

**IMPACT OF HYDROXYUREA ON FREQUENCY OF BLOOD TRANSFUSION IN CHILDREN WITH  
SICKLE CELL ANAEMIA**

**A Retrospective Quasi Experimental Study**

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**STUDENTS DECLARATION**

I the undersigned, declare that thisdissertationis my original work. It has not been presented to any other university, college or institution for the purpose of academic credit

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## LIST OF SYMBOLS, ABBREVIATIONS, NOMENCLATURES

\$ - Dollar

% - Percent

> - Greater than

~ - Approximate

$\alpha$  - Alpha

$\beta$  - Beta

cm - Centimeter

mg - Milligram

g - Gram

kg - Kilogram

sec - Second

ul - Microliter

ml - Milliliter

Ksh - Kenya shilling

ACS - Acute Chest Syndrome

Alloimmunization - An immunological response by the recipient against foreign antigens that may follow an erythrocyte transfusion and result in destruction of transfused erythrocytes.

CI - Confidence interval

Dept. - Department

DHTRs - Delayed haemolytic transfusion reactions

GGCH - Gertrude's Garden Children Hospital

Hb - Hemoglobin, oxygen-carrying pigment contained in the red blood cells

HbF - Fetal hemoglobin

HbS – Sickle hemoglobin

Hemoglobinopathy - A disorder characterized by an abnormality of the structure or function of hemoglobin.

HIV - Human immunodeficiency virus

HU - Hydroxyurea; also known as Hydroxycarbamide

IQR – Inter quartile ratio

IRR – Incidence rate ratio

KNH - Kenyatta National Hospital

MPD – Myeloproliferative disorders

N - Number

NIH - National Institutes of Health

Paed – Paediatrics

RCT - Randomized Controlled Trial

SCA – Sickle cell anaemia

SCD – sickle cell disease

SD – Standard deviation

TCD - Transcranial Doppler

WAZ – Weight for age z score

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## **ABSTRACT:**

### **Study background:**

Sickle cell anaemia (SCA) is a red blood cell disorder that occurs commonly in Sub-Saharan Africa. Most of the children affected often have low haemoglobin levels as a result of increased destruction of these abnormal red blood cells and are subjected to several blood transfusions in an attempt to replace these red blood cells. Blood however is not always readily available and transfusions may result in undesired complications. Hydroxyurea (HU) is recommended for all children with SCA from the age of 9 months. HU changes the natural progression of the disease and sickle cell related complications. Although there is considerable use of hydroxyurea in Kenya there is no formal study on the impact of its use on the frequency of blood transfusions.

### **Study Objective:**

The study's main objective was to determine the impact of hydroxyurea use over a 6-month period on the frequency of blood transfusion among children aged 1-18 years with SCD on follow up at Kenyatta National Hospital (KNH) and Gertrude's hospital. The study also aimed to describe dosage of hydroxyurea, adherence to hydroxyurea and factors affecting adherence and concurrent medication use in children with SCD on follow up at KNH and Gertrude's hospital.

### **Study design and sites:**

A retrospective quasi-experimental (single interrupted time series) design was employed to examine the frequency of blood transfusions in the 1 year period before initiating hydroxyurea (intervention) in comparison to the frequency in the 6 months - 1 year period after its introduction. The study was conducted in Kenyatta National Hospital and Gertrude's Garden Children Hospital between February and May 2017.

### **Participants and methods:**

Participants in the study were children aged 1 year to 18 years with a diagnosis of sickle cell anaemia confirmed by serum electrophoresis who had been on Hydroxyurea for at least 6

months and their caregivers. A questionnaire was used to collect data upon which the data were analysed to find any association between use of hydroxyurea and frequency of blood transfusions. Bivariate analyses were done using chi squares for categorical variables and also paired t-tests for the comparison of the means before and after initiation of hydroxyurea. A statistical comparison of time trends before and after the intervention was done. A Poisson regression analysis of the transfusion and admission counts while accounting for time periods was done to explore for any association between use of hydroxyurea (intervention) and frequency of blood transfusions and admissions. The results presented as Incidence Rate Ratios (IRR) with their respective 95% confidence intervals

## **Results**

A total of 64 children participated in the study with a mean age of 7.6 years (SD= 3.7). Majority of the respondents were male 37(57.8%). The median age at diagnosis of Sickle Cell Anemia was 2.2 years (IQR= 0.7-3.5). Mean age when respondents started using Hydroxyurea was 4.8 years (SD=2.6), with median duration of use at 2.1 years (IQR=1.3-4). All hospital admissions were due to Sickle Cell Anemia complications with a median age of 2 years (IQR=1-4) at the first hospital admission. Majority of the respondents had received blood transfusion 57(89.1%) with a median age of 2 years (IQR=0.6-4) at the first transfusion.

There was a statistically significant mean decrease of 0.9 (95%, CI 0.7 to 1.2)(P value <0.001) in the counts of blood transfusions in the 6-12 month period after adequate use of HU, that is from a mean of 1.2 (95% CI 0.9-1.4) to that of 0.2 (95% CI 0.1 - 0.4). The children had a statistically significant lower rate of transfusion after a 6 month period of having used HU with an IRR of 0.18 (95% CI 0.09 - 0.35). Majority of the participants were under dosed, with 51 (79.7%) receiving a daily dosage of < 20mg/kg/day. Most of the parents/caregivers ensured that the children took HU as prescribed with 50 (78.1%) reporting good compliance to the drug. Majority of the participants had not experienced any side effect with the use of Hydroxyurea 56(87.5%).

## **Conclusion**

This study suggests that Hydroxyurea significantly reduces the number of blood transfusions in children aged between 1 year and 18 years at KNH and Gertrude's hospital. The application of Hydroxyurea in children with SCA in these two institutions should therefore be encouraged as it reduces morbidity.

## **CHAPTER: 1.0 INTRODUCTION**

### **Sickle Cell Disease**

Sickle cell disease is a group of disorders that results in sickling of red blood cells when deoxygenated. The disease was first reported in 1910 by Herrick after he described its occurrence in a black dental student. The genetic defect in sickle cell disease is a point mutation in codon 6 of the  $\beta$ -globin gene that results in the formation of haemoglobin S (HbS). The mutation cumulates in the substitution of a valine residue for a glutamic acid residue. Homozygosity for the Hb S mutation is the most common form of Sickle cell disease (SCD) and is also known as sickle cell anaemia(SCA).

SCD is found in tropical regions, particularly Sub-Saharan Africa, the Middle-East and India and is associated with very high child mortality. There are 225,000 children born/year with sickle cell anaemia<sup>1</sup> with 75% of the births occurring in Sub- Saharan Africa and approximately 50–80% of these patients die before adulthood.<sup>2</sup> In 1990 there were 113,000 deaths due to SCD, which increased to 176,000 deaths in 2013.

### **Clinical Characteristics**

Individuals afflicted by SCD often develop Sickle cell crises generally grouped as: Acute vascular occlusion (painful crisis), acute chest syndrome (ACS), aplastic crises, haemolytic crises and splenic sequestration crisis. Painful crisis in children living with SCA is the most common presentation in emergency departments with patients with SCA experiencing episodic and chronic pain ultimately reducing their quality of life.<sup>3</sup>

## **Natural Disease Progression**

SCD related complications are often determined by the patient's age.<sup>4</sup> The disease is asymptomatic in the first 2 months of life, dactylitis and splenic problems emerge between the 3<sup>rd</sup> and 6<sup>th</sup> months of life. The period between the 6<sup>th</sup> month of life and the 1<sup>st</sup> birthday has the greatest risk for the patient often due to overwhelming septicemias, acute chest syndrome and acute splenic sequestration. As from 1–5 years of age stroke emerges. After the 5<sup>th</sup> year of life they experience several episodes of bone pain crisis.

In the adolescence period they experience enuresis, increasing bone pain crisis, leg ulceration, sexual development, delayed growth, hip disease and priapism. By the age of 25–30 years, bone pain crises become less frequent and most patients default from follow-up. After 40 years, renal complications and a reduction in Hb become common.

## **Diagnosis of SCD**

Hemoglobin electrophoresis can detect abnormal levels of Hb and is used in the diagnosis of SCD.<sup>5</sup> This technique has the ability to differentiate and quantitate various types of hemoglobin. Alkaline and/or citrate agar electrophoresis is the commonly used method. It distinguishes the different haemoglobin types using the gel electrophoresis principle. This test can help in the detection of abnormal HbS levels, associated with sickle-cell disease and other blood disorders that are associated with abnormal hemoglobin.

## **Established Treatments**

Despite SCD having been discovered more than half a century ago, a definitive treatment for SCD has yet to be discovered.<sup>6</sup> Treatment initially was almost entirely supportive and until the mid 1990's there was no clinically available drugs available to reverse or prevent the polymerization of HbS. Penicillin has been shown to reduce the risk of pneumococcal infection due to decreased immune response and/or a non-functional spleen.<sup>7</sup> Vaccinations against encapsulated organisms are given to children with SCA as they have low immunity towards *Streptococcus pneumoniae*.<sup>8</sup> Malarial chemoprophylaxis is also given in regions

where malaria is endemic, for instance the Southeast Asia and sub-Saharan African countries<sup>9</sup>

## **Hydroxyurea**

In 1995, hydroxyurea was declared as the greatest breakthrough in the mitigation of SCD.<sup>10</sup> The initial clinical trials of hydroxyurea in SCD were controlled early after clear benefits were demonstrated in the treatment arm and the drug was licensed to be used in USA by patients with severe SCD. HU has since been used in various patients with SCD and it has been incorporated in several recent studies in very young children.<sup>11</sup> However, issues on the drug's safety especially in the long term and its efficacy still arise.

The mechanisms of action of hydroxyurea are not clear but it is thought to increase haemoglobin F and the water content of RBCs. It also alters the adhesion of RBCs to the endothelium and increases the deformability of sickled cells.<sup>12</sup>

The current recommendation guideline is to offer hydroxyurea to infants from the age of 9 months, children, and adolescents with SCA, regardless of the clinical severity to reduce the occurrence of SCD-related complications (e.g., dactylitis, pain, ACS, anaemia) [13].

## **Transfusions**

Red blood cell transfusion could be utilized in the treatment of serious complications of SCD as well as the prevention of chronic complications. Transfusion is further used in the perioperative period for patients with SCD to prevent stroke, acute chest syndrome and vaso occlusive crises after surgery. It is a key intervention in decreasing morbidity and mortality in patients with SCD.

Episodic transfusions are often done in instances of acute splenic sequestration, aplastic crisis and hyperhemolysis<sup>13</sup>, whilst chronic transfusion therapy are offered for primary stroke prevention, prevention of recurrence of stroke and pulmonary hypertension.<sup>14</sup>

Children with SCD often undergo several episodes of blood transfusion which pose inherent risks to them.<sup>15</sup> Blood transfusion in all recipients, have a potential risk of causing adverse

effects including infections, iron overload allergic reactions, alloimmunization, acute or delayed haemolytictransfusion reactions (DHTRs).<sup>16</sup>

Initiating HU in children with SCA might alter the need of frequent hospitalization due to blood transfusions which also poses an imminent risk of blood transfusion related complications.

## CHAPTER 2.0 LITERATURE REVIEW

### Characteristics of children with SCA in Kenya

SCA presents a large burden of disease in Africa especially the Sub-Saharan region. A case study of children with SCA visiting a specialist out-patient clinic in Kilifi, Kenya was done to create awareness of the large burden of disease. The study evaluated 124 children with a median age of 6.3 years who were examined routinely in the outpatient clinic after every 3-month. The study identified that malaria and anaemia greatly increased morbidity and mortality in children with SCA. A positive malaria slide was also seen in 6% of the children and there was a mean haemoglobin concentration of 73 g/l in the children with SCA, as opposed to 107 g/l in non-SCA controls ( $P < 0.001$ ).<sup>17</sup>

### Effect of Hydroxyurea on disease progression in children

In 1995 Charache et al in the US and Canada, reviewed the rate of painful crises in 299 patients with SCA aged 18 years and older who received HU at a dose of 15mg/kg/day.<sup>10</sup> His study design was a randomized double-blind placebo controlled trial whereby he found that HU reduced the rate of painful crisis with 2.5 crises per year reported in the HU group and 4.5 crises per year in the placebo group, a 44 % reduction. Annual rates of hospitalization were also reduced with 1.0 hospitalization per annum reported in the HU group as compared to 2.4 in the placebo group. Incidences of ACS were also reduced with 25 events occurring in the HU group against 51 in the placebo group. HU was also seen to reduce the frequency of patients who underwent transfusions with only 48 receiving transfusions in the HU group against 73 in the placebo group.

