scores for HRQoL worsened as the pain level increased. In comparison to patients on hemodialysis, patients with SCD had worse scores for bodily pain, vitality and general health. In summary, the HRQoL of sickle cell patients was severely compromised (8).

In a clinical trial, treatment of pain and depression has been shown to improve the QoL in SCD. Chronic opioid use was shown to improve all the scales scores in the HRQoL assessment. Treatment of depression with the use of antidepressants seemed to improve the bodily pain score, social function, mental health and emotional role. Complications associated with sickle cell disease such as ACS, painful crisis, avascular necrosis, leg ulcers, transfusion-related iron overload all worsened the HRQoL scores. The most considerable impact on HRQoL was the treatment of pain and depression amongst patients (43).

Children with SCD suffer from co-morbidities associated with the disease, and this affects their physical, social and emotional well-being. In a comparative study between children with SCD and normal healthy children, parents reported an overall worse HRQoL score for their children with SCD. The self-reported HRQoL from the children revealed the disease affected mostly their physical functioning due to high bodily pain. SCD was shown to affect the lives of both the child and the family (44).

HRQoL is correlated with patients HbF and MCV levels. In a cross-sectional study, patients who had low HbF and MCV scored poorly compared to those with higher levels. The patients significantly suffered from fatigue (13).

2.7 Summary of literature review

Author	Study	Study design	Key variables	Key findings	Research limitations
Sherif M. Badawy	Barriers to hydroxyurea adherence and health-related quality of life in adolescents and young adults with sickle cell disease	Cross-sectional survey	-Adherence to hydroxyurea and barriers to adherence - Health-related quality of life score	-Patients with fewer barriers to hydroxyurea adherence were more likely to have higher adherence rates and better HRQOL scores.	- Small sample size - Self-reported measures of adherence
Olielo N. Philip	Impact of hydroxyurea on the frequency of blood transfusion in children with sickle cell anaemia	Retrospective quasi-experimental study	-Impact of hydroxyurea on blood transfusion -Adherence to hydroxyurea -Factors affecting adherence to hydroxyurea	-Mean decrease in the number of blood transfusions -Under dosing in 79.7% of participants -Good compliance in 78.1% -Side effects in 12.5% of patients	- Lack of randomization -Lack of a comparison group -Self-reported outcomes
Arlene Smarldone	A more significant number of perceived barriers to hydroxyurea was associated with more inferior health-related quality of life in youth with sickle cell disease	Cross-sectional study	- Barriers to hydroxyurea use - Health-related quality of life score	-Greater barriers were associated with poorer generic and disease-specific HRQL.	-Small sample size -Research instruments had not been thoroughly tested
Sherif M. Badawy	Beliefs about hydroxyurea in youth with sickle cell disease	Cross-sectional study	-Beliefs about hydroxyurea -Adherence -Health-related quality of life assessment	-Beliefs about hydroxyurea correlated with HRQOL scores and adherence levels.	-Small sample size -Self-reported outcomes measures not validated in SCD.

2.7 Gaps in the literature

Though it has been established that use of hydroxyurea in sickle cell diseases improves HRQoL, no studies have been done on the impact of drug therapy problems on the quality of life in patients with SCD in Kenya. This study will add to the pool of information in regards to hydroxyurea use in sickle cell disease.

2.8 Conceptual framework

The dependent variable is the quality of life in SCD patients which is directly affected by the use of hydroxyurea. Hydroxyurea has been proven to ameliorate the disease process. Optimum hydroxyurea therapy, therefore, improves the clinical outcomes of disease such as painful episodes, acute chest syndrome and other sickle cell-related complications. This has a direct impact on physical health, bodily pain, social and physical functioning and an overall improvement in the general well-being of the patient. The patient can have a better quality of life whilst on hydroxyurea therapy and have better scores in the HRQoL assessment.

Optimal HU use is dependent on various independent factors which are the drug therapy problems in this study. Hydroxyurea use needs to be at the right dose, frequency and safety for effective therapy. In instances where the dose is too low, then the patients will not have the optimum response to treatment. Drug doses that are too high then the patients are subject to more side effects such as myelosuppression, and this negatively impacts the quality of life. This can also affect treatment adherence. Barriers to adherence include negative attitudes by the patients, accessibility challenges and patients forgetting to take the medication. Poor adherence leads to poor treatment outcomes and a lower quality of life. Patients with sickle cell disease usually require additional medication such as analgesics and medication to support erythropoiesis. This has an overall effect on the quality of life of the patient. These factors described and the inter-relationships are demonstrated in Fig 2.1

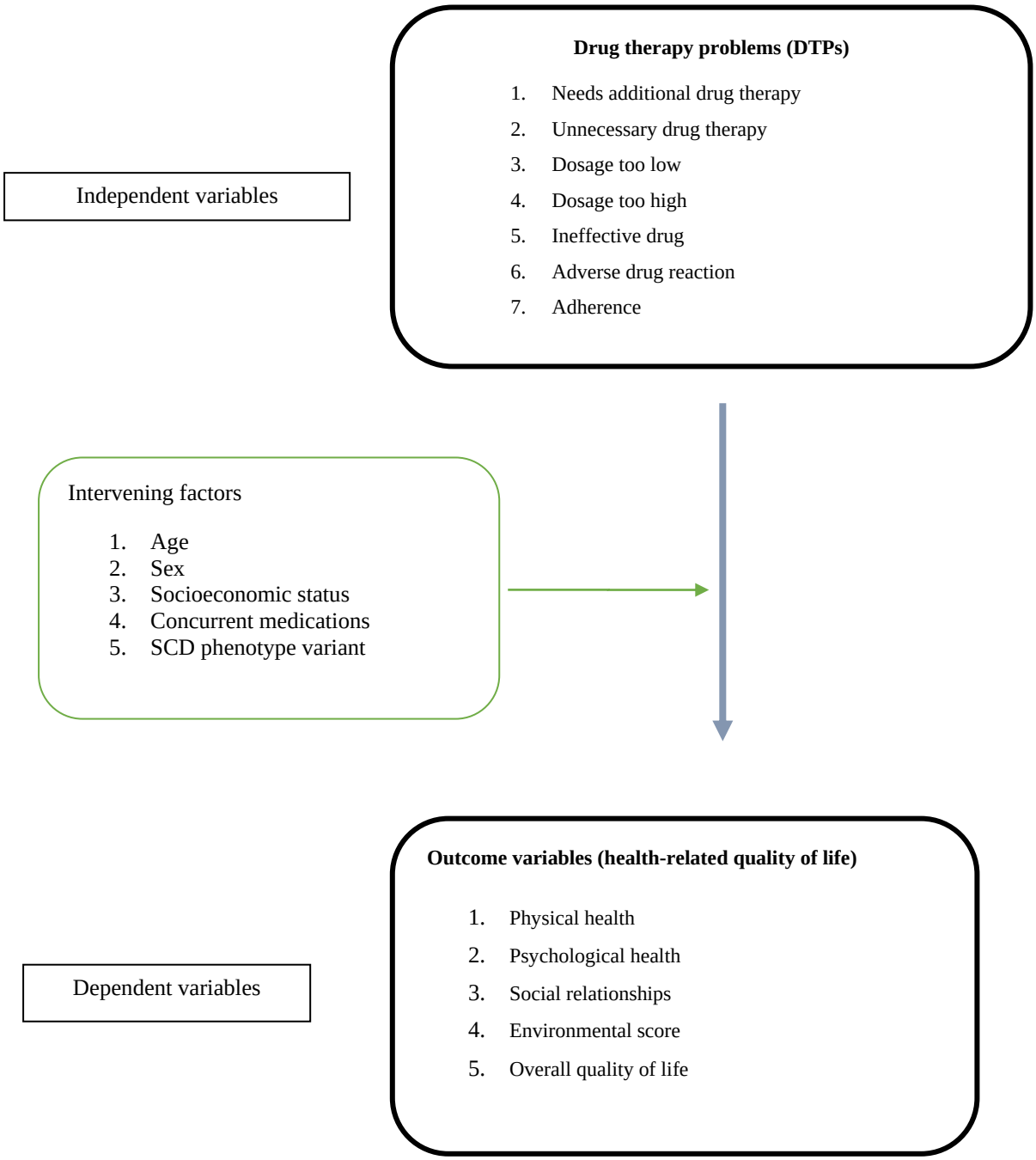


Figure 2.1: Conceptual framework: Interrelationship between drug therapy problems and health-related quality of life

CHAPTER THREE: METHODS

3.1 Introduction

The methodology section focuses on the participant process from the estimation of sample size, recruitment and interview throughout the study period. Data collection tools, recording and analyses will be discussed in detail. Issues regarding human participants will be addressed including but not limited to, ethics and review board, privacy and confidentiality.

3.2 Research Design

This study was a retrospective cross-sectional study evaluating the impact of hydroxyurea use on the QoL among sickle cell patients. This research design provided a practical way to carry out impact assessments in the real world. It allowed the study of different variables.

3.3 Study site

The study was conducted at the Kenyatta National Hospital (KNH) haematology outpatient clinic (clinic 23), and inpatients ward 8C. Located in Nairobi, Upper-hill area, KNH is the largest referral hospital in East Africa with an estimated 80,000 inpatient and 500,000 outpatient attendances annually. Kenyatta National Hospital is preferred by the public, mainly due to its accessibility, affordability and a wide range of specialized services. It offers healthcare services to patients from Central and Southern Africa and the Great lakes region. The hospital, therefore, provided an ideal location for the study and was expected to provide the required sample size. Kenyatta National hospital was also a good representation of the target population. The Hemato-oncology clinic and pharmacy is run weekly.

3.4 Study population

The study population was patients with SCD, between the ages of 13- 65 years attending the Kenyatta National Hospital. The target population is SCD patients in Kenya, who are on hydroxyurea and aged between 13-65 years.

3.5 Eligibility criteria

3.5.1 Inclusion criteria

Patients were included in the study if they:

1. Had a documented history and diagnosis of SCD.

2. Were aged 13-65 years, inclusive

3. Male or female with at least six months follow up at KNH.

4. Patient on HU therapy for not less than six months before the screening and a minimum of 3 months of HU dose stabilization. This was to ensure the patient has achieved steady-state concentrations of hydroxyurea.

5. Willingly provided written informed consent form. For participants under the age of 18 years, written assent by the parents/guardians.

3.5.2 Exclusion criteria,

Patients were excluded if they:

1. Had been diagnosed as human immunodeficiency virus (HIV) positive.
2. Suffered a stroke in the last two years
3. Cancer diagnosis in the past five years,
4. Pre-existing haematological conditions such as myelodysplastic syndrome or any other condition.
5. Any other condition deemed to compromise the patients' involvement in the study as per the judgment of the principal investigator.
6. Those who did not meet any of the inclusion criteria were also excluded.

3.6 Sample size estimation

Sample size estimation was based on the Cochran's sample size formula for categorical data(45), as presented in equation1. The estimated prevalence of drug therapy problems with hydroxyurea use is unknown; therefore, p will be considered at 0.5.

Equation 1: The Cochran formula for sample size computation for descriptive designs.

$$n = \frac{z^2 P(1-P)}{d^2}$$

Where:

n: The sample size required for the study

z^2: The standard normal deviate set at 95% CI (z = 1.96)

d: Margin of error set at 5% = 0.05

p: Prevalence of non-adherence to hydroxyurea. In a study by Olielo P, in Kenyatta, the prevalence of non-adherence was 20.3% (34).

Therefore substituting the variables

$$n = \frac{1.96^2 0.203(1 - 0.203)}{0.05^2}$$

n= 249

Applying the Cochran correction formulae correction factor for finite population,

Equation 2: The Cochran correction formula for finite population

$$n = \frac{n0}{1 + n0/N}$$

where;

n: Minimum sample size required

n_0: calculated sample size (249 Patients)

N: total number of patients on hydroxyurea that have attended hemato-oncology ward and clinic in the year 2019 on hydroxyurea

$$n = \frac{249}{1 + 249/8\,0}$$

= 60 patients

To cater for non-response and inaccuracy, an additional 15% was added to the final sample size.

60 x (1.15) = 69

Therefore the sample size required for this study was 69 participants.

3.7 Participant recruitment

A participant list was obtained from the KNH records section that generated 144 sickle cell patients who had been attended to in KNH over the past one year. Upon payment of health records access fee, the health records department was able to retrieve 130 files. The patient files were perused, and eligible participants contact information was able to be obtained from 75 of the files. Fifty-four participants were traced from the contact information. Seventeen eligible participants were also recruited from the haematology clinic 23 from the period of July 2020 to September 2020. Participants were screened for eligibility using the eligibility checklist (appendix III). It contained the inclusion and exclusion criteria. Only participants who meet all of the inclusion criteria and none of the exclusion criteria were included in the study.

Eligible participants identified were informed about the study protocol. Patients were encouraged to ask any questions seeking any clarification during this process. Four patients declined to participate in the study. Participants who were eligible for the study were then provided with the informed consent form (appendix II) in both the national languages that are English and Kiswahili. The consent forms were duly signed by the participant or a parent/guardian in case of minors. The consent forms were filled in duplicate with the participant retaining their original copy. Participants were assigned a unique patient identification number.

3.8 Research Instruments

3.8.1 Questionnaires

A case report form (appendix IV) was used to record patients' bio data, demographics, past medical history, family history and social history. This data was obtained from the medical files and also through participant interview. The principal investigator filled in the drug therapy problems form (appendix V).

Participants were provided with the WHOQOL-BREF (Appendix VI), and the patient-reported medication adherence questionnaire (Appendix VII) and the principal investigator assisted the participants in filling out the questionnaire.

3.9 Quality assurance

3.9.1 Pre-Testing

Pre-testing of the questionnaires was done before the study was conducted. The questionnaires were administered to 6 (10%) participants to identify any issues. Corrections were made based on the patients' feedback. The 6 participants were included in the final sample of participants.

3.9.2 Measures to promote external and internal validity

The external validity of the study was assured based on the study site, KNH. Kenyatta national hospital is the largest referral hospital in Kenya, serves the whole country. Therefore, participants were expected to be a representative of the country sickle cell population. The sample size estimated was based on the prevalence of SCD in Kenya; therefore using this number of patients, the sample was representative of the target population. The internal validity of the study was maintained by using standard, simple and straightforward questionnaires for data collection. A well trained principal investigator and research assistant who maintained professionalism and ethical standards during the study ensured that the validity of the study is not compromised. The WHOQOL-BREF and medication adherence questionnaire were administered and analyzed as per the guidelines provided. Data acquisition was accurate and complete.

3.10 Data management

Data was recorded into printed data collection forms (Appendices I-VI) and stored safely under lock and key. Data collected was then transferred into Epi-info version-7 software within 24 hours of data collection. Data entry was done in duplicate and entries compared in order to identify inconsistencies which were reconciled by referring to the hard copy documents. All entries were checked for missing data and attempts made to complete all missing data by contacting the clinician or patient. Data cleaning was conducted every week. At the end of the data collection period, the database was locked to prevent any changes to the main database. Data were then exported to the STATA version 13 for data analysis. Data was backed up weekly into a password-protected flash drive and stored in a second location separate from the primary data. The PI retained all the original forms in a secure and protected place.

The electronic data was password protected. This data is to be archived for ten years in compliance with the Kenyan law.

3.10.1 Study variables

The independent variables were drug therapy problems which included: the need for additional drug therapy, unnecessary drug therapy, HU dosage too low, HU dosage too high, ineffective drug, adverse drug reaction and adherence. The dependent outcome variable was the HRQoL score that entails: physical health, social relationships, psychological health and environmental scores. The key predictor variable was the use of hydroxyurea. The confounding variables in this study included social demographic characteristics such as age, gender, education level, medical characteristics such as baseline health status at recruitment such as baseline haemoglobin, MCV, WBC count amongst others.

3.10.2 Data analysis

Data was analyzed using STATA version 13 software. Data analysis was divided into 3 phases, namely; descriptive, exploratory and regression analyses. Descriptive data analysis entailed summarizing key variables. Categorical variables were summarized as frequency and proportions. Continuous variables were tested for normal distribution by drawing histograms and the Shapiro Wilk test for normality. Normally distributed continuous variables were summarized as the mean (n) and standard deviation of the mean. Continuous variables that were not normally distributed were summarized as the median and interquartile range (IQR). Generalized linear regression analysis was done in order to control for confounding and to identify the most important determinants of the quality of life of patients. The principal outcome variable for regression analysis was quality of life domains. The regression analysis was restricted to variables that had a significant association ($p < 0.2$) with the outcome on bivariable analysis.

3.11 Ethical considerations

3.11.1 Independent Human Research and Ethics committee approval

Application for ethical approval was made to the Kenyatta National Hospital/University of Nairobi Ethics and Research Committee (KNH/UoN-ERC) and was granted under the study number (P96/02/2020) (appendix I).The study was carried out as per postulated guidelines and standards provided by the committee.

3.11.2 Informed consent

All participants received oral and written information in regards to the study (Appendix II). This included full disclosure of the nature of the study, expected benefits and risks, cost and time implication. Participants were informed of personal freedom to not participate in the study. Participants were not coerced into making any decision, and adequate time was provided for before a participant was to enrol for the study. Participants willing to take part in the study filled in and signed the consent forms. Assent was obtained from both the parents and participants under the age of 18 years (Appendix II).

3.11.3 Confidentiality

Participants' right to confidentiality was maintained throughout the study, and participants were assured of the same. All documents contained only the participants' identification number and initials. Findings during the research were kept in a personal computer that was password protected according to data protection laws. Participants were informed that third parties such as regulatory bodies might require access to the data, and such provision will be made in strictest confidence. Participant identification list with the participants' names and identification numbers was kept and maintained by the principal investigator.

CHAPTER FOUR: RESULTS

4.1 Introduction

Over the period of July 2020 to September 2020, a participant list was obtained from the KNH records section that generated 144 sickle cell patients who had been attended to in KNH over the past one year. The health records department was able to retrieve 130 files. The patient files were perused, and eligible participants contact information was able to be obtained from 75 of the files. Fifty-four participants were traced from the contact information. Seventeen eligible participants were also recruited from the haematology clinic 23. Four patients declined to participate in the study.

4.2 Characteristics of study participants

4.2.1 Socio-demographic characteristics

The baseline socio-demographic characteristics of the participants are summarized in Table 4.1

Table 4.1: Socio-demographic characteristics of participants

Variable	Category	Frequency n (%)
Gender	Male	35 (52%)
	Female	32 (48%)
Age (Mean ± SD)		20.7±7.2
Level of education	None	1 (1%)
	Primary	18 (27%)
	Secondary	21 (31%)
	Tertiary	27 (40%)
Occupation	Formal	3 (4%)
	Informal	1 (1%)
	Self-employed	12 (18%)
	Unemployed	5 (7%)
	Student	46 (69%)
Marital status	Single	39 (59%)
	Married	5 (7%)
	Separated	1 (1%)
Residence	Urban	47 (72%)

	Rural	3 (5%)
	Suburban	15 (23%)
Family history of SCD		43 (64%)
Alcohol use		5 (7%)
Use of substance of abuse		3 (4%)

Sixty-seven participants were interviewed with the majority being male (35, 52.23%). The mean age of the participants was 20.7 ±7.2 years. Sickle cell disease has a genetic component, and 43 (64.2%) had a past family history of the disease. Among those with a family history, 23 (53.5%) had a sibling with sickle cell disease and 20, (47%) a distant relative. Forty-eight (71%) participants had attained secondary education, and 46 (69%) were students. Majority of the participants (39, 59%) were single.

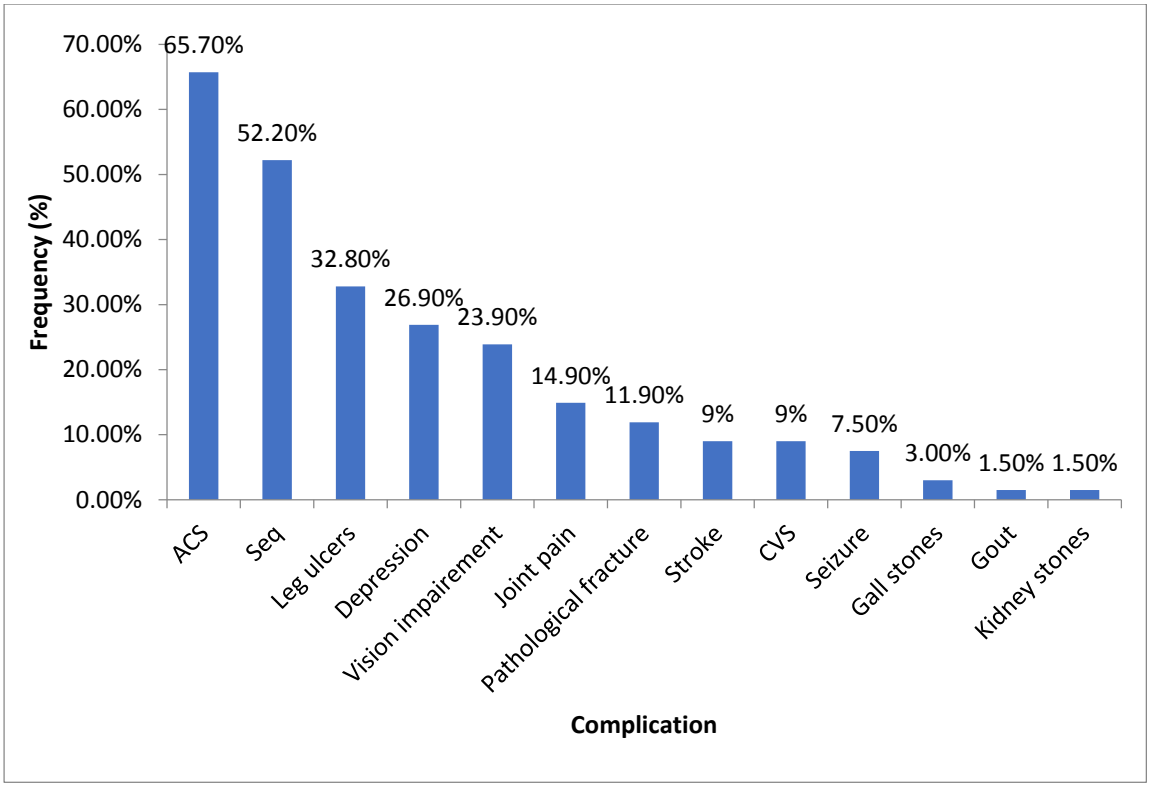
4.3 Clinical profile

Haemoglobin (Hb) electrophoresis had been done in 16 (25.8%) participants, and 14 of these (20.9%) were diagnosed with HbSS disease. Majority of the participants (60, 90%) had experienced a painful crisis in the past two years. Sixty-one (91%) had been hospitalized in the past two years, with 42 (63%) receiving a blood transfusion. This data is demonstrated in Table 4.2.

Table 4.2: Past medical history

Variable	Category	Frequency n (%)
Painful crisis in the past two years	Positive	60 (90%)
Blood transfusion in the past two years	Transfused	42 (63%)
Hospitalized in the past two years	Hospitalized	61 (91%)

Acute chest syndrome was the most commonly experienced health event, occurring in 44 (65.7%) patients. This was followed by sequestration crisis (35, 52.2%) patients and leg ulcers (22, 32.8%). Eighteen (26.90%) had suffered from depression. Cardiovascular events and stroke were each reported in only six participants. The complications are summarized in Figure 4.1.



KEY: *ACS- acute chest syndrome, Seq- Sequestration crisis, CVS- cardiovascular event*

Figure 4.1: Complications of SCD

4.4 Medications prescribed

Majority of the participants (65, 97%) were on folic acid, while 29 (42.9%) were on penicillin v 250mg. Twenty four (35.5%) of patients were on analgesics. In regards to ever receiving pneumococcal vaccination, only 9 (13%) participants have been vaccinated while 36 (53.7%) could not recall. Nine (13.4%) patients reported herbal medication use. The herbal products reported included Moringa, '*Mwarubaine'* and hibiscus.