A systematic review done by John J Strouse, in 2008 on the toxicity, effectiveness and efficacy of HU in children concluded that HU reduces hospitalization and increases total and fetal haemoglobin levels in kids with severe SCA.<sup>18</sup> The systematic review looked at 26 articles that included 1 RCT, 22 observational studies (11 with overlapping participants) and 3 case reports. The average dose of HU given was between 15mg to 20mg/kg/day. Findings included an increase in Hb F levels from 5%-10% to 15%-20% on HU. Hb concentration also



increased modestly ( $\sim 1$  g/L) significantly across all the studies. The frequency of pain crisis decreased significantly in 3 of 4 paediatric studies. In a retrospective study, pain crises declined from a median of 3 to 0.8 per year on treatment during a median follow-up of 24 months using a fixed-dose of hydroxyurea (15 mg/kg per day) in a resource-poor environment (The Caribbean and Central America). A small, high-quality prospective study found a decrease in pain events from 3.1 per year before HU to 1.2 per year during therapy.

A multicentre, randomised, controlled trial (BABY HUG) was done in children in USA by Wang et al in 2011 to determine whether HU was effective in the management of SCD in very young children. In the study 193 babies aged 9-18 months either received liquid HU, at a dose of 20 mg/kg per day, or placebo for 2 years.<sup>11</sup> Findings included a decrease in splenic function in 19 of 70 patients in the HU group compared to 28 of 74 patients in the placebo group, HU also decreased pain crises with 177 events in 62 patients seen in the treated group compared to 375 events in 75 in the placebo group. Decrease in ACS and incidences of transfusion was also seen with toxicity limited to neutropenia. HU was thus considered effective in the SCD management in very young children.

HU therefore does alter the disease progression of SCA reducing the frequency of painful crises, admission and even the number of transfusions received in adults.

HU is as effective as blood transfusions in lowering transcranial Doppler (TCD) velocities in children with SCA who are at a high risk for getting a stroke. This was concluded in the TWITCH study by Charles T. Quinn et al in 2014.<sup>19</sup> This was a phase III RCT with the study population consisting of children aged 4 to 16 years on a chronic transfusion program for at least 1yr for primary stroke prophylaxis due to abnormal TCD velocities ( $\geq 200$  cm/sec). The average TCD velocities at the end of the study were equal between both patient groups ( $138 \pm 1.6$  cm/sec in the transfusion arm and  $143 \pm 1.6$  cm/sec in the hydroxyurea arm). This demonstrated an equal risk for stroke and meeting the non-inferiority criteria ( $p = 8.82 \times 10^{-16}$ ) indicating that there was a higher likelihood of hydroxyurea being more superior ( $p = 0.023$ ).

## **Dosing**

According to the National Heart Lung and Blood institute, HU is offered to infants who are as young as 9 months, adolescents and children with SCA, despite the clinical severity to mitigate the complications related to SCA .<sup>20</sup> The recommended dosage for children and infants is 20 mg/kg/day. Monitoring is crucial with a Complete Blood Count with White Blood Cell differential at least after 4 weeks. If dose escalation is warranted increments of 5 mg/kg/day are made every 8 weeks, until mild myelosuppression (absolute neutrophil count 2,000/uL to 4,000/uL) is observed, or to a maximum of 35 mg/kg/day. The clinical responses to the treatment with HU takes 3–6 month and as a result a 6- month trial on the maximum tolerated dose is needed before considering discontinuation as a result of treatment failure.

## **Side Effects**

A retrospective cohort study of 152 patients suffering from Philadelphia-negative myeloproliferative disorders (MPD) with thrombocytosis (median follow-up 8.13 years) who were on HU therapy was done in USA to determine toxicity and side effects of HU. Unwanted side effects (two fever reactions, five symptomatic macrocytic anemia, four cases each of leg painful ulcers, three acute myelodysplasia or leukemia and two allergic reactions) caused withdrawal of therapy in 16 patients.<sup>21</sup> The major side effect of HU is myelotoxicity and it is reversible upon discontinuation of the drug. HU has a carcinogenic and a teratogenic potential that has been described in animal studies. It also has idiosyncratic side effects thought to be genetic or as a result of epigenetic phenomenon that occur in some individuals. Although these reactions are rare, they can be serious in some patients. Skin rash and nail hyperpigmentation are rarely notable short term HU therapy effects. HU is a safe and effective drug in most patients with SCA. Most of the side effects are minor usually subsiding upon drug withdrawal.

## **Formulations**

Commercially HU is available in capsule forms with the 250mg, 500mg and 1000mg strengths being the commonly available. The drug is limited to the capsulated and liquid forms approved by the FDA as the liquid form has a relatively short shelf life. However young children may be unable to swallow the capsulated form and for that reason liquid formulations are often made available to enable the administration of HU in this age group. A study done as a precursor to the Baby Hug trial to provide a liquid formulation of HU to young patients found that HU oral solutions (100mg/ml) prepared by dissolving capsule contents in water at room temperature and adding flavour and then subsequently maintaining it at room temperature had functional stability and chemical for several months (3-6 months).<sup>22</sup> A trial aimed to characterize the pharmacokinetics of HU in children and to evaluate the bioavailability of liquid vs capsule formulations found that capsule and liquid formulations of HU are bioequivalent.<sup>23</sup> The multicenter; prospective; open-label trial by Estep et al in 2016 included 39 children with SCD aged 2 to 17 years who were recruited from 7 medical centers in the United States. The children provided 682 plasma samples for pharmacokinetic analysis after administration of HU which were compared to population pharmacokinetic models. This eliminates the need for age based dosing schemes as weight based dosing schemes provided a drug exposure that was consistent. The application of liquid HU in children is supported and should be recommended to those children who for one reason or another are unable to take capsules.

## **Cost**

An adult study in United States done utilizing data collected in The Multicenter Study of Hydroxyurea in Patients With SCA (a randomized, placebo-controlled, double-blind trial involving 299 adults exhibiting SCA who had experienced more than three vaso-occlusive crises) to determine the cost- effectiveness of HU<sup>24</sup>, showed that the average cost per patient receiving HU was \$16,810 (approximately 1,681,000 Ksh). The cost estimates included all emergency and outpatient department visits as well as hospital admissions that were as a result of a crisis. Although this indicates a high expense incurred by the use of HU it is prudent to note that in the study patients who were not on HU incurred an annual cost

of \$22,020 (approximately 2,202,000ksh). Though this value was not statistically significant, the findings suggest that HU therapy is cheaper in the management of adults with sickle cell anaemia. The use of HU also attributed with lower costs for transfusion, emergency department visits and use of opiate analgesics.

### **Challenges in blood transfusions**

The amount of blood donated annually worldwide is approximated to be 80 million units.<sup>25</sup> Of this total, the Sub-Saharan Africa donates 2 million units, since there is a greater demand for blood transfusions due to malnutrition, maternal morbidity and heavy instances of infectious diseases for instance malaria.<sup>26</sup> There is chronic shortage of blood products and safe blood particularly in medium and low-income countries and blood safety is still a major issue in transfusion practice in most of these countries. National blood transfusion policies and services do exist but trained personnel, financial resources and appropriate infrastructure are not enough to support the functioning of a voluntary transfusion service.<sup>27</sup> There is a predominance of commercially remunerated donors and family replacement donors in most developing countries.

### **Non-adherence and effect of poor adherence**

Hydroxyurea is poorly utilized in SCA infected patients. Patel et al in 2010 in a 1-year retrospective cohort analysis of 93 children determined that in children with SCA on HU, patients were only adherent to HU depending on their medication records and thus did not receive all the benefits of this medication.<sup>28</sup> The average refill prescription rate in the study was 58.4%. HU reduces the frequencies of various crises and improves the QOL but as any other medication its effectiveness depends on the adherence of the patient to the treatment advanced.<sup>28</sup> Poor adherence contributes to worsening of disease and increased costs of health care.

## **Barriers to adherence**

Barriers to HU treatment can be grouped into four categories: patient, provider, caregiver and system.<sup>30</sup> The most common provider reported barrier is compliance. A cross-sectional survey was emailed to 1316 pediatric oncology/hematology providers selected from the published 2008 American Society of Pediatric Oncology/ Hematology (ASPHO) membership directory, identified medication compliance, contraception compliance and laboratory monitoring compliance and as the main barriers. Most patients listed the fear of cancer as well as other side effects as the main reason for not wanting to take medication. Frequent lab monitoring and the perception of the patient that the drug would not work also ranked high as common reasons why the patients didn't take HU.<sup>31</sup>

## **Current ongoing studies in Kenya**

The REACH Trial investigating HU therapy for children with sickle cell anaemia in Sub-Saharan Africa (Angola, DRC, Kenya, and Uganda) is a prospective multicenter research protocol, which seeks to scrutinize the feasibility and safety of open-label HU in this patient sample. It will also provide data on the benefits of HU.<sup>32</sup> The study will further examine the severe haematological toxicities that is experienced during the treatment phase. Careful toxicities' assessment will be done to identify a safe HU dose for this population. The REACH trial will provide data that addresses critical gaps in knowledge for SCA treatment in sub-Saharan Africa with the intention of establishing treatment guidelines.

## **Local experience**

Despite its use in developed countries for the management of SCA in children, in Kenya and generally in low income countries HU is not used in this age group. In the Kenyan clinical guidelines HU is currently only recommended for adults with SCA yet many SCA related deaths occur in early childhood.<sup>33</sup>

## **2.1 Justification**

SCD and primarily SCA confers a large burden of disease especially in Sub-Saharan Africa. Most of the patients with sickle cell anaemia are exposed to frequent blood transfusion posing inherent risks to them and multiple hospital admission.

Availability of blood for transfusions also varies across different regions throughout Sub Saharan Africa. Blood safety poses an additional challenge in the proper management of these patients as blood transfusions inflates the burden of health care cost to the patient, household, state and local governments.

Hydroxyurea has shown effectiveness in management of sickle cell anaemia in different settings. Despite its use locally no formal studies to evaluate its effectiveness have been done. It is a simple cost effective measure that would decrease the frequency of transfusions and subsequently hospital admissions. Quality of life may also be improved in the patients minimizing their hospital stay enabling them participate as active members of the community.

Currently there is no treatment guidelines in Kenya that recommends the use of HU in children with SCA and therefore knowledge gaps for the treatment of SCA in the young exists.

Poor adherence to HU is also significantly seen in the management of children with SCD, this poses a challenge in the management of these children and it is therefore crucial to identify local barriers which cause non adherence as well as poor adherence with an aim to address them to ultimately potentiate the management of children living with SCD in the region.

Children with SCD on HU are often always prescribed concurrent medication, the study also aims to describe these medications.

## **2.2 Study Question**

Does hydroxyurea use lead to a reduction in the frequency of blood transfusions in children with sickle cell anaemia ages 1-18 years on follow-up at Kenyatta National Hospital and Gertrude's Children's Hospital?

## **2.3 Objectives**

### **2.3.1 Main Objective**

To determine the impact of hydroxyurea use over a 6-month period on the frequency of blood transfusion among children aged 1-18 years with SCD on follow up at KNH and Gertrude's hospital.

### **2.3.2 Secondary Objectives**

1. To describe dosage of hydroxyurea prescribed to children with SCD on follow up at KNH and Gertrude's hospital.
2. To describe adherence to hydroxyurea & factors affecting adherence in children with SCD aged 1-18 years on follow up at KNH and Gertrude's hospital. Factors of interest include cost, availability, side effects and forgetting to refill prescriptions.
3. To describe concurrent medication use in patient with SCD on follow up at KNH and Gertrude's hospital.

## CHAPTER 3.0 METHODOLOGY

### 3.1 Study Design

In this study a retrospective quasi-experimental (single interrupted time series) design was employed to examine the frequency of blood transfusions in the period before initiating hydroxyurea in comparison to the frequency in the period after its introduction. Participants are asked to retrospect (literally, to “look back”) and try to remember how many events of blood transfusions they had at a particular time point with the aid of medical records.

Quasi-experimental methods offer practical options for the execution of impact evaluations in real world. It uses self-selected or pre-existing groups such as individuals who are already in a programme. Quasi- experimental methods evade ethical concerns that are attributed with random assignment for instance delaying or withholding a potentially effective treatment or the provision of a less effective treatment for one group of study participants. As in the case in SCA it is not possible to identify a valid comparison group as HU has already proven to be beneficial to patients with SCA and hence it will be unethical to identify a control group. Quasi-experimental methods can be used retrospectively which is appropriate as the study design is essentially an ex-post impact evaluation design.

A period of 1 year prior to the initiation of HU and a period of 6 months to 1 year after a 6-month period of continuous HU intake was evaluated.

**Table 1: Table showing time points to be evaluated in the study**

Time 1	Treatment	Time 2
1 year period before HU	Child on HU for at least 6 months	6 months to 1 year period starting 6 months after start of HU



The time series design sets to investigate whether a change in frequency of transfusion occurred between two time points with a treatment intervention occurring between the two time points.

In our study our first time point was that 1 year period when the children with SCD had not initiated HU therapy. All transfusions that occurred during this time were recorded and compared to the transfusions that occurred after the treatment intervention, which constituted the second time point. HU often takes 3-6 months to exert its effect on circulating red blood cells and therefore our treatment intervention period was 6 months.

### **3.2 Study Area**

The study took place in two hospitals in Nairobi as they provide not only a pool of patients on management for sickle cell anaemia but more importantly the use of hydroxyurea by these patients.

The two hospitals were:

1. Kenyatta National Hospital: where a Haematology clinic is held weekly on Monday with children with sickle cell anaemia being followed up.
2. Gertrude's Garden Children Hospital: where a Haematology clinic is held on Friday

Kenyatta National Hospital, located in Upper Hill, Nairobi, is currently the largest public referral and teaching hospital in Kenya. It has a capacity of 2000 beds and has over 6,000 staff members that include nurses, medical officers, residents and consultants who provide basic and highly specialized healthcare services, which include haematology clinics overseen by certified haematologists.

Gertrude's Children's Hospital, a private institution, is the Largest Paediatric Hospital in East and Central Africa.

Based in Muthaura in Nairobi it has a wide range of services and includes giving specialist care to children key of which is providing haematology clinics where children are followed up by qualified haematologists.

### **3.3 Study Population**

This study's participants were selected from paediatric SCA patients who received care from the aforementioned paediatric hematology clinics. The study population consists female and male patients who were evaluated in any of the stated clinics to ascertain the eligibility as compared to the exclusion/ inclusion criteria listed below.

#### **3.3.1 Inclusion criteria:**

1. Diagnosis of sickle cell anaemia (typically HbSS confirmed by Serum electrophoresis)
2. Children with sickle cell anaemia on follow up in the haematology clinic in KNH and Gertrude's hospital for at least 6 months
3. Hydroxyurea use, irrespective of dosage, for at least 6 months before the study
4. Children aged 1-18 years
5. Consent from the caregiver or both consent and assent from a child aged 7 years and above where applicable

#### **3.3.2 Exclusion criteria:**

1. Pre-existing severe haematological conditions like myelodysplastic disorders and human immunodeficiency virus (HIV) infection confirmed by Bone marrow aspirated and Rapid antibody tests respectively.

### **3.4 Patient recruitment**

Opportunistic sampling was employed whereby participants were recruited based on convenience at the respective hematology clinics with the help of the multidisciplinary health care team at the clinics consisting of consultants, registrars and nurses. Individuals who were on HU for at least six months was noted as prospective subjects for the study. The legal guardian/ parent of the pediatric participants were then approached directly during the clinical appointment by the principal investigator and briefed about the study. Prospective participants and their parent/legal guardian were offered the opportunity to enroll in the study upon satisfying the inclusion/ exclusion criteria. The principal investigator

provided review of the research study, research team expectations and protocol procedures.

The participating children and parent/legal guardian were required to ask questions at any time during the session. All prospective participants were informed about the voluntary nature of study and that they could withdraw from the study at any time with no consequences on their service provision at the hematology clinic. Consent was obtained from a parent/legal guardian for all participants with an assent being obtained from those participants over 7 years of age whenever possible.

### 3.5 Sample Size:

The Sample size required was calculated by the sample size equation by Corty and Corty(2011)

The sample size equation by Corty and Corty is useful to estimate sample size for correlations with pre-specified confidence interval.

$$N=15.37/(\ln(B))^2+3$$

$$\text{Where } B= \sqrt{(1+r+w) (1-r+w)} / \sqrt{(1-r-w) (1+r-w)}$$

Whereby: r is the sample correlation coefficient = 0.5(Predetermined by the investigator as use of HU in patients with SCA has been shown to have a correlation with a reduction of blood transfusions in previous studies.<sup>10,11,13,18,19</sup> A r value of 0.5 signifying moderately correlation between the variables, was then chosen)

w is the significance level =0.05

N will therefore be 63 and therefore the study will focus on a sample size of 63

Citation: Moinester M and Gottfried, R. Sample size estimation for correlations with pre-specified confidence interval. *The Quantitative methods for Psychology*. 2014: 10(2); 124-130.<sup>34</sup>

### **3.6 Study Instrument**

Questionnaires were employed to capture relevant data from the enrolled patients. Demographic as well as medical information specifically associated with their history and management of SCA was collected from the study participants. The questionnaires were devised and handed out directly to the participants/respondents during the regular clinic visit to achieve a higher response rate. The questionnaire was designed for self-completion but an option of being administered by the investigator was also provided. The questionnaire was available in both Kiswahili and English language for easy understanding to the responders and it contained a general information section as well as a medical information section.

### **3.7 Ethical Considerations**

Authority to conduct the study was sought from the Ethics and Research Committee in University of Nairobi/Kenyatta National Hospital. After which approval was obtained from Gertrude's Garden Children's Hospital to enable collection of data in their institution.

All respondents were given information on the purpose and procedure of the study before the study was carried out.

A consent and where applicable an assent form was issued to study participants who met the inclusion criteria prior to enrolment. The respondents were informed that there will be no victimization or any consequences for not participating or for withdrawing from the study. Questions and clarifications were welcomed before and during the study.

All respondents were assured of confidentiality. The questionnaires were coded and did not include the respondents' names. The questionnaires were placed in envelopes that were sealed and the information was only accessible to the researcher.

### 3.8 Data Collection

Data were collected in form of;

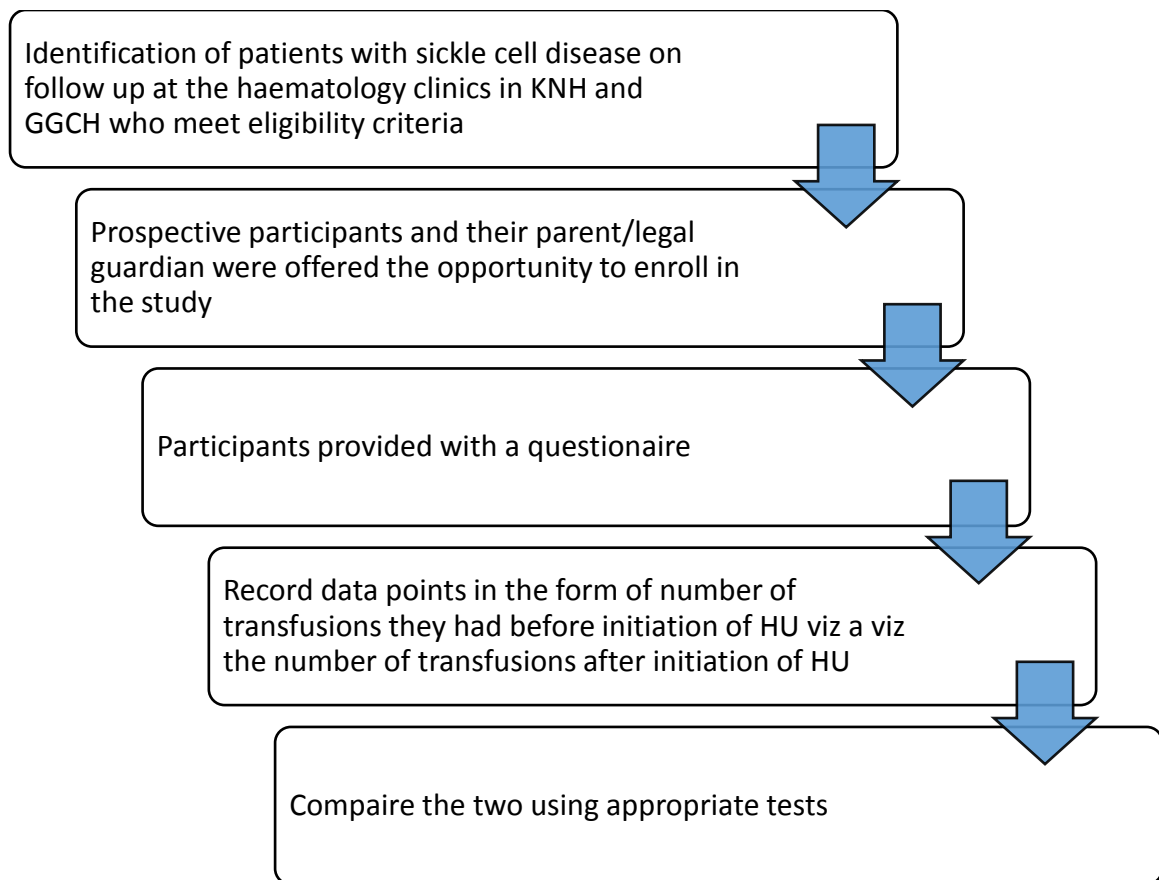
- **Categorical variables:** age, gender, weight, residence, use of concurrent medication, adherence, HU dose.
- **Independent variables:** time before and after initiation of HU
- **Dependent variables:** number of admissions, number of transfusions.

The data were then entered into a Microsoft Excel spreadsheet.

### 3.9 Data Analysis

The data were analyzed using Stata version 13 (StataCorp. 2013. Stata Statistical Software: Release 13. College Station, TX: StataCorp LP). Categorical variables were presented using counts and percentages. Continuous data were presented descriptively using means (standard deviations) and medians (interquartile range) as appropriate. The dependent variables were the data points, the number of transfusions and number of admissions. The independent variables were the time before and after initiation of hydroxyurea. Bivariate analyses were done using chi squares for categorical variables and also paired t-tests for the comparison of the means before and after initiation of hydroxyurea. A statistical comparison of time trends before and after the intervention was done. A Poisson regression analysis of the transfusion and admission counts while accounting for time periods was done to explore for any association between use of hydroxyurea (intervention) and frequency of blood transfusions and admissions. The results presented as Incidence Rate Ratios (IRR) with their respective 95% confidence intervals. Predicted transfusion data were presented graphically on a box plot to depict the change in the number of transfusions after the intervention. All statistical tests were evaluated at 5% level, with p values less than 0.05 considered statistically significant.

### 3.10 Flow Chart



*Figure 1: Flow Chart depicting how the study will be conducted*

## CHAPTER 4.0 RESULTS

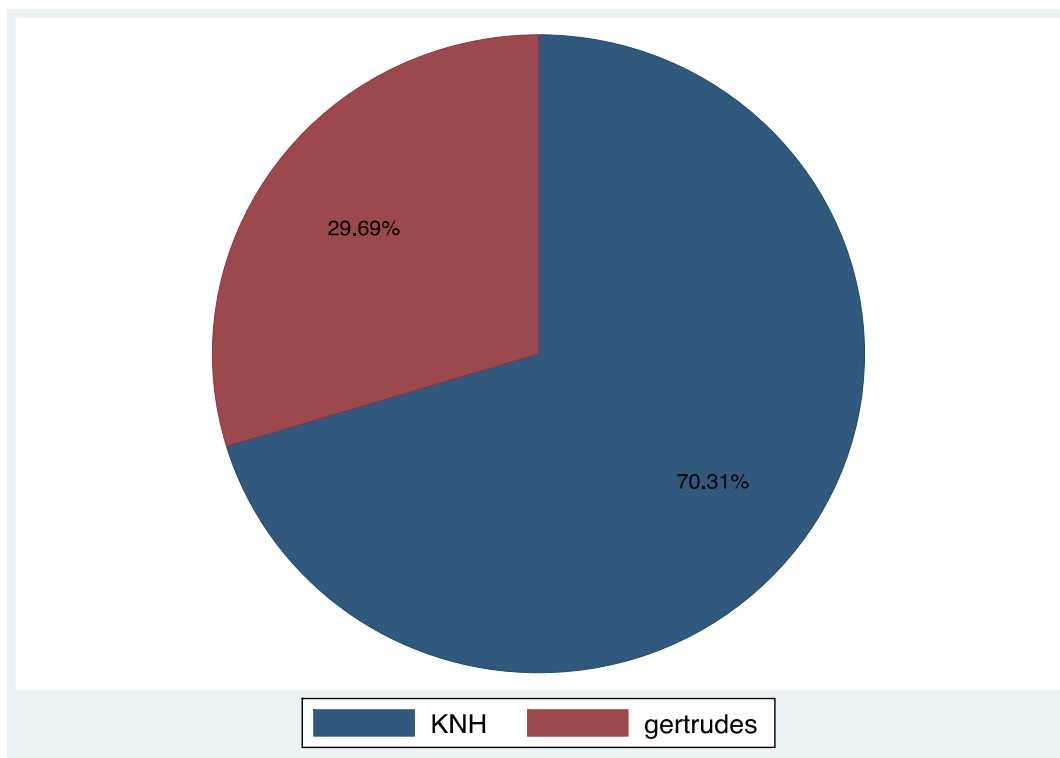
### Demographics

A total of 64 children were recruited in the study majority of whom were male 37(57.8%) with a mean age of 7.6 years (SD= 3.7)