4.5 Finding on clinical assessment

The participants were screened for constitutional symptoms associated with sickle cell disease. Headache was the most commonly reported symptom in 30 (44.8%) cases. Twenty-six (38.8%) reported painful episodes. Respiratory symptoms presenting as chest pain and cough were present in 14 (20.9%) and 6 (9%) participants, respectively. Gastrointestinal symptoms included nausea, diarrhea, vomiting, with

abdominal pain reported in 18 (26.9%) participants. The clinical assessment findings are summarized in Figure 4.2.

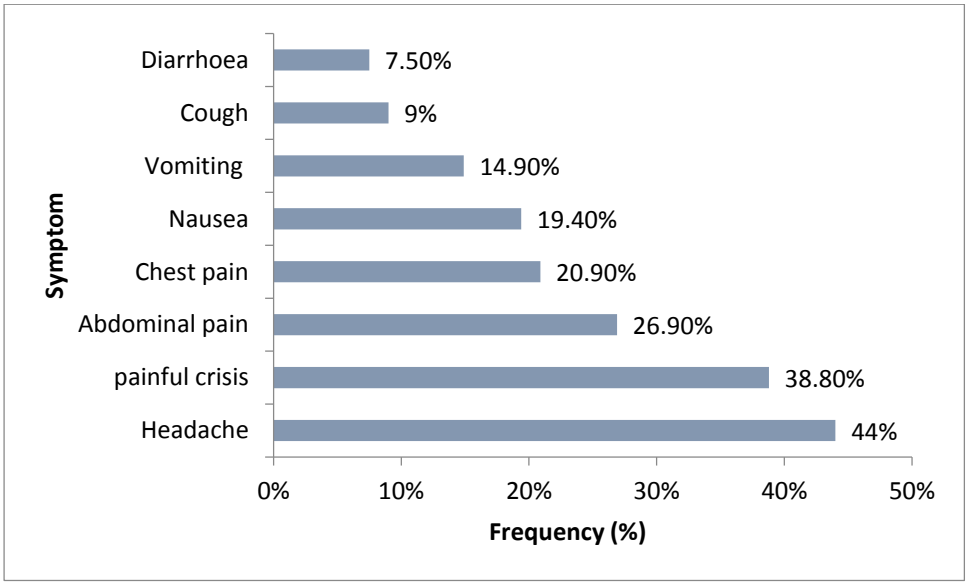


Figure 4.2: Clinical symptoms

4.6 Health-related quality of life measurements

The HRQoL measurements are summarized in figure 4.3. The overall HRQOL mean score was 56.0 ± 12.0. Psychological health had the highest mean score of 68.2±15.8, with the lowest being social relationships with a mean score of 49.4±21.3.

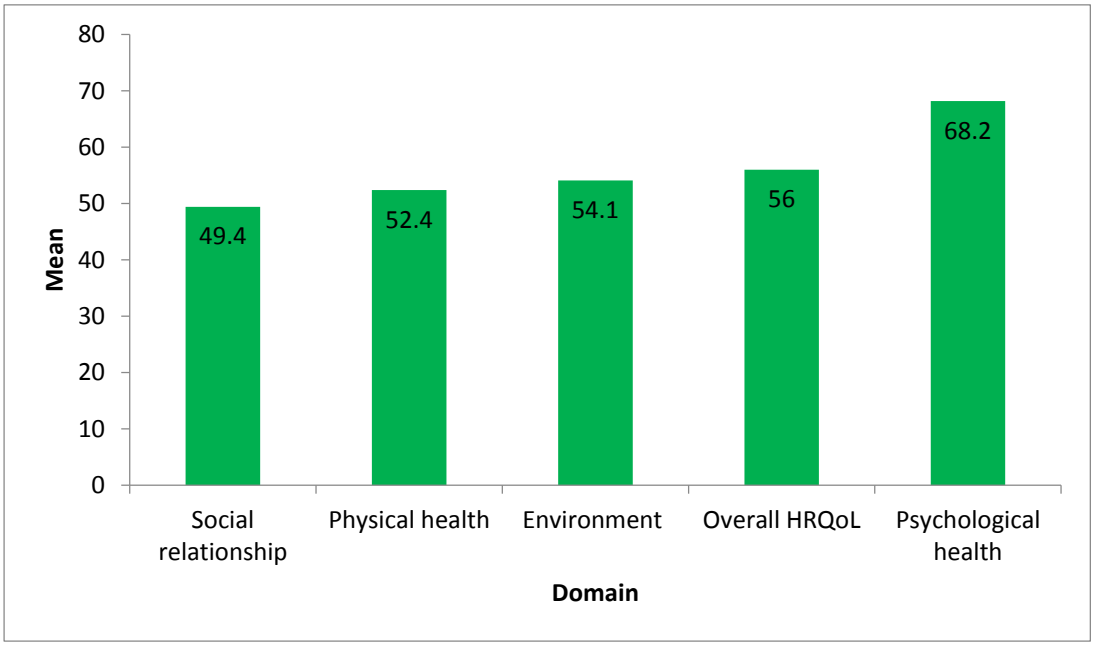


Figure 4.3: Mean scores of health-related quality of life domains

4.7 Adherence to hydroxyurea

The total adherence scores are categorized into three levels: high adherence (score =8), medium adherence (score of 6 to <8) and low adherence (score <6). The mean score for adherence to hydroxyurea was 4.51±1.90. Majority of the participants (51, 77.3%) had a low adherence score. Only 10.6% were highly adherent. This was due to forgetting to take hydroxyurea and inability to afford hydroxyurea. Categorizations of participants by levels of adherence are summarized in Figure 4.4.

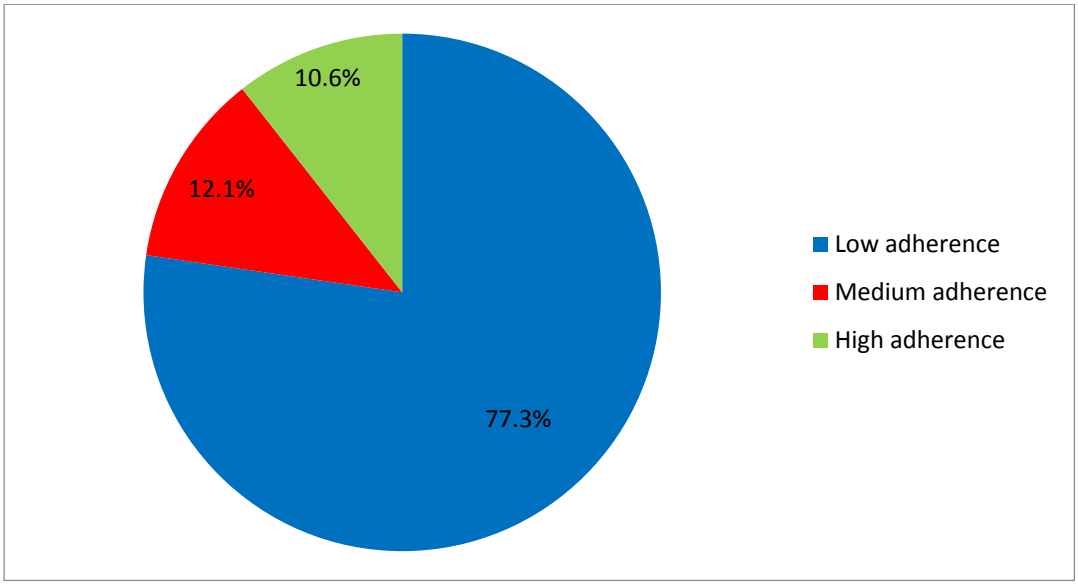


Figure 4.4: The levels of adherence to hydroxyurea

4.8 Drug therapy problems

The most prevalent DTP was non-compliance to medication (58, 86.6%). The cause of non-compliance in 50 (74.6%) patients forgot to take HU, while 46 (68.7%) cannot afford HU. Sixteen (23.9%) patients, preferred not to take HU and 2 (3%) could not access HU.

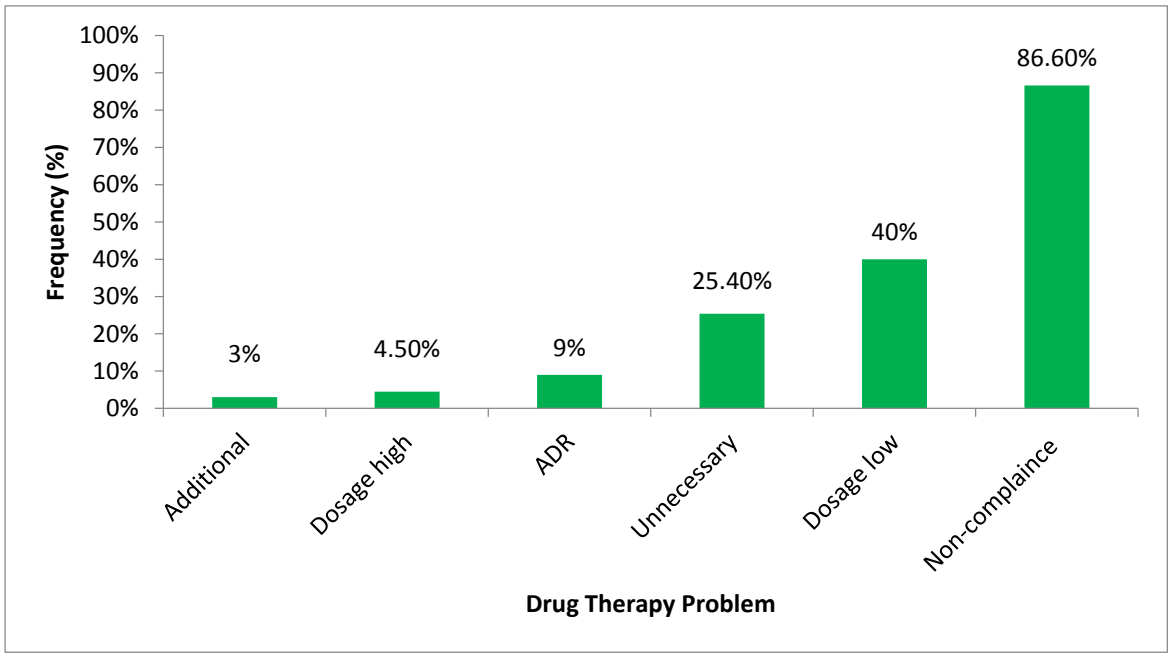
Hydroxyurea dosage was too low in 27 (42.2%) participants due to taking hydroxyurea dose less than 15mg/kg/day, which is an ineffective dose.

The other relevant DTP was unnecessary drug therapy in 17 (25.4%) patients, attributable to the use of Penicillin V in participants over the age of 15, which is not recommended.

Hydroxyurea dosage was too high in 3 (4.50%) participants. This was due to the total hydroxyurea dosage being more than the recommended 35mg/kg/day in 2 (3%)

participants. The frequency of hydroxyurea was too short in 1 (1.5%) participant with a reported frequency of three times daily.

Adverse drug reaction to HU was reported in 6 (8.96 %), the cause being undesirable effect. The reported ADR included darkening of nails in 2 (3%) participants. Nausea was reported in 1 (1.5%) participant and abdominal discomfort in 2 (3%) participants. The categories of drug therapy problems (DTPs) are summarized in Figure 4.5 and Table 4.3.



Key: *Unnecessary: Unnecessary drug therapy, Additional: Needs additional drug therapy ADR: Adverse drug reaction*

Figure 4.5: Drug therapy problem classes.

Table 4.3: Prevalence of drug therapy problems

DTP and CAUSE	N (%)	DTP and CAUSE	N (%)
Unnecessary drug therapy		**Adverse drug reaction**	
No medical indication	17 (**25.4%**)	Undesirable effect	6 (8.96%)
Needs additional drug therapy		**Dosage too high**	
Preventive/prophylactic therapy required	2 (3%)	Dose too high	2 (3%)
Synergistic/ potentiating therapy	1 (1.5%)	Frequency short	1 (1.5%)
Dosage too low		**Non-compliance**	
Ineffective dose	27 (**42.2%**)	Patient prefers not to take	16 (23.9%)
		Patient forgets to take	50 (**74.6%**)
		The patient cannot afford drug product	46 (**68.7%**)
		Drug product not available	2 (3%)

4.9 Correlates of physical health

Physical health refers to the ability of a person to perform their daily activities and capacity of work. It also encompasses energy and fatigue, mobility, pain, discomfort and dependence on medical substances and aids. Sleep and rest of a person are integrated as part of physical health. The correlates of physical health are shown in Table 4.4.