*Table 2: Table depicting male and female distribution of study participants*

Gender	N (%)
Female	27 (42.2)
Male	37 (57.8)
Total	64 (100)

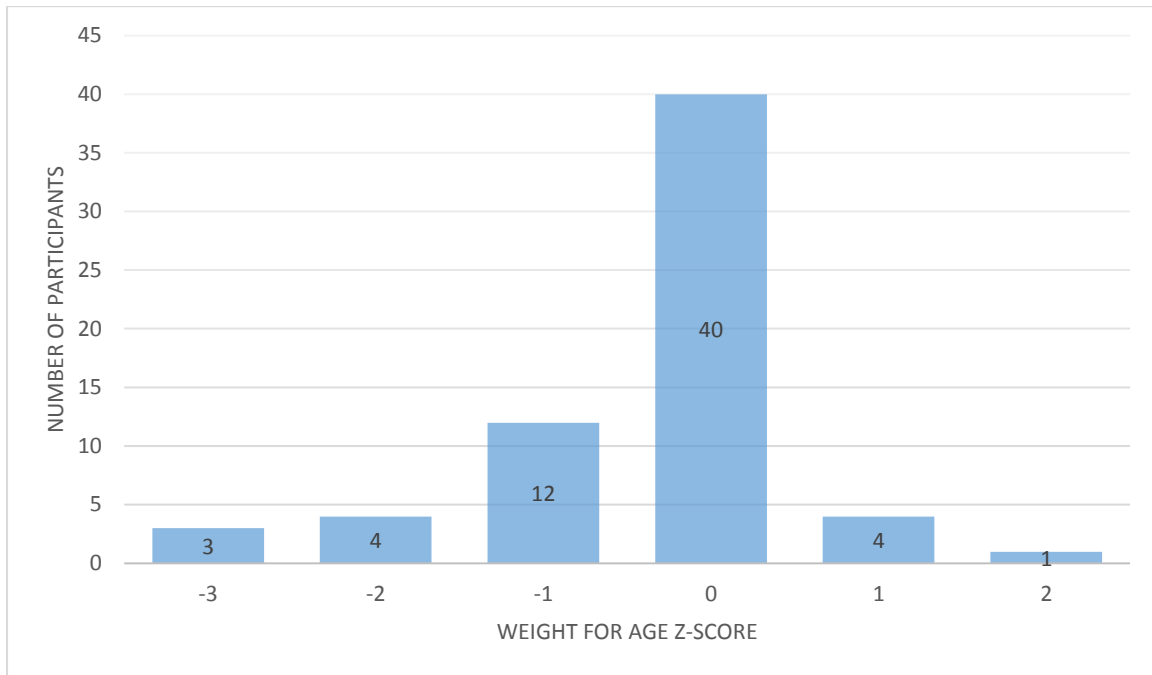
With a greater number being recruited from Kenyatta National Hospital 45 (70.3%)



*Figure 2: Pie Chart showing distribution of patients between the two clinics*

Majority of the respondents were residing in Kariobangi South 12(18.8%) in Nairobi, Kenya.

Majority of the participants were well-nourished with 40 (62.5%) having weight for age z-score (WAZ) of 0. However 4 (6.3%) were underweight with a WAZ of -2 with a further 3 (4.7%) being severely underweight with a WAZ of -3.



**Figure 3: Chart showing WAZ of participants**

On family history, majority of the patients had siblings 54(84.4%) who had not done Hb electrophoresis 38(70.4%). Similarly, neither the mother nor the father of the patients had done Hb electrophoresis, 52(81.2%) and 56(87.5%), respectively.



**Table 3: Hb electrophoresis done by relatives of the participants**

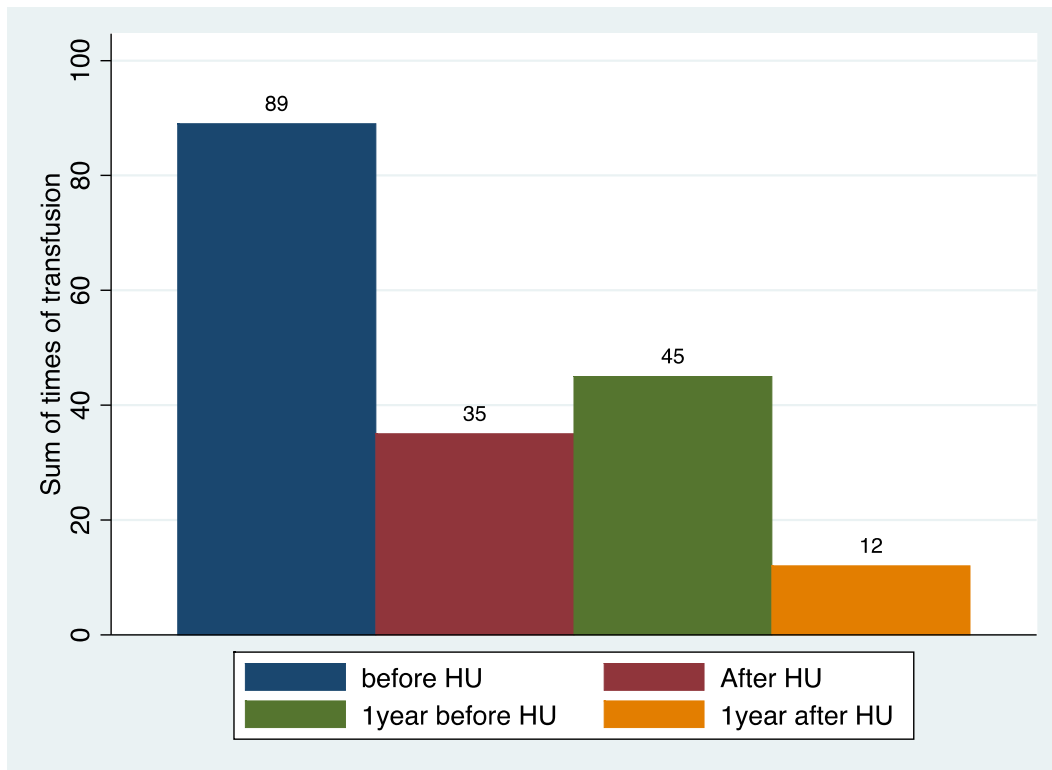
Family History (N=64)	N (%)
Patients who had other siblings	
No	10 (15.6)
Yes	54 (84.4)
Total	64 (100)
Siblings who had done Hb electrophoresis	
No	38 (70.4)
Yes	16 (29.6)
Total	54 (100)
Mother done Hb electrophoresis	
No	52 (81.2)
Unknown	1 (1.6)
Yes	11 (17.2)
Total	64 (100)
Father done Hb electrophoresis	
No	56 (87.5)
Unknown	2 (3.1)
Yes	6 (9.4)
Total	64 (100)

The median age at diagnosis of Sickle Cell Anemia was 2.2 years (IQR= 0.7-3.5). Mean age when respondents started using Hydroxyurea (HU) was 4.8 years (SD=2.6), with median duration of use at 2.1 years (IQR=1.3-4). All the respondents, agreed to being admitted due

to Sickle Cell Anemia complications with a median age of 2 years (IQR=1-4) at the first episode. Majority of the respondents had received blood transfusion 57(89.1%) with a median age of 2 years (IQR=0.6-4) at the first transfusion.

The median number of times a respondent had been admitted to hospitals due to Sickle Cell Anemia related complications before the use of Hydroxyurea was 2 times (IQR=1-3). Before the onset of Hydroxyurea use, the median number of times a patient had been admitted in the last one year was 1 time (IQR=1-2). In the immediate 6 months to 1 year period after use of Hydroxyurea for at least 6 months, the median number of times the patient had been admitted was 0 times (IQR=0-0.2). After onset of Hydroxyurea use, the median number of times a patient had been admitted due to Sickle Cell Anemia complications was 0 times (IQR=0-1.2).

The median number of times a patient had received blood transfusion before the use of Hydroxyurea was 1 time (IQR=1-2). In the last one year, the median number of times a patient had received blood transfusion before the onset of Hydroxyurea use was 1 time (IQR= 0.8-2). In the immediate 6 months to 1 year period after Hydroxyurea use for at least 6 months, the median number of times a patient had received blood transfusion was 0 times (IQR=0-0). After onset of Hydroxyurea use, the median number of times a patient had received blood transfusion was 0 times (IQR=0-1).



**Figure 4: Histogram showing number of transfusions before and after use of Hydroxyurea for 6 months**

### Comparison of admissions before and after HU

There was a statistically significant mean decrease of 2.3 (95% CI 1.5 - 3) in the total number of admission times after HU from a mean of 3.4 (95% CI 2.5-4.4) to 1.2 (95% CI 0.7 - 1.6).

Similarly, there was a statistically significant mean decrease of 1.3 (95% CI 0.9- 1.7)(P value <0.001) in the number of admission times 6 months to 1 year after HU from a mean of 1.7 (95% CI 1.3-2.1) to 0.4 (95% CI 0.2 - 0.6).

**Table 4: Comparison of frequencies of admissions before and after HU use**

Admission (N=64)	Mean (95% CI)	Paired t-test on difference
Number of admission before HU	3.4 (2.5 - 4.4)	
Number of admission after HU	1.2 (0.7 - 1.6)	
Difference	2.3 (1.5 - 3)	P value <0.001
Number of admission 1year before HU	1.7 (1.3 - 2.1)	
Number of admission 6 months to 1year after HU	0.4 (0.2 - 0.6)	
Difference	1.3 (0.9 - 1.7)	P value <0.001

#### **Comparison of transfusions before and after HU**

With respect to transfusion, there was a statistically significant mean decrease of 1.4 (95% CI 0.9-1.9) in the total number of transfusion after HU from a mean of 2.1 (95% CI 1.5-2.8) to 0.7 (95% CI 0.4 - 1.1). Similarly, there was a statistically significant mean decrease of 0.9 (95% CI 0.7 - 1.2)(P value <0.001) in the number of transfusions 6 months to 1 year after HU from a mean of 1.2 (95% CI 0.9-1.4) to 0.2 (95% CI 0.1 - 0.4).