Table 4.4 Correlates of physical health of life

Variable	Bivariable analysis		Multivariable analysis	
	β co-efficient (95% CI)	**P value**	**β co-efficient (95% CI)**	**P value**
Age	-0.18 (-0.60, 0.24)	0.390	-	-
Gender	-1.35 (-7.34, 4.64)	0.653	-	-
Education	1.36 (-2.15, 4.88)	0.442	-	-
Occupation	-0.54 (-3.25, 2.16)	0.691	-	-
Residence	-0.26 (-0.3.93, 3.4)	0.890	-	-
Marital status	-0.50 (-1.56 0.57)	0.358	-	-
Alcohol use	8.23 (-2.90, 19.36)	0.145	7.87 (-2.98, 18.7)	0.152
Substance use	2.03 (-12.34, 16.4)	0.779	-	-
Family history of SCD	7.34 (1.33, 1336)	**0.018***	5.76(-0.21, 11.7)	0.058
Headache	-4.45 (-10.36, 1.46)	0.138	-3.18 (-9.10, 2.8)	0.287
Diarrhea	0.01 (-11.31, 11.33)	0.999	-	-
Cough	-3.55 (-13.93, 6.83)	0.497	-	-
Vomiting	-8.60 (-16.67, 0.52)	**0.037***	-4.39 (-13.16, 4.39)	0.321
Nausea	0.18 (-7.35, 7.71)	0.962	-	-
Painful crisis	-2.87 (-8.96, 3.21)	0.350	-	-
Chest pain	-6.76 (-13.89, 0.38)	0.063	-4.35 (-12.0, 3.29)	0.259
Abdominal pain	1.52 (-5.19, 8.24)	0.653	-	-
Unnecessary drug therapy	2.87 (-3.93, 9.69)	0.402	-	-
Needs additional drug therapy	-5.6 (-22.98, 11.86)	0.526	-	-
Dosage too low	-0.85 (-6.94, 5.23)	0.780	-	-
Adverse drug reaction	8.45 (-2.68, 19.57)	0.134	10.4 (-0.25, 21.1)	0.055
Dosage too high	-4.60 (-18.94, 9.73)	0.524	-	-
Non compliance	5.86 (-2.75, 14.46)	0.179	5.58 (-2.7, 13.9)	0.183

***- Statistically significant p- value**

The variables that showed an association with physical health were family history and vomiting. A positive family history caused a 7.34 (1.33, 13.36) (p = 0.018) increase in physical health in bivariable analysis. In multivariable analysis, family history caused a 5.76 (-0.21, 11.73) (p=0.058) increase in physical health; but this relationship was not statistically significant.

Patients who experienced vomiting had an 8.60 (-16.69, 0.52) (p= 0.037) times decrease in physical health score, in bivariable analysis. In multivariable analysis, vomiting caused a 4.39 (-13.16, 4.39) (p=0.321) decrease in physical health score, though this was not statistically significant.

4.10: Correlates of psychological health

Psychological health is dependent on how a person perceives their body image, appearance and self-esteem. Positive and negative feelings also determine psychological health. A person's spirituality/ personal beliefs/ religion have an impact on psychological health. Thinking, learning, memory and concentration are facets within psychological health.

The correlates of psychological health are shown in Table 4.5. Variables with a significant association include age, gender and family history of SCD. In the bivariable analysis for each unit increase in age, there was a 0.60 (-1.12, -0.74) (*p*= 0.026) times decrease in psychological health score. In the multivariable analysis, having controlled for other variables, advancing age caused a 0.24 (-0.83, 0.35) (*p*=0.420) times decrease in psychological health, though not statistically significant.

In the bivariable analysis, females seemed to have a 7.66 (0.06, 15.26) (*p*=0.048) times higher score in psychological health compared to males. Multivariable analysis showed that females have 9.32 (1.83, 16.82) (p=0.016) times higher psychological health score, which is statistically significant.

Presence of a positive family history of SCD in bivariable analysis led to a 9.96 (2.14, 17.78) (p=0.013) times increase in psychological health score. In multivariable analysis, family history of SCD caused a 8.49 (0.40, 16.58) (p=0.040) times increase in psychological health, which was statistically significant. The predictors of psychological health are shown in Table 4.5.

Table 4.5 Correlates of psychological health

Variable	Bivariable analysis		Multivariable analysis	
	β co-efficient (95% CI)	**P value**	**β co-efficient (95% CI)**	**P value**
Age	-0.60 (-1.12, -0.74)	**0.026***	-0.24 (-0.83, 0.35)	0.420
Gender	7.66 (0.06, 15.26)	**0.048***	9.32 (1.83, 16.82)	**0.016***
Education	-0.40 (-5.02, 4.20)	0.860	-	-
Occupation	1.25 (-2.27, 4.78)	0.480	-	-
Marital status	0.21 (-1.19, 1.61)	0.763	-	-
Residence	4.18 (-0.43, 8.79)	0.075	2.08 (-2.80, 6.96)	0.396
Family history of SCD	9.96 (2.14, 17.78)	**0.013***	8.49 (0.40, 16.58)	**0.040***
Alcohol use	-0.68 (-15.46, 14.10)	0.927	-	-
Substance use	5 (-13.74, 23.74)	0.596	-	-
Diarrhea	-11.50 (-26.0, 3.00)	0.118	-10.37 (-24.71, 3.98)	0.153
Cough	-10.7 (-24.04, 2.64)	0.114	-6.88 (-20.90, 7.14)	0.329
Vomiting	-9.58 (-20.22, 1.06)	0.077	-1.62 (-13.67, 10.43(	0.788
Nausea	-1.62 (-11.45, 8.20)	0.742	-	-
Headache	-6.47 (-14.15, 1.22)	0.098	-6.00 (-13.65, 1.64)	0.121
Painful crisis	-2.85 (-10.82, 5.12)	0.478	-	-
Chest pain	-6.36 (-15.80, 3.07)	0.183	0.03 -10.12, 10.18)	0.996
Abdominal pain	1.90 (-6.87, 10.67)	0.666	-	-
Unnecessary drug therapy	3.81 (-5.08, 12.71)	0.395	-	-
Needs additional drug therapy	3.89 (-18.91, 26.69)	0.734	-	-
Dosage too low	3.31 (-4.60, 11.23)	0.406	-	-
ADR	10.14 (-4.42, 24.70)	0.169	12.07 (-2.79, 26.94)	0.897
Dosage too high	16.17 (-2.16, 34.51)	0.083	1.24 (-18.00, 20.50)	0.109
Non compliance	1.55 (-9.84, 12.94)	0.787	-	-

***- Statistically significant p- value**

4.11: Correlates of social relationships

Social relationships encompass personal relationships, sexual activity and social support. The determinants of social relationship are shown in Table 4.6. Education, marital status and chest pain had a significant relationship in the bivariable analysis. Increase in level of education caused 6.96 (0.95, 12.90) (p=0.024) times increase in social relationships in bivariable analysis and 1.97 (-5.90, 9.83) (p=0.618) in multivariable analysis.

In regards to marital status, in the bivariable analysis, participants who were not married had a 2.82 (-4.58, -1.06) (p= 0.020) times decrease in social relationships. In multivariable analysis, they had a 1.97 (-4.45, 0.51) (p=0.118) times decrease in social relationship, though not statistically significant.

Those who suffered from chest pain had a 10.56 (-23.26, 2.07) (p= 0.010) times decrease in their social relationships compared to those without, in bivariable analysis. In multivariable analysis, controlling for other variables, chest pain caused a 7.20 (-19.44, 5.03) (p=0.243) times decrease in social relationships. The predictors of social relationships are shown in Table 4.6.

Table 4.6 Correlates of social relationship

Variable	Bivariable analysis		Multivariable analysis	
	β co-efficient (95% CI)	**P value**	**β co-efficient (95% CI)**	**P value**
Age	-0.15 (-0.89, 0.58)	0.683	-	-
Gender	-0.80 (-11.37, 9.77)	0.880	-	-
Education level	6.96 (0.95, 12.90)	**0.024***	1.97 (-5.90, 9.83)	0.618
Occupation	-0.10 (-4.87, 4.68)	0968	-	-
Marital status	-2.82 (-4.58, -1.06)	**0.002***	-1.97 (-4.45, 0.51)	0.118
Alcohol use	4.55 (-15.35, 24.46)	0.650	-	-
Substance use	4.83 (-20.47, 30.12)	0.704	-	-
Family history of SCD	3.67 (-7.36, 14.71)	0.508	-	-
Diarrhea	-2.16 (-22.09, 17.77)	0.830	-	-
Cough	-0.43 (-18.78, 17.92)	0.963	-	-
Vomiting	-7.42 (-22.02,7.18)	0.314	-	-
Nausea	-9.50 (-22.55, 3.56)	0.151	-8.46 (-21.15, 4.24)	0.188
Headache	-3.53 (-14.09, 7.02)	0.506	-	-
Pain crisis	-4.20 (-14.95, 6.54)	0.437	-	-
Chest pain	-10.56 (-23.20, 2.07)	**0.010***	-7.20 (-19.44, 5.03)	0.243
Abdominal pain	-4.44 (-16.23, 7.36)	0.455	-	-
Unnecessary drug therapy	-0.77 (-12.83, 11.29)	0.899	-	-
Needs additional drug therapy	-9.17 (-39.86, 21.52)	0.553	-	-
Dosage too low	-1.73 (-12.45, 8.99)	0.748	-	-
ADR	-10.16 (-29.94, 9.61)	0.308	-	-
Dosage too high	-21.37(-46.12, 3.39)	0.090	5.98 (-11.57, 23.53)	0.498
Non compliance	12.29 (-2.77, 27.36)	0.108	-4.30 (-33.41, 24.81)	0.769

***- Statistically significant p- value**

4.12 Correlates of environment domain

The facets that are encompassed in the environment domain include financial, physical aspect, opportunities and transport. These include financial resources, accessibility to healthcare and social care. An individual's environment also includes opportunities for acquiring new skills, information and recreation. The physical aspect entails home quality, personal safety, security and aspects of the environment such as noise, pollution, traffic and climate.

The correlates of the environment score are shown in Table 4.7. Variables that had an association with the environment were age, occupation and family history of SCD. A unit increase in age caused a 0.63 (-1.20, -0.07) (p=0.028) times decrease in environment domain in the bivariable analysis. In multivariable analysis, controlling for confounders, increasing age led to a 0.02 (-0.85, 0.81) (p= 0.969) times decrease in the environment, but it did not have statistical significance.

In bivariable analysis students had a 4.42 (0.80, 8.04) (p= 0.018) times higher environment score compared to those with other occupations 4.04 (-0.81, 8.89) (p=0.101) in multivariable analysis.

A positive family history showed an 11.60 (3.30, 19.89) (p=0.007) times increase in environment score in the bivariable analysis. Family history of SCD statistically significant effect on environment, score causing a 9.55 (0.74, 18.35) (p=0.034) times increase in environment domain. The predictors of environment domain are shown in Table 4.7.