**Table 5: Comparison of frequencies of transfusions before and after HU use**

Transfusion (N=64)	Mean (95% CI)	Paired t-test on difference
Number of transfusion before HU	2.1 (1.5 - 2.8)	
Number of transfusion after HU	0.7 (0.4 - 1.1)	
Difference	1.4 (0.9 - 1.9)	P value <0.001
Number of transfusion 1year before HU	1.2 (0.9 - 1.4)	
Number of transfusion 6 months - 1year after HU	0.2 (0.1 - 0.4)	
Difference	0.9 (0.7 - 1.2)	P value <0.001

**Analysis of transfusions before and after intervention**

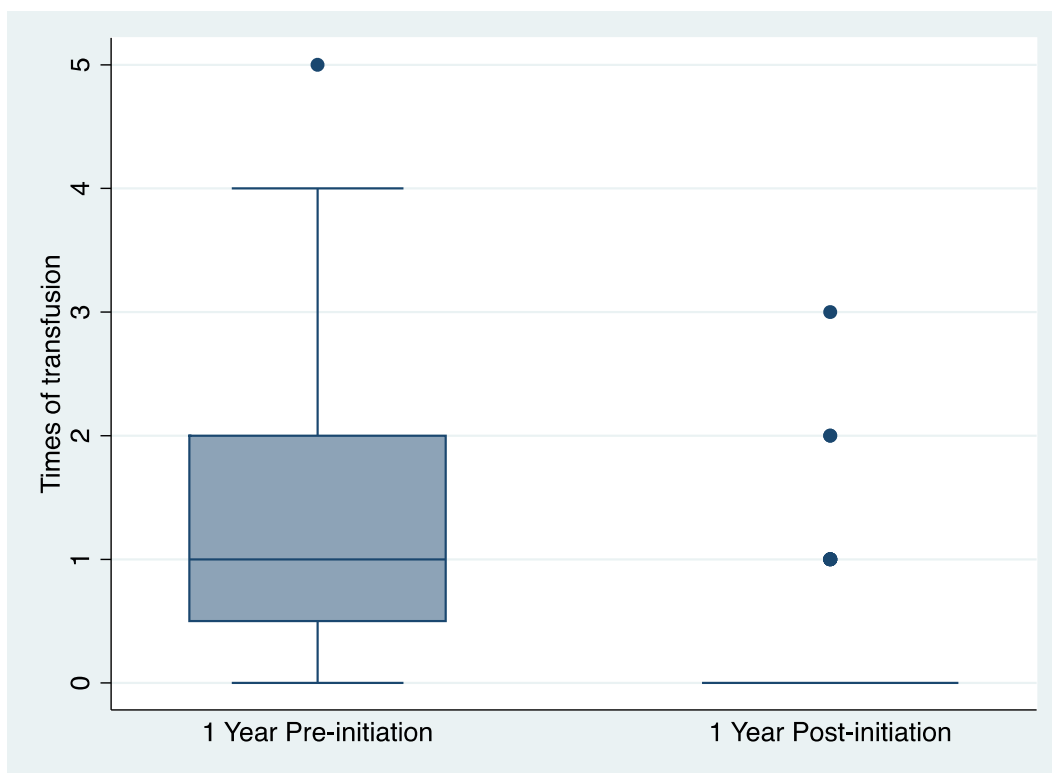
The total person-years before HU was 306.7, with an incident rate of transfusion events of 44.02 per 100 person-years before the use HU. The total person-years after HU was 181.5, with an incident rate of transfusion events of 25.34 per 100 person-years after the use of HU.

The intervention compared to pre-intervention, holding the time points constant, the children had a statistically significant lower rate of transfusion IRR = 0.18 (95% CI 0.09 - 0.35).

Overall the rate of transfusion seems to increase slightly for each unit increase in the time points while holding intervention constant, IRR = 1.38 (95% CI 1.02 - 1.86).

**Table 6: Analysis of transfusions before and after intervention**

Times of transfusions	Incident Rate Ratio (IRR) (95% CI)	P value
Intervention		
Pre-Intervention	Reference group	<0.001
Intervention	0.18 (0.09 - 0.35)	
Time points	1.38 (1.02 - 1.86)	0.032



**Figure 1: Box plot showing change in the number of transfusions after 6 months of Hydroxyurea**

## Dosage of Hydroxyurea

A greater proportion of the patients were under the capsule formulation of HU 53(82.8%) and on alternate day dosing 37(57.8%). The median dosage of Hydroxyurea was 14.5 mg/kg/day (IQR = 11.3-19).

Majority of the respondents in both haematology clinics were under dosed with 51 (79.7%) receiving a daily dosage of < 20mg/kg/day.

**Table 7: Dosage classification of HU used by the participants**

Dosage Classification	N (%)
Under dose '<20 mg/kg/day'	51 (79.7)
Required '20-35 mg/kg/day'	13 (20.3)

There were statistically significantly ( $p=0.001$ ) more children, 37 (72.5%) vs. 14 (27.5%), who were on alternate day dosing who under dosed compared to those not on alternate day dosing.

**Table 8: Comparison between different dosing modalities**

	Alternate Day Dosing		Chi square test, P value
	No	Yes	
Dosage Classification (N=64)			
Under dose '<20 mg/kg/day'	14 (51.8)	37 (100)	P value <0.001
Required '20-35 mg/kg/day'	13 (48.2)	0 (0)	
Total	27 (100)	37 (100)	

### Times of transfusions after HU by Dosage classification

There were less children, 9 (17.6%) vs. 42(82.4%), who had more than two transfusions after HU who had under dosed compared to those who had less than two transfusions, with no statistical significance (p=0.847).

**Table 9: Number of transfusions after HU by Dosage classification**

Dosage Classification (N=64)	Number of transmission after HU		Chi square test, P value
	<2 times	2+ times	
Under dose '<20 mg/kg/day'	42 (79.3)	9 (81.8)	P value = 0.847
Required '20-35 mg/kg/day'	11 (20.7)	2 (18.2)	

### Barriers to adherence

A greater number of the children take Hydroxyurea as prescribed 50(78.1%) whereas majority of the reasons as to why HU was not taken as prescribed was attributed to other factors 8(12.5%) other than cost and availability like forgetting to buy drugs 6(9.4%), no prescription during strikes 1(1.6%), and was advised that HU use was not to be stopped 1(1.6%).



**Table 10: Barriers to adherence**

Factors affecting adherence to Hydroxyurea	N (%)
It is costly	2 (3.1)
Drug not available	1 (1.6)
No one available to administer drug	3 (4.7)
Other	8 (12.5)
Total	14 (21.9)
Other, specified	
Forgetting to buy drugs	6 (9.4)
No prescription during strike	1 (1.6)
Was told that drug was not to be stopped	1 (1.6)

### **Participant perceived side effect**

Majority of the children had not experienced any side effect experience with the use of Hydroxyurea 56(87.5%), however, the few who had nausea and vomiting 4(6.2%) were the most reported side effect. Some specified other side effects as diarrhea 1(1.6%) abdominal pains 1(1.6%), alopecia 1(1.6%), change in nail color 1(1.6%), and coughing 1(1.6%).

**Table 11: Perceived side effect**

Side effects	N (%)
None	56 (87.5)
Nausea and vomiting	4 (6.2)
Diarrhoea	1 (1.6)
Other	4 (6.4)
Total	64 (100)
Other side effects specified	
Abdominal pain	1 (1.6)
Alopecia	1 (1.6)
Change in nail colour	1 (1.6)
Coughing	1 (1.6)

### **Use of other medication**

Apart from Hydroxyurea, majority of the children were using Folic Acid 64(100%) and Penicillin V 64(100%), while majority of the other specified drugs was Ranferon/Vitamin C 8(12.5%) followed by Neurobion 2(3.1%) and antimalarial drugs 2(3.1%).

**Table 12:Other medication used**

Medications Used	N (%)
Folic acid	64 (100)
Penicillin v	64 (100)
Anti- malarial drugs	2 (3.1)
Other	11 (17.2)
Other medications specified	
Neurobion	2 (3.1)
Ranferon/ vitamin c	8 (12.5)

## DISCUSSION

Sickle cell disease (SCD) remains an important health problem in Kenya and the frequency of hospital admissions and blood transfusion remains unacceptably high. Multiple approaches for the management and prevention of hospitalization exist, however access to these is variable due to financial and technical constraints. Despite HU currently being the mainstay of treatment, reports available in literature on its impact of treatment in children are limited. Hydroxyurea use has been shown in other settings to reduce the frequency of blood transfusions but this has not been locally demonstrated given the different landscape. Our study therefore set to examine the impact of hydroxyurea on frequency of blood transfusions in these children. It also investigated the dosage of HU, the barriers to adherence of HU, the perceived side effects of HU, and concurrent medication use.

In this study we found a significant reduction in the frequency of blood transfusion in children with SCD following 6 months of hydroxyurea as there was a mean decrease of 0.9 (95% CI 0.7 - 1.2) (P value <0.001) in the number of transfusions in the 6 months to 1 year period after the use HU from a mean of 1.2 (95% CI 0.9-1.4) to 0.2 (95% CI 0.1 - 0.4). A similar observation was made by Charache et al 1995 whereby incidences of transfusions in adults receiving HU reduced in comparison to a placebo group.<sup>10</sup> In that study the number of patients who received transfusions differed significantly with 48 patients in the HU group receiving blood transfusions vs. 73 in the placebo group, (P = 0.001). In our study this decrease remained significant whether the entire 12 month post-HU period or the 6 month period was considered. The total person-years before HU was 306.7, with an incident rate of transfusion events of 44.02 per 100 person-years before the use HU which decreased to a total person-years of 181.5 after HU, with an incident rate of transfusion events of 25.34 per 100 person-years after HU use.

Wang et al (BABY HUG) 2011, also demonstrated an identical outcome with a decrease in transfusion incidences between patients who were on HU in comparison to those who were on placebo.<sup>11</sup> In the study, done on babies aged 9-18 months, 35 events of transfusions were recorded in 20 patients in the HU group against 63 transfusion events in 33 patients in the placebo group.

As previously noted the intervention compared to pre-intervention, holding the time points constant, the children had a statistically significant lower rate of transfusion IRR = 0.18 (95% CI 0.09 - 0.35). This result is both clinically meaningful and statistically significant.

HU therefore should be encouraged even for use in children in Sub Saharan Africa, and more specifically Kenya as it does reduce incidences of transfusions in children with SCD.

The second aim of the study was to examine the dosage of HU and drug formulation used by these children with SCD. According to the National Heart Lung and Blood Institute HU should be offered to all children, from infants 9 months of age at a recommended starting dose of 20mg/kg/day to a maximum of 35mg/kg/day.<sup>19</sup> Analysis in our study revealed that majority of the participants were actually under dosed as per the above guidelines, with 51 (79.7%) receiving a daily dosage of < 20mg/kg/day. Majority of the patients had access only to the capsule formulation of HU 53(82.8%) which provided challenges to daily dosing as 37 (57.8%) were on alternate day dosing. There were also statistically significantly ( $p=0.001$ ) more children, 37 (72.5%) vs. 14 (27.5%), who were on alternate day dosing who under dosed compared to those not on alternate day dosing. A clinical response to treatment may be suboptimal due to under dosing however analysis of a possible association between a higher rate of frequency of transfusion and under dosing bore no statistical significance ( $p=0.847$ ). A documented decrease in frequency of blood transfusion was still reported and it might be concluded that such doses are unnecessary for all patients. However, our study design is too limited to permit such a conclusion, but evaluation of alternative dosage regimens may be needed for patients in Sub Saharan Africa and more so in Kenya. Health care workers and those involved in the management of children with SCD should still prescribe the required dose of HU under the current international guidelines, with an aim also toward giving daily doses of HU.

Our third objective was to describe adherence to HU and factors affecting adherence in children with SCD aged 1-18 years. Most of the parents/caregivers ensured that the children took HU as prescribed with 50 (78.1%) reporting good compliance to the drug. This is a higher incidence in comparison to the study done by Patel et al 2010 whereby in his study the average refill prescription rate was 58.4%.<sup>28</sup> In our study those who did not take the medication as required cited other factors 8(12.5%) other than cost and availability of HU like forgetting to buy drugs 6(9.4%), no prescription during strikes 1(1.6%), and was advised

that HU use was not to be stopped 1(1.6%) as being the main reasons to their poor compliance. However, more formal strategies are required to identify barriers to prescription refills among children with SCD as these contribute to poor management of these children as HU should be taken consistently to achieve maximum benefit of the drug. Forgetting to buy drugs which contributed to the most cause of poor adherence can however be corrected with little effort and therefore patients should be educated on the benefits of drug adherence viz a viz disadvantages of poor adherence to the drug.

Tied to this we also examined perceived participant side effect of hydroxyurea. It is encouraging that majority of the participants had not experienced any side effect with the use of Hydroxyurea 56(87.5%), however, the few who had 8 (12.5%), had nausea and vomiting 4(6.2%) being the most reported side effect. This is comparable to the study done by Randi et al 2005 where 16 (10.5%) of the patients reported unwanted side effects.<sup>21</sup> In our study, some specified other side effects as diarrhea 1(1.6%) abdominal pains 1(1.6%), alopecia 1(1.6%), change in nail color 1(1.6%), and coughing 1(1.6%). This signifies that HU is well tolerated in children an additional positive aspect in the management of SCD. However this findings do not apply to long –term adverse effects which would require longer time follow up that was not feasible in our study.

Our final objective set out to investigate concurrent medication use with HU in patients with SCD. Apart from Hydroxyurea, all of the children were using Folic Acid 64(100%) and were also on oral Penicillin V 64(100%). This is in keeping with the current international guidelines, Evidence-Based Management of Sickle Cell Disease Expert Panel Report, 2014 whereby at least all children under 5 years of age should be on folic acid and oral penicillin V.<sup>20</sup> This is encouraging as the use of these two drugs minimizes the chances of getting complications of SCD. Of the other drugs used Ranferon/Vitamin C 8(12.5%) was used more followed by Neurobion 2(3.1%) and antimalarial drugs 2(3.1%).

## **LIMITATIONS OF THE STUDY**

The study was carried out in Kenyatta national Hospital and Gertrude's Children Hospital and only included children with SCD that visit these two institutions. As such it is possible that generalizability of the study may be limited by the fact the children studied are not a random sample of all children with SCD in Kenya and this may result in some level of confounding. Nonetheless considering the consistent results both in a public (KNH) and private (GGCH) health facility implies that confounding by economic status may not represent a major problem.

Due lack of a valid comparison group in the quasi-experimental design issues with internal validity of the study like maturation and history effect may not have been addressed adequately. Sample bias also does exist due to the methodology used in the study where by opportunistic sampling was employed to recruit patients.

The patient population used in this study was selected based on their use of hydroxyurea. Therefore, the study sample does not capture the barriers and thoughts of individuals who have poor adherence to HU or who might have declined the use of HU or who have been on the medication for less than 6 months.

Recall bias of the participants, poor record keeping and incomplete documentation in the patients' files were also limitations of the study.

## **CONCLUSION AND RECOMENDATIONS**

The study suggests that Hydroxyurea does reduce the frequency of blood transfusions in children aged between 1 year and 18 years. Most children with SCD who are followed up in KNH and Gertrude's hospital are given HU doses below the recommended doses of 20mg – 35mg/kg/day. Most children with SCD on HU do tolerate the drug well and are on appropriate concurrent adjunctive medications.

It appears that this study population has good adherence. Further research could define how interventions to these barriers influence the outcomes of adherence to hydroxyurea.

Our data supports the use of hydroxyurea therapy for the prevention of frequent blood transfusions in children and it is strongly recommended that the use HU should be considered for all children with SCA in Kenya.



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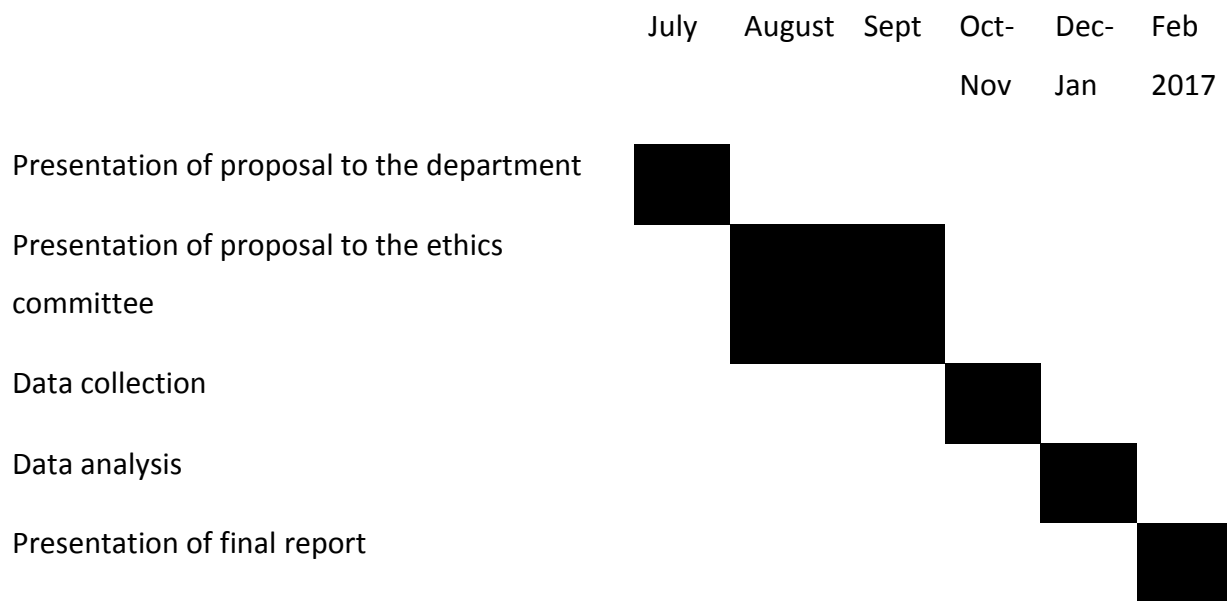
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## APPENDIX: 1. WORK SCHEDULE/ TIME PLAN



*Table 13: A timeline depicting the stipulated study progression*

## APPENDIX: 2. RESEARCH BUDGET

	Kshs.	
Printing, photocopying and binding of research booklets and questionnaires	8,000	both
Travel costs during data collection to Gertrude's Children's Hospital estimated at 100kshs per return trip for 5 clinic days	500	
Payment to Statistician/Analyst to enable appropriate analysis of the collected data	30,000	
<b>Total Costs</b>	<b>38,500</b>	

## **APPENDIX 3. CONSENT FORM**

### **IMPACT OF HYDROXYUREA ON FREQUENCY OF BLOOD TRANSFUSION IN CHILDREN WITH SICKLE CELL ANAEMIA**

**Informed Consent form for \_\_\_\_\_**

The principal investigator is Dr Philip Olielo under supervision from Prof Dalton Wamalwa and Dr Nyambura Kariuki on a study looking into the effect of Hydroxyurea on transfusion rates in children with Sickle cell anaemia, a study done under the department of Paediatrics and Child Health in the University of Nairobi.

**This Informed Consent Form has two parts:**

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

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

#### **PART I: Information Sheet**

##### **Introduction**

I am a Student currently doing my Masters in Paediatrics and Child health at the University of Nairobi and as such will be doing a study looking at the effect Hydroxyurea, a common drug used in the management of Sickle Cell Anaemia, on its effect on the rate of blood transfusions in children with sickle cell anaemia. Information will be given to you and you may feel free to ask questions before participating in the research.

There may be some words that you do not understand. Please ask me to stop as we go through the information and I will take time to explain. If you have questions later, you can ask them to me, the study doctor.

### **Purpose of the research**

Sickle cell anaemia is quite common in the Sub-Saharan region of which Kenya is part of, it is an inherited disease that affects a number of children in our region who spend many days of their lives in hospital if not properly managed. Hydroxyurea a drug used in the management of these children though not many studies have been done in the region looking at the effect the drug has on the disease burden, the purpose of the study will be to enable us know the characteristics of these children on Hydroxyurea, and largely on its effect on the number of times these children will require transfusions as most of these children receive frequent transfusions.

### **Risks**

The study poses no risk to the participant and all information given will be treated with utmost confidentiality.

### **Benefits**

The study aims at advocating for the use and availability of Hydroxyurea in the management of Sickle cell anaemia.

### **Participant selection**

We invite all children who are on follow up for Sickle cell anaemia at Kenyatta National Hospital and Gertrude's Garden Children hospital and are on Hydroxyurea therapy to participate in the research.

## **Voluntary Participation**

Your participation in this research is entirely voluntary as such no remuneration or compensation will be offered to the participants of the study. It is your choice whether to participate or not. Whether you choose to participate or not, all the services you receive at this clinic will continue and nothing will change. If you choose not to participate in this research project, you will still be offered the treatment that is routinely offered in this clinic/hospital for Sickle cell anaemia.

## **Procedures and Protocol**

### **Description of the Process**

Once consented, a set of questions will be presented to you mainly asking on the general condition and number of hospitalization of the child before and after the child was initiated on hydroxyurea. Questions will mainly be targeted on the number of transfusions and number of painful crises experienced before and after the use of hydroxyurea. Information will also be extracted from the files available at the clinic to better capture the timelines of each events.

### **Duration**

The research takes place over 90 days in total. During that time, we will just require 15 minutes of your time gathering information from you.

### **Confidentiality**

With this research, a better understanding of the treatment of Sickle cell anaemia in our region will be draw. It is possible that if others in the community are aware that you are



participating, they may ask you questions. We will not be sharing the identity of those participating in the research.

The information that we collect from this research project will be kept confidential. Information about you and your child that will be collected during the research will be put away and no-one but the researchers will be able to see it. Any information about you will have a number on it instead of your name. Only the researchers will know what your number is and we will lock that information up. It will not be shared with or given to anyone except the department of Paediatrics and Child Health in the University of Nairobi.

### **Right to Refuse**

You do not have to take part in this research if you do not wish to do so and refusing to participate will not affect your treatment at this clinic in any way. You will still have all the benefits that you would otherwise have at this clinic. Your treatment at this clinic will not be affected in any way.

**This proposal has been reviewed and approved by the department of Paediatrics and Child health and the Ethics committee in Kenyatta National Hospital, which is a committee whose task it is to make sure that research participants are protected from any harm.**

You can ask me any more questions about any part of the research study, if you wish to. Do you have any questions?

**PART II: Certificate of Consent**

**Serial Number:** \_\_\_\_\_

I have read the foregoing information, or it has been read to me. I have had the opportunity to ask questions about it and any questions that I have asked have been answered to my satisfaction. I as a guardian/parent to:

\_\_\_\_\_ consent voluntarily to participate as a participant in this research.

**Name of Participant** \_\_\_\_\_

**Researchers Name:** DR PHILIP OLIELO

**Signature of Participant** \_\_\_\_\_

**Researchers**

**Signature** \_\_\_\_\_

**Date** \_\_\_\_\_

**Date** \_\_\_\_\_

**Who to Contact**

If you have any questions you may ask them now or later, even after the study has started.

If you wish to ask questions later, you may contact any of the following:

**Name: Dr Philip N Olielo (Primary Researcher)**

**Mobile Number: 0721370746**

**Email: [polielo@yahoo.com](mailto:polielo@yahoo.com)**

**Name: Prof Dalton Wamalwa**

**Mobile Number: 0721239493**

**Email: [dalton@africaonline.co.ke](mailto:dalton@africaonline.co.ke)**

**Name: Dr Nyambura Kariuki**

**Mobile Number: 0722679119**

**Email: [kariukin1@yahoo.co.uk](mailto:kariukin1@yahoo.co.uk)**

**Kenyatta National Hospital/University of Nairobi Ethics and Research Committee**

**College of Health Sciences**

**P. O. Box 19676 00202 Nairobi**

**Tel. (254-020) 2726300-9 Ext 44355**

**E-mail: [uonknh\\_erc@uonbi.ac.ke](mailto:uonknh_erc@uonbi.ac.ke)**

## **APPENDIX 4. IDHINI**

### **IMPACT OF HYDROXYUREA ON FREQUENCY OF BLOOD TRANSFUSION IN CHILDREN WITH SICKLE CELL ANAEMIA**

**Fomu ya Idhini ya \_\_\_\_\_**

Mpelelezi mkuu ni Dr Philip Olielo chini ya usimamizi wa Profesa Dalton Wamalwa na Dr Nyambura Kariuki katika utafiti wa kuangalia athari ya hydroxyurea katika kuongezewa damu kwa watoto wanayoishi na Ugonjwa wa Selmundu. Utafiti itafanyika chini ya Idara ya Afya ya Watoto katika Chuo Kikuu cha Nairobi.

**Hi fomu ya idhini ina sehemu mbili:**

- **Sehemu ya Maelezo (kukuelezea zaidi kuhusu utafiti )**
- **Shahada ya Idhini ( sahihi ikiwa umekubali kujihusisha na utafiti huu)**

**Utapewa nakala ya maalezo ya utafiti huu.**

#### **SEHEMU YA I: Maelezo**

Mimi ni mwanafunzi katika chuo kikuu cha Nairobi, ninapofanya shahada kuu kwenye Idara ya Afya ya watoto. Ningependa pamoja na wasimaizi wangu kutafiti adhari ya matumizi ya hydroxyurea dawa moja wapo inayotumiwa na wanaougua Ugonjwa wa Selimundu,na hasaa kutafuta uhusiano wake na kuwepo na haja ya kuongezwa damu kwa wagonjwa hawa. Kando na haya utapewa maalezo zaidi kuhusu mada na pia una uhuru wa kuuliza maswali yoyote ili kuelewa uafiti huu zaidi.

## **Nia**

Ugonjwa wa Selimundu ni ugonjwa moja wapo unaoathiri watoto kweye sehemu yetu bara Afrika. Ugonjwa huu umeadhiri maisha ya watoto hawa hasa wakati wao mwingi hutumiwa hospitalini wanapolazwa ili kupokea matibabu zaidi.