Table 4.7: Correlates of overall quality of life

Variable	Bivariate analysis		Multivariable analysis	
	β co-efficient (95% CI)	**P value**	**β co-efficient (95% CI)**	**P value**
Age	-0.63 (-1.20, -0.07)	**0.028***	-0.02 (-0.85, 0.81)	0.969
Gender	0.83 (-7.55, 9.21)	0.844	-	-
Marital status	6.65 (-0.85, 2.14)	0.389	-	-
Residence	4.16 (-0.91, 9.22)	0.106	2.64 (-2.35, 7.62)	0.294
Education level	-1.86 (-6.78, 3.05)	0.451	-	-
Occupation	4.42 (0.80, 8.04)	**0.018***	4.04 (-0.81, 8.89)	0.101
Family history of SCD	11.60 (3.30, 19.89)	**0.007***	9.55 (0.74, 18.35)	0.034
Alcohol use	3.81 (-11.98, 19.60)	0.631	-	-
Substance use	-1.83 (-21.92, 18.27)	0.857	-	-
Diarrhea	-0.30 (-16.12, 15.52)	0.970	-	-
Cough	0.28 (-14.28, 14.84)	0.970	-	-
Vomiting	-8.46 (-19.94, 3.02)	0.146	-1.53 (-14.46, 11.40)	0.814
Nausea	-3.83 (-14.31, 6.65)	0.468	-	-
Headache	-5.88 (-14.16, 2.39)	0.160	-5.83 (-14.22, 2.56)	0.170
Painful crisis	2.16 (-6.39, 10.71)	0.616	-	-
Chest pain	-6.99 (-17.08, 3.10)	0.171	-3.36 (-14.62, 7.90)	0.553
Abdominal pain	-0.41 (-9.81, 8.99)	0.931	-	-
Unnecessary drug therapy	3.07 (-6.47, 12.61)	0.523	-	-
Needs additional drug therapy	15.39 (-8.73, 39.51)	0.207	-	-
Dosage too low	-3.70 (-12.16, 4.76)	0.386	-	-
ADR	6.41 (-9.33, 22.15)	0.419	-	-
Dosage too high	2.06 (-18.07, 22.11)	0.842	-	-
Non compliance	-4.03 (-16.19, 8.13)	0.510	-	-

***- Statistically significant p- value**

4.13: Correlates of overall health-related quality of life

Quality of life (QoL) is described as an individual's perception of their life position in regards to the value systems and culture of the society they live in and concerning their standards, goals, expectations and concerns. The overall quality of life is a function of the physical health, psychological health, social relationships and environment of an individual.

The predictors for the overall HRQoL are shown in Table 4.8; the variables with a statistically significant association with overall HRQoL are family history, chest pain and vomiting. A positive family history caused 8.14 (2.24, 14.05) (p=0.008) times increase in the overall HRQoL in the bivariable analysis and 6.58 (0.66, 12.50) (p=0.030) times in multivariable analysis. Chest pain caused a 7.67 (-14.69, 0.64) (p=0.033) times decrease in the overall health-related quality of life. After controlling for other variables, chest pain caused a 1.71 (-10.43, 7.02) (p=0.697) times decrease in the overall HRQoL. Participants with vomiting had an 8.50 (-16.54, 0.49) (p=0.038) times decrease in the overall HRQoL in the bivariable analysis. In multivariable analysis, after controlling for other variables, vomiting caused a 4.77 (-10.46, 0.93) (p=0.099) decrease in the HRQoL. The predictors of overall quality of health are shown in Table 4.8.

Table 4.8 Predictors of overall quality of life

Variable	Bivariable analysis		Multivariable analysis	
	β co-efficient (95% CI)	**P value**	**β co-efficient (95% CI)**	**P value**
Age	-0.39 (-0.79, 0.12)	0.057	-0.31 (-0.71, 0.08)	0.120
Gender	1.58 (-4.37, 7.53)	0.600	-	-
Marital status	-0.61 (-167,0.44)	0.251	-	-
Education	1.50 (-1.99, 4.99)	0.392	-	-
Occupation	1.26 (-1.42, 3.93)	0.351	-	-
Residence	1.06 (-2.55, 4.67)	0.560	-	-
Alcohol use	3.98 (-7.22, 15.18)	0.481	-	-
Substance use	2.51 (-11.77, 16.78)	0.727	-	-
Family history of SCD	8.14 (2.24, 14.05)	**0.008***	6.58 (0.66, 12.50)	**0.030***
Headache	-5.08 (-10.92, 0.76)	0.087	-4.31 (-11.64, 3.02)	0.244
Painful crisis	-1.94 (-8.01, 4.13)	0.525	-	-
Chest pain	-7.67 (-14.69, 0.64)	**0.033***	-1.71 (-10.43, 7.02)	0.697
Abdominal pain	-0.35 (-7.03, 6.33)	0.916	-	-
Diarrhea	-3.47 (-14.70, 7.73)	0.537	-	-
Cough	-3.60 (-13.91, 6.71)	0.488	-	-
Vomiting	-8.50 (-16.54, -0.49)	**0.038***	-4.77 (-10.46, 0.93)	0.099
Nausea	-3.69 (-11.21, 3.73)	0.324	-	-
Unnecessary drug therapy	2.25 (-4.53,9.03)	0.510	-	-
Needs additional drug therapy	1.14 (-16.22, 18.50)	0.900	-	-
Dosage too low	-0.74 (-6.79, 5.31)	0.807	-	-
ADR	3.71 (-7.50, 14.92)	0.511	-	-
Dosage too high	-1.94 (-16.22, 12.33)	0.787	-	-
Non-compliance	3.92 (-4.70, 12.53)	0.367	-	-

***- Statistically significant p- value**

CHAPTER FIVE: DISCUSSION, CONCLUSIONS AND RECOMMENDATIONS

5.1 Introduction

This chapter highlights the key findings of the study in the context of existing literature. The proceeding section offers a summary of the results and discussions, with an overall conclusion of the study. The limitations of the study are highlighted as well. Finally, recommendations for policy, practice and further research emerging from the research findings are given.

5.2 Discussion

In this study, the HRQoL scores ranged from 31.2 to 82.8, with a group mean of 56 ±12.0. This score is lower compared to the general population (8). The quality of life among patients with SCD seems to be generally fair. Patients with SCD tend to score worse than patients with other chronic diseases such as rheumatoid arthritis, asthma and chronic back pain (8). Environment domain mean score was 54.1± 16.9. Social relationships mean score was 49.4±21.3. The results showed that the disease could strongly impact personal relationships, social support and sexual activity among SCD patients.

Increasing age caused a decrease in overall HRQoL, though not statistically significant. This could be attributed to worsening physical health with increasing age. The association echoes a similar study in Saudi Arabia and Jamaica, where increasing age was associated with lower QoL scores (47,48). With advancing age, there could be progressive organ damage due to vaso-occlusion and infarcts, leading to low perfusion and health. Increasing age is associated with declining organ function, increased responsibilities with reduced time and resources for better self-care, which adversely affects feelings, attitudes and aspects of psychological health. An increase in age caused a decrease in social relationships score, though not statistically significant. In a study by Sherif et al., older participants with SCD had more pain, anxiety, severe fatigue and worse QoL scores (48).

Females had a higher score in the overall QoL compared to men. Women are known to have better social and emotional support which can lower risks of depression compared to men (49). This finding differed from findings by Ami et al., whereby females had lower QoL scores compared to males. The study was carried out in Saudi

Arabia, and the differences in religion and society beliefs could have contributed (46). Females had a better psychological score compared to their male counterparts. This could be attributed to better health-seeking behaviors among women. Females had a lower score of social relationships compared to males. Females had a better score in the environment compared to males. In a study by Varni et al., females had lower QoL scores (50). Another study showed that male counterparts had better scores in all domains compared to females (46).

A positive family history of SCD was associated with a better quality of life scores, and the relationship was statistically significant. This could be associated with better social, psychological support. These patients could have a lower incidence of depression which may improve pain and lead to better physical health scores. Parents could be keener to the needs of the sicklers in the family, therefore improving various aspects of their lives. In regards to occupation, students had a better environment score compared to those working. This could be probably attributed to a safer school environment, opportunities for leisure/ recreation activities and acquisition of new skills. Those who were working may have experienced more financial constraints. This is in contrast to a quality of life study in Jamaica, where SCD patients who were employed had a better QoL (47).

Living in an urban area had a negative impact on physical health compared to rural areas. Higher costs of living in an urban area may lead to a lower quality of life due to social and economic stresses that arise. Residing in urban areas was shown to lead to lower environmental score compared to a rural residence. Urban living tends to be more expensive, and public transport can be unreliable at times, thereby disrupting movement. Urban areas have industries and larger populations leading to higher levels of noise and air pollution, which could have a detrimental effect on health. This is in line with the findings by Asnani et al., whereby living in rural areas was associated with better QoL, with better physical and mental scores compared to urban areas (47). This was associated with lower levels of social support in urban areas and fewer limitations in their daily lives among those living in rural areas. In a study in Saudi Arabia, the rural residence was, however, associated with lower HRQoL scores (46).

Attainment of a higher level of education improved the social relationships score. There was an association between marital status and social relationships. Those who

were married had better social relationships compared to those who were not. These findings are in line with a study by Jady et al. that showed that married persons had significantly better scores in the social domains of QOL compared to the unmarried and single cohort (49). Married people generally have a more significant household income, health insurance, homeownership, and children providing more social support.

History of alcohol use did not cause a decrease in the QoL domains. Unexpectedly, alcohol users had better scores for all domains apart from social relationships. This correlates to similar findings by Erica et al. in Brazil (49) and could be attributed to higher income, and education as well as being employed among alcohol consumers. Low to moderate alcohol use has been suggested to have beneficial effects on some health conditions such as diabetes mellitus, ischemic heart disease, ischemic stroke and total mortality. The findings on the relationship between alcohol and QoL are conflicting, and the association is complicated due to different demographics, attitudes about alcohol, gender differences and other confounding factors (52).

Clinical symptoms lowered the scores of the HRQoL domains. Respiratory symptoms, such as cough and chest pain led to lower PH scores. Chest pain had a significant association with overall QoL and decreased the environment score. Chest pain had a negative association with social relationships. Cough had a negative impact on the quality of life of patients by causing lower psychological health scores. The respiratory system is vital to body functioning by maintaining oxygen levels in the blood. Impaired respiratory function leads to hypoxia, which causes sickling of RBCs and subsequent painful crisis. Respiratory symptoms in SCD can be associated with acute chest syndrome or sickle cell chronic lung disease and pulmonary hypertension which are sequelae of SCD (4).

Gastrointestinal sequelae occur due to vaso-occlusion, infarcts or sequestration (4). Vomiting showed a negative association with psychological domain and overall QoL. It negatively impacted physical health; this indicates gastrointestinal disturbance which could be due to the disease process or side effects of hydroxyurea. Nausea lowered the psychological, social and environmental score. Vomiting causes an imbalance of body electrolytes, which can lead to dehydration, which predisposes the

patient to RBC sickling and painful crises. Diarrhea led to lower psychological health score, and abdominal pain lowered the overall QoL and social relationships score.

Headaches negatively affected the physical health score, causing lower scores. The presence of headache also led to poorer scores in psychological health and environmental score. Vaso-occlusion in arteries supplying the brain or retina may result in headaches (4).

Presence of painful episodes caused a decrease in the social domain score. Clinical symptoms of pain negatively affected the overall QoL. In a study by Anie et al., severe pain associated with SCD impaired HRQoL(53). Pain management is one of the major cornerstones in improving the QoL of patients with SCD (8).

The presence of clinical symptoms lowered the quality of life scores, and this is consistent with findings in other studies that showed that symptoms burden were associated with depression, anxiety and lower HRQoL scores (48,54,55).

SCD is a chronic debilitating disease and predisposes the patients to mental health disorders such as depression and anxiety. Depression was associated with a worse psychological health domain. In a study by S. Adam et al., depression was found in 35.2% of patients and was strongly associated with worse mental and physical quality of life outcomes (56). Patients with more painful episodes are more likely to suffer from depressive episodes. Health care costs in SCD patients with depression are about five times higher than those without depression (8); this affects the overall quality of life of the patients due to increased medical costs. Depressed patients experience lower scores in all quality-of-life domains (8).

The drug therapy problems identified were categorized into seven major classes (57). Unnecessary drug therapy led to a lower social relationship score. Higher pill burden may affect a patient's adherence due to increased cost, and side effect profile which negatively affects the quality of life (58). Need for additional drug therapy was occasioned by omitting folic acid as synergistic therapy to hydroxyurea for hematopoietic support. In a Cochrane review, there was mixed evidence on the effect of folate on outcomes in sickle cell disease, and the effects of supplementation on anaemia remain unclear (59). Additional preventive therapy was required in 3% of patients and entailed the addition of penicillin v 250mg in their therapy plan. The

need for additional therapy led to lower PH scores, indicating the significance of supportive/synergistic therapy. Penicillin prophylaxis is associated with reduced incidence of pneumonia, acute chest syndrome and morbidity among children (60).

A low dosage of hydroxyurea was reported in 42.2% of patients contrary to the recommended one (61). In a study by Titilola et al. fixed dose of HU at 10mg/kg/day was associated with an improved laboratory picture in patients (28). Chandy et al. found that HU with dose escalation had superior clinical and laboratory efficacy, compared to a fixed-dose (39). A low dosage of hydroxyurea also caused a lower score in the social relationships domain. Inadequate treatment of SCD impairs physical functioning, and this impairs the capacity to engage in social activities, thus affecting social relationships.

High dose of hydroxyurea led to lower physical health, social relationships and overall quality of life score; this could be due to more side effects with higher doses, increased cost of hydroxyurea and increased pill burden. Adverse drug reaction to hydroxyurea was reported in 8.96% of participants. In a study carried out in Nigeria, a low dose of hydroxyurea was associated with a low adverse outcome rate (28). In contrast, a clinical trial by Chandy et al. showed that patients on an escalated dose of HU had fewer adverse events (39).

Non-compliance was the most reported DTP, and this was mainly attributed to the inability to afford HU as well as forgetting to take it. Patients who preferred not to take hydroxyurea as prescribed were 23.9%, this is comparable to the 28.6% of youths that did not want to take HU in the Barriers to hydroxyurea use study (13). More than half forgot to take the drug similar to findings by Smaldon et al. reported 53.6% (13). Most participants reported an inability to afford to buy hydroxyurea, and 3% had issues in accessing it. Non-compliance led to lower scores in the environment domain. Hydroxyurea has been shown to improve all quality of life domains, and therefore poor adherence would negatively affect this domain. Low adherence to hydroxyurea was associated, with significantly worse fatigue scores in as study by Sherif et al. (13). There was an association between patients forgetting to take hydroxyurea, leading to a lower score of the overall QoL. Failure to take hydroxyurea will lead to more sickling of RBCs, more vaso-occlusion and eventually painful crises, affecting the physical, psychological and social aspects of life. Findings in a study done by

Sherif et al. showed that young adults with recall barriers to taking HU had more fatigue, depression, worse pain and lower physical functioning (13).

5.3 Conclusions

1. HRQoL among sickle cell patients was sub-optimal. Significant determinants of HRQoL included family history, chest pain and vomiting.
2. Non-compliance, low dosage of hydroxyurea and unnecessary drug therapy were the most common DTPs among SCD patients.

5.4 Recommendations for policy and practice

1. The most common drug therapy problem was non-compliance, and this was mainly due to financial constraints in getting hydroxyurea; therefore, a strategy to address this DTP needs consideration.
2. Low dosage of hydroxyurea and unnecessary drug therapy require pharmacovigilance and measures to ensure appropriate drug therapy.
3. HRQoL was suboptimal and mitigating measures such as pain control, screening and treatment of depression, should be considered in order to improve the quality of life.
4. Patient education and adherence counseling should be done on every clinical visit in order to address any barriers to taking hydroxyurea.

5.5 Recommendation for further research

1. Interventional studies to determine the optimum dosing of HU in a Kenyan population. A multicenter randomized study comparing low dose HU and escalated dose HU to determine safety and effectiveness of HU in this demographic.
2. Prospective intervention studies with larger sample size addressing drug therapy problems related to HU cost, forgetfulness, access, and other actionable barriers could lead to higher adherence levels, and therefore improve HRQOL and other important clinical outcomes.
3. Family history of sickle cell disease showed significant associations with various domains of HRQoL. Further research is recommended to determine the relationship between positive family history and its effect on HRQoL in SCD.

5.6 Study limitations

The study was conducted at Kenyatta National Hospital, which is an urban hospital and a single center; the study sample may not be representative of the general population. This affected the generalizability of the study to the Kenyan population. There was a risk of selection bias based on the location of the hospital.

The study was a cross-sectional study and with a small sample size (n=67) may affect the power of the study and this also impedes some statistical analysis to identify a statistically significant relationship between HRQoL and hydroxyurea use. Data collection was done using questionnaires and self-reported outcomes from the participants. This method of data collection is prone to response and recall bias in some participants.

The COVID-19 pandemic was an unforeseeable event, which greatly affected the lives of people. Data collection was done during the pandemic. Aspects of quality of life are determined by the day to day lives; therefore, COVID-19 was a confounding factor in this study, due to its negative impact.

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APPENDICES

APPENDIX I: ETHICS COMMITTEE APPROVAL LETTER

UNIVERSITY OF NAIROBI
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KENYATTA NATIONAL HOSPITAL
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Ref: KNH-ERC/A/177

10th June 2020

APPROVED
10 JUN 2020
KNH-UoN-ERC

Dr. Marjorie Watetu Kagiri
Reg.No.U56/11628/2018
Dept. of Pharmaceutics and Pharmacy Practice
School of Pharmacy
College of Health Sciences
University of Nairobi

Dear Dr. Kagiri

RESEARCH PROPOSAL – HEALTH RELATED QUALITY OF LIFE AND DRUG THERAPY PROBLEMS IN PATIENTS WITH SICKLE CELL DISEASE ON HYDROXYUREA AT KENYATTA NATIONAL HOSPITAL (P96/02/2020)

This is to inform you that the KNH- UoN Ethics & Research Committee (KNH- UoN ERC) has reviewed and **approved** your above research proposal. The approval period is 10th June 2020 – 9th June 2021.

This approval is subject to compliance with the following requirements:

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

Protect to discover

APPPENDIX II: CONSENT FORM

HEALTH RELATED QUALITY OF LIFE AND DRUG THERAPY PROBLEMS IN PATIENTS WITH SICKLE CELL DISEASE ON HYDROXYUREA AT KENYATTA NATIONAL HOSPITAL

Informed consent for . . . . . .

The principal investigator, Dr Marjorie Watetu, under the supervision of Dr Peter N. Karimi and Professor Faith A. Okalebo conducting a study on the Health related quality of life and drug therapy problems in patients with sickle cell disease on hydroxyurea disease at Kenyatta National Hospital.

SECTION I: PARTICIPANT INFORMATION SHEET

Introduction

I am Dr Marjorie Watetu, a postgraduate student pursuing a Masters in Clinical Pharmacy at the University of Nairobi. I am conducting a clinical trial at the Kenyatta National Hospital and this type of study is carried out on patients who have willingly agreed to participate in the study. The principal investigator will provide you will all the information in regards to this study. You have been selected to participate in this trial as you are a diagnosed patient with Sickle Cell Disease and the drug under study is used in management of sickle cell disease. You are free to discuss this study with your doctor, family and friends before making a decision to participate.

Purpose of this research

The study will determine your quality of life and will look into problems you may be facing while using hydroxyurea.

Who is conducting the research?

The study is being conducted by Dr Marjorie Watetu, (Bachelor of Pharmacy), currently a postgraduate student doing Masters in Clinical Pharmacy, at University of Nairobi, School of Pharmacy, Pharmaceutics and Pharmacy Practice department. P.O. Box 4038-20100, mobile number 0723761866/ 077177275, email watetumarj@gmail.com.

Who are the supervisors of this research?

This study is being done under the supervision of:

Dr Peter N. Karimi, clinical pharmacist and lecturer, department of Pharmaceutics and Pharmacy practice, School of Pharmacy University of Nairobi.

Professor Faith A. Okalebo, department of Pharmacology and Pharmacognosy, School of Pharmacy, University of Nairobi.

Ethical approval

This study will be conducted only after acquiring ethical approval from the Kenyatta National Hospital/ University of Nairobi Ethics and Research Committee (KNH/UON ERC), P.O. Box 20723-00100 Nairobi. Telephone number (020) 2726300/2716450 extension 44102.

Participant's rights

It is your individual right to participate or not participate in the study. It is your right to ask any questions and seek more information about the study as you see fit. You will not be victimized because of your choices. You will continue to receive the best standard care at Kenyatta National Hospital. You will also receive a signed copy of the informed consent form.

I have checked with the child and they understand participation is voluntary

_____ (sign)

What will happen if I participate in this study?

Before participating in the study, you will be given all the information about the study and you will sign a consent form agreeing to participate in the study. You will be asked questions about your illness and different aspects of your life. You will then be asked to fill in questionnaires that will be provided in the best way possible. You will be provided assistance in filling in the questionnaire.

I have checked with the child and they understand the procedure

_____ (sign)

Duration of the study

The collection of information will be done during your clinic visit and will take an average of one hour to go through the questionnaires.

What risks associated with participating in the study?

You will not be harmed in any way by participating in this study.

I have checked with the child and they understand the risks _____
(sign)

What are the benefits of the study?

The information collected from this study will help give an overview of the quality of life in sickle cell patients and assess issues related with hydroxyurea use. This information can be used by doctors, pharmacists, nurses to improve patient care.

What if I do not want to participate in the study?

If you do not want to participate in the study you will continue with your standard care at the Kenyatta National Hospital. You will not be victimized for refusing to participate in the study.

What are the costs of participating in the study?

You will not incur any extra costs during the study outside your normal standard care that you receive at the hematology clinic.

Will my medical information be kept private?

A unique number will be used instead of your name during the study to ensure privacy. All information collected during this study will be kept by the principal investigator in a safe secure and password protected manner. No one shall have access to this information unless required by and authorized by the KNH/UON ethics and research committee. If the findings of this study are published or presented in a conference, your name or any other information will not appear.

Complaints or concerns

Any complaints, concerns or enquiries may be further addressed to:

Secretary, KNH/UON

University of Nairobi, School of Pharmacy

P.O.Box 20723-00100 Tel: (020) 2726300/2716450 Extension 44102

Email: uonknh-erc@uonbi.ac.ke.

This information sheet is for you to keep.

SECTION II: CERTIFICATE OF CONSENT

Research study title: **HEALTH RELATED QUALITY OF LIFE AND DRUG THERAPY PROBLEMS WITH HYDROXYUREA USE IN ADOLESCENTS AND ADULTS WITH SICKLE CELL DISEASE AT KENYATTA NATIONAL HOSPITAL**

UON/KNH ERC Approval Number:

Researchers' Name: Dr Marjorie Watetu

Researchers' relationship to institution: Masters of Pharmacy in Clinical Pharmacy, University of Nairobi.

Participant consent, Serial No. . . . . .

I have read and understood the information regarding the study. I have had the opportunity to ask questions and seek clarification in regards to the study.

I _____willingly consent to participate in this study.

(Surname, First name, other name)

Signature _____

Date _____

Contact _____

Witness _____

I _____ being the parent/guardian of _____

willingly consent for my child to participate in this study.

(Full names)

Signature _____

Date _____

Contact _____

Investigator Statement

I _____ have fully explained to the participant the study protocol, the risks and benefits involved.

Name _____

Signature _____

Date _____

Consent discussion

Investigator _____

Date _____

University of Nairobi, Department of Pharmaceutics and Pharmacy Practice.

P.O.Box 4038-20100. Tel: 0723761866/0717772750.

Witness _____

Date _____

Relationship of witness to investigator /participant _____

CONTACT INFORMATION

For any inquiries, the following can be contacted:

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Dr Peter N. Karimi

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Professor Faith A. Okalebo

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APPENDIX 1 (UTANGULIZI): TAARIFA YA MSHIRIRKI UTAFITI

MADA

UTAFITI UNAOANGALIA UBORA UNAOHUSIANA NA AFYA NA SHIDA ZA MATIBABU YA HYDROXYUREA KWA MATIBABU YA UGONJWA WA SELI KWA VIJANA NA WATU WAZIMA KATIKA HOSPITALI KUU YA KENYATTA.

Idhini ya kujua . . . . . .