Utafiti wa athari ya hydroxyurea haujafanywa sana katika sehemu letu la bara Africa. Kwa hio utafiti huu utalenga kuelewa hasa athari ya kutumia dawa hii na kuwepo haja ya kuongezwa damu kwa watoto hawa na kuangazia iwapo matumizi ya dawa hii inapunguza idadi ya nyakati watoto hawa watahitaji kuongezwa damu.

## **Hatari**

Hakuna hatari yoyote itakayotarajiwa utakaposhiriki utafiti huu.

## **Faida ya utafiti**

Utafiti huu unalenga kutetea na kuunga mkono kuwepo na matumizi ya hydroxyurea kwa wagonjwa wanaouugua Ugonjwa wa Selimundu.

## **Waanaoalikwa kujihusisha na utafiti**

Mtafiti anawakaribisha watoto wote wanaopokea matibabu ya Ugonjwa wa Selimundu na kufuatiliwa katika Hospitali ya Taifa Ya Kenyatta na Gertrude's Garden Childrens Hospital.

## **Kushiriki**

Kushiriki utafiti huu utakuwa kwa njia ya kujitolea na kwa hivyo hakuna malipo yoyote atakayolipwa mshiriki wa utafiti huu. Iwapo hungependa kushiriki ,uamuzi huu hautakuathiri kwa njia yoyote iwe matibabu yako au utakavyiohudumiwa.

### **Maelezo kuhusu mchakato**

Iwapo utakubali kushiriki utapewa fomu ya kujaza iliyo na seti ya maswali hasa kuhusu hali ya afya ya watoto hawa na idadi ya nyakati waliyohitajiwa kuongezwa damu kabla na baada ya kuanzishwa matibabu kutumia hydroxyurea. Maswali yatalenga zaidi idadi ya nyakati ya kuongezwa damu na pia maumivu kali wanayopitia watoto hawa wanaougua ugonjwa huu. Maelezo zaidi pia yanaweza kutolewa kwenye file yako ya kliniki ili kuboresha utafiti.

### **Wakati utakaotumika**

Kwa ujumla, utafiti huu utachukua siku tisini (90). Kwa wakati huu tutahitaji dakika kumi na tano tu kujaza fomu na kuchukua maelezo mengine yatakayohitajika.

### **Usiri**

Matokeo ya utafiti huu yatawekwa siri wala hayatapatiwa mtu yeyote asiyehusika ma utafiti huu. Zaidi ya hayo badala ya jina la mtoto, numbari zitatumwa kutambuliwa watoto hawa. Matokeo yatazungumziwa na idara ya afya ya watoto pekee wala sio mtu mwingine.

### **Haki ya kutoshiriki**

Kushiriki utafiti huu ni kwa kujitolea na iwapo hungenda kushiriki, uamuzi wako utaheshimiwa na pia hautathiri kwa njia yoyote matibabu yako. Bali utaendelea kupokea matibabu na huduma ya hospitali hii kama hapo awali.

**Pendekezo hili limeangaliwa na kuidhinishwa na Idara ya afya ya watoto ya Chuo kikuu cha Nairobi na kamiti ya maadili ya utafiti katika hospitali ya Kenyatta inayohakikisha kuwa haki za wanaoshiriki utafiti wowote inchini, zinazingatiwa.**

Iwapo utakuwa na swali lolote kumbuka una uhuru kuuliza.

SEHEMU YA II: Shahada ya Idhini

Nambari Maalum: \_\_\_\_\_

Nimesoma maelezo yote ya utafiti huu au nimesomewa maelezo haya na nimekuwa na fursa ya kuuliza maswali ambayo yamejibiwa kadri na matarajio yangu kwa njia ya kuridhisha. Kwahio kama mzazi/ mgarini wa :

\_\_\_\_\_ ningependa kupeana idhini yangu na pia kujitolea kushiriki kwa utafiti huu .

Jina la mshiriki: \_\_\_\_\_

Mtafiti mkuu: DR PHILIP OLIELO

Sihihi la mshiriki: \_\_\_\_\_

sahihi ya mtafiti mkuu:

\_\_\_\_\_

Tarehe: \_\_\_\_\_

Tarehe: \_\_\_\_\_

Kwa maelezo zaidi hata baada ya utafiti huu una uhuru wakuwasiliana na watu wafuatao kupitia anwani na numbari za simu silizoandikwa hapa chini.

**Jina: Dr Philip N Olielo (mtafiti mkuu)**

**Nambari ya simu: 0721370746**

**Barua pepe: [polielo@yahoo.com](mailto:polielo@yahoo.com)**

**Jina: Prof Dalton Wamalwa**

**Nambari ya simu: 0721239493**

**Name: Prof Dalton Wamalwa**

**Barua pepe: [dalton@africaonline.co.ke](mailto:dalton@africaonline.co.ke)**

**Jina: Dr Nyambura Kariuki**

**Nambari ya simu: 0722679119**

**Barua Pepe: [kariukin1@yahoo.co.uk](mailto:kariukin1@yahoo.co.uk)**

**Kenyatta National Hospital/University of Nairobi Ethics and Research Committee**

**College of Health Sciences**

**P. O. Box 19676 00202 Nairobi**

**Simu. (254-020) 2726300-9 Ext 44355**

**Barua pepe: [uonknh\\_erc@uonbi.ac.ke](mailto:uonknh_erc@uonbi.ac.ke)**



## **APPENDIX 5. ASSENT FORM**

### **IMPACT OF HYDROXYUREA ON FREQUENCY OF BLOOD TRANSFUSION IN CHILDREN WITH SICKLE CELL ANAEMIA**

**Informed Assent Form for \_\_\_\_\_**

This informed assent form is for children above 7 years of age who attend the Haematology Clinics at Kenyatta National hospital and Gertrude's Garden Children's Hospital and who we are inviting to participate in research to study the impact of Hydroxyurea on frequency of blood transfusion in children with Sickle Cell Anaemia.

**The principal investigator is Dr Philip Olielo under supervision from Prof Dalton Wamalwa and Dr Nyambura Kariuki on a study looking into the effect of Hydroxyurea on transfusion rates in children with Sickle cell anaemia, a study done under the department of Paediatrics and Child Health in the University of Nairobi.**

**This Informed Assent Form has two parts:**

- **Information Sheet (gives you information about the study)**
- **Certificate of Assent (this is where you sign if you agree to participate)**

**You will be given a copy of the full Informed Assent Form**

**Part I: Information Sheet**

## **Introduction**

My name is Philip Olielo and I am a doctor at Kenyatta National Hospital. I am interested in doing a research on Sickle Cell Anaemia that might help the children with Sickle Cell Disease live a better life. We want to know the drug called Hydroxyurea helps reduces hospital admissions and need of blood transfusions and we think this research could help tell us that.

I am going to give you information and invite you to be part of a research study. You can choose whether or not you want to participate. We have discussed this research with your parent(s)/guardian and they know that we are also asking you for your agreement. If you are going to participate in the research, your parent(s)/guardian also have to agree. But if you do not wish to take part in the research, you do not have to, even if your parents have agreed.

You may discuss anything in this form with your parents or friends or anyone else you feel comfortable talking to. You can decide whether to participate or not after you have talked it over. You do not have to decide immediately.

There may be some words you don't understand or things that you want me to explain more about because you are interested or concerned. Please ask me to stop at any time and I will take time to explain.

### **Purpose: Why are you doing this research?**

We want to advocate for better treatment for children living with Sickle Cell anaemia. There is a drug used to manage Sickle Cell Anaemia and we want to see if it reduces the need for admission and blood transfusions in children.

### **Choice of participants: Why are you asking me?**

We want to get some information from children with Sickle Cell Anaemia who have been taking Hydroxyurea for at least six months.

**Participation is voluntary: Do I have to do this?**

You don't have to be in this research if you don't want to be. It's up to you. If you decide not to be in the research, it's okay and nothing changes. This is still your clinic, everything stays the same as before.

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

\_\_\_\_\_ (signature)

**Procedures: What is going to happen to me?**

If you allow us we are going to ask you some questions mostly asking you how well you have been and also how many times you have been admitted to hospital for the blood transfusions before you were started on hydroxyurea and also after you were started on hydroxyurea.

**I have checked with the child and they understand the procedures \_\_\_\_\_(signature)**

**Risks: Is this bad or dangerous for me?**

You will not be in any harm when you take part in this research

**I have checked with the child and they understand the risks and discomforts**

\_\_\_\_\_(signature)

**Benefits: Is there anything good that happens to me?**

Nothing might happen to you, but the information you give us might help us learn more about Hydroxyurea.

**I have checked with the child and they understand the benefits\_\_\_\_\_ (Signature)**

**Reimbursements: Do I get anything for being in the research?**

Unfortunately there will be no gifts if you choose to participate in the study.

**Confidentiality: Is everybody going to know about this?**

We will not tell other people that you are in this research and we won't share information about you to anyone who does not work in the research study.

Information about you that will be collected from the research will be put away and no-one but the researchers will be able to see it. Any information about you will have a number on it instead of your name. Only the researchers will know what your number is and we will lock that information up with a lock and key. It will not be shared with or given to anyone.

**Sharing the Findings: Will you tell me the results?**

When we are finished with the research we will not contact you personally to give you the results but you can come find out about the research at the Department of Paediatrics, University of Nairobi. We will be telling more people, scientists and others, about the research and what we found. We will do this by writing and sharing reports.

**Right to Refuse or Withdraw: Can I choose not to be in the research? Can I change my mind?**

You do not have to be in this research. No one will be mad or disappointed with you if you say no. It's your choice. You can think about it and tell us later if you want. You can say "yes" now and change your mind later and it will still be okay.

**Who to Contact: Who can I talk to or ask questions to?**

You can ask me questions now or later. I have written a number and address where you can reach us or, if you are nearby, you can come and see us. If you want to talk to someone else that you know like your teacher or doctor or auntie, that's okay too.)

**If you choose to be part of this research I will also give you a copy of this paper to keep for yourself. You can ask your parents to look after it if you want.**

You can ask me any more questions about any part of the research study, if you wish to. Do you have any questions?

**PART II: Certificate of Assent**

**Serial Number:** \_\_\_\_\_

I understand the research is about finding out if hydroxyurea reduces the number of times a child with Sickle Cell Anaemia has blood transfusions and I will be asked a set of questions if I choose to participate in the research.

**I have read this information (or had the information read to me) I have had my questions answered and know that I can ask questions later if I have them.**

**I agree to take part in the research.**

***OR***

**I do not wish to take part in the research and I have NOT signed the assent below. \_\_\_\_\_ (initialled by child/minor)**

**Only if child assents:**

**Print name of child \_\_\_\_\_**

**Signature of child: \_\_\_\_\_**

**Date: \_\_\_\_\_**

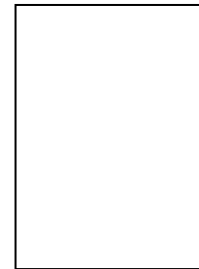
***If illiterate:***

**I have witnessed the accurate reading of the assent form to the child, and the individual has had the opportunity to ask questions. I confirm that the individual has given consent freely.**

**Print name of witness (not a parent) \_\_\_\_\_ AND Thumb print of participant**

**Signature of witness \_\_\_\_\_**

**Date \_\_\_\_\_**



**I have accurately read or witnessed the accurate reading of the assent form to the potential participant, and the individual has had the opportunity to ask questions. I confirm that the individual has given assent freely.**

**Name of researcher: DR PHILIP OLIELO**

**Signature of researcher \_\_\_\_\_**

**Date \_\_\_\_\_**

**Statement by the researcher/person taking consent**

**I have accurately read out the information sheet to the potential participant, and to the best of my ability made sure that the child understands the purpose and procedure of the study**

I confirm that the child was given an opportunity to ask questions about the study, and all the questions asked by him/her have been answered correctly and to the best of my ability. I confirm that the individual has not been coerced into giving consent, and the consent has been given freely and voluntarily.

A copy of this assent form has been provided to the participant.

Name of Researcher: DR PHILIP OLIELO

Signature of Researcher \_\_\_\_\_

Date \_\_\_\_\_

Copy provided to the participant \_\_\_\_\_(initialed by researcher)

Parent/Guardian has signed an informed consent: Yes \_\_\_\_\_ No \_\_\_\_\_

#### Who to Contact

If you have any questions you may ask them now or later, even after the study has started.