Mpelelezi mkuu , Dkt Marjorie Watetu , anayesimamiwa na Dkt Peter N. Karimi na Profesa Faith A. Okalebo wakifanya uchunguzijuuya ubora unaohusiana na afya na shida za matibabu ya dawa na utumiajiwa hydroxyurea kwavijana na watu wazima wenye ugonjwa wa seli katika Hospitali ya Kitaifa ya Kenyatta .

SEHEMU YA I: SEHEMU YA USHIRIKIANO WA HABARI

Utangulizi

Mimi ni Dkt. Marjorie Watetu, Mwanafunzi wa Uzamifu katika Matibabu katika Idara ya Famasia na Mazoezi ya Ufamasia, Kitivo cha Ufamasia, Chuo Kikuu cha Nairobi. Ninafanya uchunguzi wa kliniki katika Hospitali ya Kitaifa ya Kenyatta n aina hii ya uchunguzi hufanywa kwa wagonjwa ambao wamekubali kwa hiari kushiriki. Mpelelezi mkuu atakupa habari zote kuhusu utafiti huu. Umechaguliwa kushiriki katika jaribio hili kuwa wewe ni mgonjwa unayepatikana na ugonjwa wa seli ya sickle na dawa unayo tumia hutumika katika usimamizi wa seli ya sickle. Uko huru kujadili utafiti huu na daktari wako, familia na marafiki kabla ya kufanya uamuzi wa kushiriki.

Kusudi la utafiti huu

Utafiti utabaini ubora wa maisha yako n autaangalia shida ambazo unawezakuwa unazo wakati wakutumia hydroxyurea.

Ni nani anayefanya utafiti?

Utafiti huu unafanywa na Dkt. Marjorie Watetu, Mwanafunzi wa Uzamifu katika Matibabu katika Idara ya Famasia na Mazoezi yaUfamasia, Kitivo cha Ufamasia, Chuo Kikuu cha Nairobi.

SLP 4038-20100, Simu 0723761866/077177275, Barua pepe watetumarj@gmail.com .

Ni nani wakurugenzi wautafiti huu?

Utafiti huu unafanywa chini ya usimamizi wa:

Dr Peter N. Karimi: Mhadiri, Idara ya Famasia na Mazoezi yaUfamasia. Kitivo cha Ufamasia. Profesa Faith A. Okalebo: Idara ya Famakolojia na Ufamaknosia, Kitivo cha Ufamasia.

Idhini ya maadili

Utafiti huu utafanywa tu baada ya kupata idhini ya kimaadili kutoka kwa Kamati ya Maadilina Utafitiya Hospitali ya Kitaifaya Kenyatta pamoja na Chuo Kikuu cha Nairobi (KNH/UON-ERC) SLP 20723-00100 Nairobi. Simu (020) 2726300/2716450 ext: 44102.

Hakizamshiriki

Ni haki yako binafsi kushiriki au kutoshiriki katika utafiti. Ni haki yako kuuliza maswali yoyote na kutafuta habari zaidi juu ya utafiti unavyoona inafaa. Hauta nyanyasw kwa sababu ya uchaguzi wako. Utaendelea kupatahuduma bora zaidi katika Hospitali ya Kitaifaya Kenyatta. Pia utapokea fomu ya idhini iliyotiwasaini.

Nimemweleza motto na anaelewa ushiriki ni wa hiari

Ishara

……

Je! Nini kitatokea ikiwa nitashiriki katika utafiti huu?

Kabla ya kushiriki katika utafiti, utapewa habari zote kuhusu utafiti huu na utasaini fomu ya idhini ya kukubali kushiriki katika masomo. Utaulizwa maswali juu ya ugonjwa wako na halitofautiza maisha yako. Kisha utaulizwa kujaza dodoso ambazo zitatolewa kwa njia bora zaidi. Utapewa msaada katika kujaza dodoso.

Nimemweleza mtoto na anaelewa utaratibu

Ishara……

Muda wa masomo

Mkusanyiko wa habari utafanywa wakati wa ziara yako ya kliniki na itachukua wastani wasaa moja kupitia maswali.

Kuna hatari gani zinazohusiana na kushiriki katika utafiti?

Hautaumizwa kwa njia yoyote kwa kushiriki katika utafiti huu .

Nimemweleza mtoto na anaelewa utaratibu

Ishara ……...

Je! Ni faida gani za utafiti huo?

Habari iliyokusanywa kutoka kwa utafiti huu utasaidia kutoa muhtasari wa ubora wamaisha kwa wagonjwa wa seli na kutathmini masuala yanayo husiana na utumiaji wa hydroxyurea. Njia hii inaweza kutumiwa na ma daktari,wafamasia, wauguziiliku boresha huduma kwa mgonjwa.

Je! Ikiwa sitaki kushiriki katika utafiti?

Ikiwa hutaki kushiriki katika utafiti huu utaendelea na utunzaji wako wa kawaida katika Hospitali ya Kitaifa ya Kenyatta. Hautanyanyaswa kwa kukataa kushiriki katika utafiti.

Je! Ni gharamaganizakushirikikatikautafiti?

Hautaleta gharama zozote za ziada wakati wa kusoma njeya, utunzaji wako wa kawaida unaopokea katika kliniki ya hematolojia.

Je! Habariyanguyamatibabuitawekwafaragha?

Nambari ya kipekee itatumika badala ya jina lako wakati wa kusoma ili kuhakikisha faragha. Habari zote zilizo kusanywa wakati wa uchunguzi huu zitatunzwa na mpelelezi mkuu kwa njia salama na salama yanywila. Hakuna atakaye weza kupata habari hii isipokuwa ikihitajika na kuidhinishwa na maadili na kamati ya utafiti ya KNH/UON. Ikiwa matokeo ya utafiti huu yamechapishwa au kuwasilishwa katika mkutano, jina lako au habari nyingine yoyote haitaonekana.

Malalamiko au wasiwasi

Malalamiko yoyote, wasiwasi au maoni yanaweza kushughulikiwa zaidi kwa :

Katibuya KNH /UON- ERC

Chuo Kikuu cha Nairobi, Kitivo cha Ufamasia

SLP 20723-00100 Simu: (020) 2726300/2716450 Ext 44102

Barua pepe: uonknh-erc@uonbi.ac.ke .

Karatasi hii ya habari ni kwako kutunza.

SEHEMU YA II: FOMU YA IDHINI YA MSHIRIKI

MADA: UTAFITI UNAOANGALIA UBORA UNAOHUSIANA NA AFYA NA SHIDA ZA MATIBABU YA HYDROXYUREA KWA MATIBABU YA UGONJWA WA SELI KWA VIJANA NA WATU WAZIMA KATIKA HOSPITALI KUU YA KENYATTA.

Nambari ya idhinisho: UON / KNH-ERC:

Jina la mtafiti: Dr Marjorie Watetu

Uhusiano wamtafitina Chuo kikuu cha Nairobi au Hospitali y akitaifaya Kenyatta: Mwanafunzi wa Uzamifu katika koziya matibabu ya Famasia. Chuo Kikuu cha Nairobi.

Mshirikiridhaa, Serial No . . . . . .

Nimesoma na nimeelewa habari inayo husu utafiti huu. Nimepata nafasi ya kuuliza maswali na kutafuta ufafanuzi kuhusu masomo.

Ninakubali kushiriki katika utafiti huu

……
…….

(Jina la mwisho, Jina la kwanza, Jina lingine)

……..
……

(Sahihi)
(Tarehe)

……
…….....

(Simu) (Shahidi)

Mimi …… kama mzazi au mlezi wa …… napatiana idhini ya hiari kwa motto wangu kushiriki katika utafiti huu.

…… ……
……..

Sahihi . . . . . ……..

Tarehe ……

Simu ……..

Taarifa ya Mpelelezi

Naidhinisha kuwa nimemweleza mshiriki kwa kikamilifu hatari na faida zinazo husikana utafiti huu.

Jina …….

Tarehe ……. Saini ……..

Majadiliano ya ridhaa

Mpelelezi……
Tarehe ……

Idara ya Famasia naMazoezi yaUfamasia, Kitivo cha Ufamasia, Chuo Kikuu cha Nairobi.

SLP 4038-20100. Simu: 0723761866/0717772750

Shahidi ……

Tarehe ……..

Uhusiano …….

Washahidi kwa mpelelezi /mshiriki

MAHUSIANO YA MAHUSIANO

Kwa maswali yoyote, yafuatayo wanaweza kuwasiliana:

Dkt Marjorie Watetu (Mchunguzi mkuu)

Simu: 0723761866

Barua pepe: **watetumarj@gmail.com**

Dkt Peter N. Karimi

Simu: 0722436019

Barua pepe: ndirangupk@yahoo.com

Profesa Faith A. Okalebo

Simu: 0737434204 Barua pepe: **okalebof@yahoo.com**

APPENDIX III: ELIGIBILITY CRITERIA

Participant initials ☐☐☐ Participant ID ☐☐☐☐☐ Date ☐☐☐

Inclusion criteria

Patients who meet the any of the following qualify for the study

	Yes	**No**
1. History and diagnosis of sickle cell disease		
2. Age 13-65 inclusive		
3. At least 6 months follow up at Kenyatta National Hospital		
4. If on hydroxyurea therapy prescription for at least 6 months, and dose stabilization for at least 3 months.		
5. Patient willing to comply to study protocols and has signed informed consent/ assent.		

Exclusion Criteria

Patients who meet *any* of these criteria are *not* eligible for enrollment as study participants:

	Yes	**No**
1. Human Immuno-deficiency virus (HIV) positive or history of HIV antibodies suffered a stroke in the last 2 years, cancer diagnosis in the past 5 years,		
2. Pre-existing hematological conditions such as myelodysplastic syndrome or any other condition.		
3. Planning to start, adjust or stop HU use within the study period, apart for safety reasons such as development of adverse effects to hydroxyurea.		
4. Any other condition deemed to compromise the patients' involvement in the study as per the judgment of the principal investigator.		

Form completed by _____ Date _____

Form checked by _____ Date _____

APPENDIX IV: DATA COLLECTION TOOL

Participant ID ☐☐☐☐☐☐

Participant Initials ☐☐☐

Date ☐ / / ☐

Participant's Demographics

1. What is the participants' gender?

   Male (0) ☐ Female (1) ☐

2. What is the participants' age? ☐
3. What is the participants' level of education?

   None (0) ☐ Primary (1) ☐ Secondary (2) ☐ Tertiary (3) ☐

4. What is the participants' occupation?

   Formal (1) ☐ Informal (2) ☐ Self-employed (3) ☐

   Unemployed (4) ☐ Student (5) ☐

5. What is the participants' marital status?

   Single (1) ☐ Married (2) ☐ Partner (3) ☐ Divorced (4) ☐

   Separated (5) ☐ Widowed (6) ☐ Minor (7) ☐

6. Where does the participant reside?

   Urban (1) ☐ Rural (2) ☐

7. What is the participants' weight in kilograms? ☐
8. What was the participants' age at diagnosis of sickle cell disease? ☐
9. Has Hb electrophoresis ever been done?

   Yes (1) ☐ No (0) ☐

10. If yes, what genotype of sickle cell disease was diagnosed?

    HbSS (1) ☐ HbSC (2) ☐ Other (3) ☐ Unknown (4) ☐

11. If other, specify _____

12. Has the participant experienced a painful crisis in the past 2 years?

Yes (1) ☐ No (0) ☐

13. If yes, how many times? ☐

14. Has the participant received a blood transfusion in the past 2 years?

Yes (1) ☐ No (0) ☐

15. If yes, how many times? ☐

16. Has the participant been hospitalized in the past 2 years?

Yes (1) ☐ No (0) ☐

17. If yes, how many times? ☐

18. Has the participant ever suffered from:

19.	Acute chest syndrome	Yes (1) ☐	No (0) ☐
20.	Sequestration crisis	Yes (1) ☐	No (0) ☐
21.	Cardiovascular event	Yes (1) ☐	No (0) ☐
22.	Stroke	Yes (1) ☐	No (0) ☐
23.	Seizure	Yes (1) ☐	No (0) ☐
24.	Loss in vision	Yes (1) ☐	No (0) ☐
25.	Pathological fracture	Yes (1) ☐	No (0) ☐
26.	Leg ulcers	Yes (1) ☐	No (0) ☐
27.	Gout	Yes (1) ☐	No (0) ☐
28.	Kidney stones	Yes (1) ☐	No (0) ☐
29.	Depression	Yes (1) ☐	No (0) ☐

30. Has the participant ever suffered from other condition

Yes ☐ No ☐

31. If yes, specify _____

_____

32. Does the participant use any herbal medication?

Yes (1) ☐ No (0) ☐

33. If yes, which one (substance, dose, frequency, duration)

34. Does the patient use tobacco?

Yes (1) ☐ No (0) ☐

35. If yes, which one?

Cigarettes (1) ☐ Chews tobacco (2) ☐

36. If yes, how many sticks of cigarettes does the participant smoke per day? ☐

37. Does the participant use any substance of abuse?

Yes (1) ☐ No (0) ☐

38. If yes, which one?

Cocaine (1) ☐ Miraa (2) ☐ Heroine (3) ☐

Prescription pills (4) ☐ Other (5) ☐

39. If yes, how often?

Daily (1) ☐ Weekly (2) ☐ Monthly (3) ☐ Occasionally (4) ☐

40. Does the participant take alcohol?

Yes (1) ☐ No (0) ☐

41. If yes, how often?

Daily (1) ☐ Weekly(2) ☐ Monthly (3) ☐ Occasionally (4) ☐

42. Are there other family members with sickle cell disease?

Yes (1) ☐ No (0) ☐

43. If yes, who?

Sibling (1) ☐ Parent (2) ☐ Other relatives (3) ☐

44. Does the participant have any other medical conditions running in the family?

Yes (1) ☐ No (0) ☐

45. If yes, specify? _____

46. In the past 2 weeks, has the participant experienced any of the following?

	Present (1)	Absent (0)
47. Nausea		
48. Vomiting		
49. Abdominal pain		
50. Diarrhea		
51. Headache		
52. Cough		
53. Painful crises		
54. Chest pain		

55. Has the participant had any other symptoms in the past 2 weeks?
Yes (1) ☐ No (0) ☐

56. If yes, specify _____

57. Is the participant on any of the following drugs?

58. Folic acid? Yes (1) ☐ No (0) ☐

59. Iron supplementation? Yes (1) ☐ No (0) ☐

60. Pneumococcal vaccination? Yes (1) ☐ No (0) ☐

61. List the medications the participant is currently taking (drug, dose, frequency, duration)

Drug	Dose	Frequency	Duration

Adverse effects assessment

62. Has the participant had any adverse drug reaction in the past 2 weeks?

Yes (1) ☐ No (0) ☐

63. If yes, specify _____

_____

APPENDIX V: DRUG THERAPY PROBLEMS

64.	Unnecessary drug therapy	Additive drug use causing the problem	Present (1) ☐	Absent (0) ☐
65.	Needs additional drug therapy	Untreated condition	Present (1) ☐	Absent (0) ☐
66.		Preventive/prophylactic therapy required to reduce risk of developing new condition	Present (1) ☐	Absent (0) ☐
67.		Synergistic/potentiating therapy	Present (1) ☐	Absent (0) ☐
68.	Ineffective drug	Dosage form inappropriate	Present (1) ☐	Absent (0) ☐
69.	Dosage too low	Ineffective dose	Present (1) ☐	Absent (0) ☐
70.		Frequency inappropriate	Present (1) ☐	Absent (0) ☐
71.		Drug interaction	Present (1) ☐	Absent (0) ☐
72.	Adverse drug reaction	Undesirable effect	Present (1) ☐	Absent (0) ☐
73.		Drug interaction	Present (1) ☐	Absent (0) ☐
74.		Dosage administered or changed too rapidly	Present (1) ☐	Absent (0) ☐
75.		Allergic reaction	Present (1) ☐	Absent (0) ☐
76.		Contraindications present	Present (1) ☐	Absent (0) ☐
77.	Dosage too high	Dose too high	Present (1) ☐	Absent (0) ☐
78.		Frequency too short	Present (1) ☐	Absent (0) ☐
79.		Drug interaction	Present (1) ☐	Absent (0) ☐
80.	Non compliance	Instructions not understood	Present (1) ☐	Absent (0) ☐
81.		Patient prefers not to take	Present (1) ☐	Absent (0) ☐
82.		Patient forgets to take	Present (1) ☐	Absent (0) ☐

83.		Patient cannot afford drug product	Present (1) ☐	Absent (0) ☐
84.		Cannot swallow /administer the drug	Present (1) ☐	Absent (0) ☐
85.		Drug product not available	Present (1) ☐	Absent (0) ☐

DRUG THERAPY PROBLEM CLASS

86. Unnecessary drug therapy	Present (1) ☐	Absent (0) ☐
87. Needs additional drug therapy	Present (1) ☐	Absent (0) ☐
88. Ineffective drug	Present (1) ☐	Absent (0) ☐
89. Dosage too low	Present (1) ☐	Absent (0) ☐
90. Adverse drug reaction	Present (1) ☐	Absent (0) ☐
91. Dosage too high	Present (1) ☐	Absent (0) ☐
92. Non-compliance	Present (1) ☐	Absent (0) ☐

93. Overall QoL score ☐
94. Domain 1: physical health score ☐
95. Domain 2: psychological health score ☐
96. Domain 3: social health score ☐
97. Domain 4: environmental score ☐
98. Medication Adherence Score ☐
99. Adherence score

Low (1) ☐ Medium (2) ☐ High (3) ☐

APPENDIX VI WHOQOL-BREFQUESTIONNAIRE

Before you begin we would like to ask you to answer a few general questions about yourself: by circling the correct answer or by filling in the space provided.

What is your **gender**? Male ☐ Female ☐

What is you **date of birth**? _____ / _____ / _____

Day / Month / Year

Are you currently **ill**? Yes ☐ No ☐

If something is wrong with your health what do you think it is? _____illness/ problem

Instructions

This assessment asks how you feel about your quality of life, health, or other areas of your life. **Please answer all the questions.** If you are unsure about which response to give to a question, **please choose the one** that appears most appropriate. This can often be your first response.

Please keep in mind your standards, hopes, pleasures and concerns. We ask that you think about your life **in the last two weeks.** For example, thinking about the last two weeks, a question might ask:

	Do you get the kind of support from others that you need?	Not at all	Not much	moderately	A great deal	Completely
		1	2	3	4	5

You should circle the number that best fits how much support you got from others over the last two weeks. So you would circle the number 4 if you got a great deal of support from others as follows.

	Do you get the kind of support from others that you need?	Not at all	Not much	moderately	A great deal	Completely
		1	2	3	4	5

You would circle number 1 if you did not get any of the support that you needed from others in the last two weeks.

Please read each question, assess your feelings, and circle the number on the scale for each question that gives the best answer for you.

		Very poor	Poor	Neither poor or Good	Good	Very good
1(G1)	How would you rate your quality of life?	1	2	3	4	5

		Very dissatisfied	Dissatisfied	Neither satisfied nor dissatisfied	Satisfied	Very satisfied
2(G4)	How satisfied are you with your health?	1	2	3	4	5

The following questions ask about **how much** you have experienced certain things in the last two weeks.

		Not at all	A little	A moderate amount	Very much	An extreme amount
3 (F1.4)	To what extent do you feel that physical pain prevents you from doing what you need to do?	1	2	3	4	5
4(F11.3)	How much do you need any medical treatment to function in your daily life?	1	2	3	4	5
5(F4.1)	How much do you enjoy life?	1	2	3	4	5
6(F24.2)	To what extent do you feel your life to be meaningful?	1	2	3	4	5

		Not at all	A little	A moderate amount	Very much	Extremely
7(F5.3)	How well are you able to concentrate?	1	2	3	4	5
8 (F16.1)	How safe do you feel in your daily life?	1	2	3	4	5
9 (F22.1)	How healthy is your physical Environment?	1	2	3	4	5

The following questions ask about **how completely** you experience or were able to do certain things in the last two weeks.

		Not at all	A little	Moderately	Mostly	Completely
10 (F2.1)	Do you have enough energy for life?	1	2	3	4	5
11 (F7.1)	Are you able to accept your bodily appearance?	1	2	3	4	5
12 (F18.1)	Have you enough money to meet your needs?	1	2	3	4	5
13 (F20.1)	How available to you is the information that you need in your day-to-day life?	1	2	3	4	5
14 (F21.1)	To what extent do you have the opportunity for leisure activities?	1	2	3	4	5

		Very poor	Poor	Neither poor or Good	Good	Very good
15 (F9.1)	How well are you able to get around?	1	2	3	4	5

The following questions ask you to say how **good or satisfied** you have felt about various aspects of your life over the last two weeks.

		Very dissatisfied	Dissatisfied	Neither satisfied nor dissatisfied	Satisfied	Very satisfied
16 (F3.3)	How satisfied are you with your sleep?	1	2	3	4	5
17 (F10.3)	How satisfied are you with your ability to perform your daily living activities?	1	2	3	4	5
18(F12.4)	How satisfied are you with your capacity for work?	1	2	3	4	5
19 (F6.3)	How satisfied are you with yourself?	1	2	3	4	5
20(F13.3)	How satisfied are you with your personal relationships?	1	2	3	4	5
21(F15.3)	How satisfied are you with your sex life?	1	2	3	4	5
22(F14.4)	How satisfied are you with the support you get from your friends?	1	2	3	4	5
23(F17.3)	How satisfied are you with the conditions of your living place?	1	2	3	4	5
24(F19.3)	How satisfied are you with your access to health services?	1	2	3	4	5
25(F23.3)	How satisfied are you with your transport?	1	2	3	4	5

The following question refers to **how often** you have felt or experienced certain things in the last two weeks.

		Never	Seldom	Quite often	Very often	Always
26 (F8.1)	How often do you have negative feelings such as blue mood, despair, anxiety, depression?	1	2	3	4	5

Did someone help you to fill out this form?

……..

How long did it take to fill this form out?

…….

Do you have any comments about the assessment?

.....

.....

APPENDIX VII: MEDICATION ADHERENCE QUESTIONNAIRE

Participant initials ☐☐☐

Participant ID ☐☐☐☐☐☐☐

Date ☐ / / ☐

We would like to ask you to answer a few general questions about yourself: by circling the correct answer or by filling in the space provided.

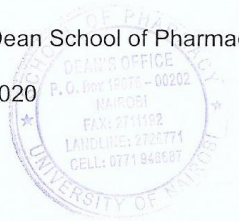
1. Do you sometimes forget to take hydroxyurea?	Yes (1) ☐	No (0) ☐
2. People sometimes miss taking their medications for reasons other than forgetting. Thinking over the past two weeks, were there any days when you did not take hydroxyurea?	Yes (1) ☐	No (0) ☐
3. Have you ever cut back or stopped taking hydroxyurea without telling your doctor, because you felt worse when you took it?	Yes (1) ☐	No (0) ☐
4. When you travel or leave home, do you sometimes forget to bring along your hydroxyurea?	Yes (1) ☐	No (0) ☐
5. Did you take hydroxyurea medicine yesterday?	Yes (1) ☐	No (0) ☐
6. When you feel like your sickle cell disease is under control, do you sometimes stop taking hydroxyurea?	Yes (1) ☐	No (0) ☐
7. Taking medication every day is a real inconvenience for some people. Do you ever feel hassled about sticking to your sickle cell treatment plan?	Yes (1) ☐	No (0) ☐
8. How often do you have difficulty remembering to take all your medications?	☐ (0) Never/rarely ☐ (1) Once in a while ☐ (2) Sometimes ☐ (3) Usually ☐ (4) All the time	
9. Are you able to afford hydroxyurea to take it as required?	Yes (1) ☐ No (0) ☐	

Dr P.N. Karimi

6/12/2020

Signed, Dr K A Sinei, Dean School of Pharmacy

7th December, 2020



HEALTH-RELATED QUALITY OF LIFE AND DRUG THERAPY PROBLEMS IN PATIENTS WITH SICKLE CELL DISEASE ON HYDROXYUREA AT KENYATTA NATIONAL HOSPITAL

ORIGINALITY REPORT

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