If you wish to ask questions later, you may contact any of the following:

**Name: Dr Philip N Olielo (Primary Researcher)**

**Mobile Number: 0721370746**

**Email: [polielo@yahoo.com](mailto:polielo@yahoo.com)**

**Name: Prof Dalton Wamalwa**

**Mobile Number: 0721239493**

**Email: [dalton@africaonline.co.ke](mailto:dalton@africaonline.co.ke)**



**Name: Dr Nyambura Kariuki**

**Mobile Number: 0722679119**

**Email: [kariukin1@yahoo.co.uk](mailto:kariukin1@yahoo.co.uk)**

**Kenyatta National Hospital/University of Nairobi Ethics and Research Committee**

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**P. O. Box 19676 00202 Nairobi**

**Tel. (254-020) 2726300-9 Ext 44355**

**E-mail: [uonknh\\_erc@uonbi.ac.ke](mailto:uonknh_erc@uonbi.ac.ke)**

## **APPENDIX 6. FOMU YA KUTIWA SAINI NA WATOTO**

### **IMPACT OF HYDROXYUREA ON FREQUENCY OF BLOOD TRANSFUSION IN CHILDREN WITH SICKLE CELL ANAEMIA**

**Fomu ya kutiwa saini na watoto ya \_\_\_\_\_**

Fomu hii ni ya kutiwa saini na watoto wenye umri wa miaka saba na juu wanao hudumiwa katika Kliniki ya Ugonjwa wa Damu katika Hospitali ya Taifa Ya Kenyatta na Gertrude's Garden Childrens Hospital. Watoto hawa wanakaribishwa na Mpelelezi mkuu ni Dr Philip Olielo chini ya usimamizi wa Profesa Dalton Wamalwa na Dr Nyambura Kariuki katika utafiti wa kuangalia athari ya hydroxyurea katika kuongezewa damu kwa watoto wanayoishi na Ugonjwa wa Selimundu. Utafiti itafanyika chini ya Idara ya Afya ya Watoto katika Chuo Kikuu cha Nairobi.

**Hi fomu ya kutiwa saini na watoto ina sehemu mbili:**

- **Sehemu ya Maelezo (kukuelezea zaidi kuhusu utafiti )**
- **Shahada ya Kutiwa saini na watoto ( sahihi ikiwa umekubali kujihusisha na utafiti huu)**

**Utapewa nakala ya maalezo ya utafiti huu.**

#### **SEHEMU YA I: Maelezo**

Mimi ni mwanafunzi katika chuo kikuu cha Nairobi, ninapofanya shahada kuu kwenye Idara ya Afya ya watoto .Ningependa pamoja na wasimaizi wangu kutafiti adhari ya matumizi ya hydroxyurea dawa moja wapo inayotumiwa na wanaougua Ugonjwa wa Selimundu ,na hasaa kutafuta uhusiano wake na kuwepo na haja ya kuongezwa damu kwa wagonjwa

hawa. Kando na haya utapewa maalezo zaidi kuhusu mada na pia, wazazi wako na mgarini wako ameelezewa kuhusu utafiti huu na wamekubali kijihusisha nayo, lakini una uhuru wa kukataa kujihusicha na utafiti huu na pia una uhuru wa kuuliza maswali yoyote ili kuelewa uafiti huu zaidi.

### **Nia**

Ugonjwa wa Selimundu ni ugonjwa moja wapo unaoathiri watoto kweye sehemu yetu bara Afrika. Ugonjwa huu umeadhiri maisha ya watoto hawa hasa wakati wao mwingi hutumiwa hospitalini wanapolazwa ili kupokea matibabu zaidi.

Utafiti wa athari ya hydroxyurea haujafanywa sana katika sehemu letu la bara Africa. Kwa hio utafiti huu utalenga kuelewa hasa athari ya kutumia dawa hii na kuwepo haja ya kuongezwa damu kwa watoto hawa na kuangazia iwapo matumizi ya dawa hii inapunguza idadi ya nyakati watoto hawa watahitaji kuongezwa damu.

### **Hatari**

Hakuna hatari yoyote itakayotarajiwa utakaposhiriki utafiti huu.

**Nimethibitisha kuwa mtoto ameelewa ya kwamba hakuna hatari yoyote ile itayomkabili \_\_\_\_\_ (saini)**

### **Faida ya utafiti**

Utafiti huu unalenga kutetea na kuunga mkono kuwepo na matumizi ya hydroxyurea kwa wagonjwa wanaouugua Ugonjwa wa Selimundu.

**Nimethibitisha kuwa mtoto ameelewa faida ya utafiti \_\_\_\_\_ (saini)**

### **Waanaoalikwa kujihusisha na utafiti**

Mtafitii anawakaribisha watoto wote wanaopokea matibabu ya Ugonjwa wa Selimundu na kufutuliwa katika Hospitali ya Taifa Ya Kenyatta na Gertrude's Garden Childrens Hospital.

### **Kushiriki**

Kushiriki utafiti huu utakuwa kwa njia ya kujitolea na kwa hivyo hakuna malipo yoyote atakayolipwa mshiriki wa utafiti huu. Iwapo hungependa kushiriki, uamuzi huu hautaathiri kwa njia yoyote matibabu yako au utakavyiohudumiwa.

**Nimethibitisha kuwa mtoto ameelewa ya kwamba kujihusisha na hii utafiti ni kwa njia ya kujitolea \_\_\_\_\_ (saini)**

### **Maelezo kuhusu mchakato**

Iwapo utakubali kushiriki utapewa fomu ya kujaza iliyo na seti ya maswali hasa kuhusu hali ya afya ya watoto hawa na idadi ya nyakati waliyohitajiwa kuongezwa damu kabla na baada ya kuanzishwa matibabu kutumia hydroxyurea. Maswali yatalenga zaidi idadi ya nyakati ya kuongezwa damu na pia maumivu kali wanayopitia watoto hawa wanaougua ugonjwa huu. Maelezo zaidi pia yatatolewa kwenye file yako kliniki ili kuboresha utafiti.

**Nimethibitisha kuwa mtoto ameelewa maelezo kuhusu mchakato \_\_\_\_\_ (saini)**

### **Wakati utakaotumika**

Kwa ujumla, utafiti huu utachukua siku tisini (90). Kwa wakati huu, tutahitaji dakika kumi na tan tu kujaza fomu na kuchukua maelezo mengine yatakayohitajika

## **Usiri**

Matokeo ya utafiti huu yatawekwa siri wala hayatapatiwa mtu yeyote asiyehusika na utafiti huu. zaidi ya hayo badala ya jina la mtoto, numbari zitatumiwa kutambuliwa watoto hawa. Matokeo yatazungumziwa na idara ya afya ya watoto pekee wala sio mtu mwingine.

## **Haki ya kutoshiriki**

Kushiriki kwa utafiti huu ni kwa kujitolea na iwapo hungependa kushiriki, uoamuzi wako utaheshimiwa na pia hautathiri kwa njia yoyote matibabu yako. Bali utaendelea kupokea matibabu na huduma ya hospitali hii kama hapo awali.

**Pendekezo hili limeangaliwa na kuidhinishwa na Idara ya afya ya watoto ya Chuo kikuu cha Nairobi na kamiti ya maadili ya utafiti katika hospitali ya Kenyatta inayohakikisha kuwa haki za wanaoshiriki utafiti wowote inchini, zinazingatiwa .**

Iwapo utakuwa na swali lolote kumbuka una uhuru kuuliza.

Nimesoma maelezo yote ya utafiti huu au nimesomewa maelezo haya na nimekuwa na fursa ya kuuliza maswali ambayo yamejibiwa kadri na matarajio yangu kwa njia ya kuridhisha. Kwahio ningependa kupeana saini langu na pia kujitolea kushiriki kwa utafiti huu.

Nakubali kujihusisha na utafiti huu.

**AMA**

Si kubali kujihusisha na utafiti huu na sijatia saini lolote. \_\_\_\_\_ (alama ya mshiriki)

**Moto akikubali:**

Jina la mtoto: \_\_\_\_\_

Saini la mtoto: \_\_\_\_\_

Tarehe: \_\_\_\_\_

***Iwapo mtoto awezi akasoma:***

Nimeona na ninaweza thibitisha ya kwamba mtoto amesomewa yaliyo kwenye hii fomu ya kutiwa saini na mtoto, na mtoto mwenyewe ameweza kuuliza maswali atakayo. Na thibitisha ya kwamba mtoto amekubali kwa hiari yake kushirikiana na hii utafiti.

Jina la shahidi (isiwe mzazi): \_\_\_\_\_ NA

Alama ya Kidole ya

Mshiriki

Saini la shahidi: \_\_\_\_\_

Tarehe: \_\_\_\_\_



**Nememsomea ama nimeona na ninaweza thibitisha ya kwamba mtoto amesomewa yaliyo kwenye hii fomu ya kutiwa saini na mtoto, na mtoto mwenyewe ameweza kuuliza maswali atakayo. Na thibitisha ya kwamba mtoto amekubali kwa hiari yake kushirikiana na hii utafiti.**

**Jina la mpelelezi: DR PHILIP OLIELO**

Saini ya mpelelezi: \_\_\_\_\_

Tarahe: \_\_\_\_\_

**Nakala imepewa kwake mshiriki \_\_\_\_\_ (alama ya mpelelezi)**

**Mzazi/Mgarini amaitia saini Shahada ya Idhini: Ndiyo \_\_\_\_\_ Hapana \_\_\_\_\_**

Kwa maelezo Zaidi hata baada ya utafiti huu una uhuru wakuwasiliana na watu wafuatao kupitia anwani na numbari za simu silizoandikwa hapa chini.

**Jina: Dr Philip N Olielo (mtafiti mkuu)**

**Nambari ya simu: 0721370746**

**Barua pepe: [polielo@yahoo.com](mailto:polielo@yahoo.com)**

**Jina: Prof Dalton Wamalwa**

**Nambari ya simu: 0721239493**

**Name: Prof Dalton Wamalwa**

**Barua pepe: [dalton@africaonline.co.ke](mailto:dalton@africaonline.co.ke)**

**Jina: Dr Nyambura Kariuki**

**Nambari ya simu: 0722679119**

**Barua Pepe: [kariukin1@yahoo.co.uk](mailto:kariukin1@yahoo.co.uk)**

**Kenyatta National Hospital/University of Nairobi Ethics and Research Committee**

**College of Health Sciences**

**P. O. Box 19676 00202 Nairobi**

**Simu. (254-020) 2726300-9 Ext 44355**

**Barua pepe: [uonknh\\_erc@uonbi.ac.ke](mailto:uonknh_erc@uonbi.ac.ke)**



## APPENDIX 7: QUESTIONNAIRE

### IMPACT OF HYDROXYUREA ON FREQUENCY OF BLOOD TRANSFUSION IN CHILDREN WITH SICKLE CELL ANAEMIA

QUESTIONNAIRE:

Serial Number: \_\_\_\_\_

#### INSRTUCTIONS

1. Please answer all of the questions provided to the best of your ability
2. Answer each question on the space provided and where options are given mark only your intended response
3. The questionnaire will take approximately 15minutes of your time
4. Please answer the questions as truthfully as you can
5. You may ask for any assistance throughout the filling in of the questionnaire

#### General Information

Please indicate the following information about the patient's participants

Date of Birth: \_\_\_\_\_

Age: \_\_\_\_\_

Sex: \_\_\_\_\_

Current weight: \_\_\_\_\_

Place of residence: \_\_\_\_\_

Date: \_\_\_\_\_

#### Medical Information

1. At what age was the diagnosis of Sickle Cell Anaemia made?

\_\_\_\_\_

2. Was the diagnosis confirmed by Serum electrophoresis? Yes/No
3. At what age did the patient start using Hydroxyurea? \_\_\_\_\_
4. Has the patient used Hydroxyurea for at least 6 months? Yes/No

-If the above response is yes, how many month/years has the patient been using hydroxyurea? \_\_\_\_\_

5. Has the patient ever been admitted due to sickle Cell Anaemia related complications? Yes/No

-If Yes when was the 1<sup>st</sup> ever episode of hospital admission. Please state the age:

\_\_\_\_\_

6. Has the patient ever received any blood transfusion? Yes/No

-If yes when was the 1<sup>st</sup> episode of blood transfusion? Please state the age:

\_\_\_\_\_

7. How many times has the patient been admitted to hospital due to sickle cell anaemia related complications before the use of hydroxyurea? \_\_\_\_\_
8. How many times was the patient admitted in the last 1 year before the onset of Hydroxyurea use? \_\_\_\_\_
9. How many times has the patient been admitted in the immediate 6 months to 1 year after taking hydroxyurea for at least 6 months? \_\_\_\_\_
10. How many times has the patient been admitted due to sickle cell anaemia related complications after onset of hydroxyurea use? \_\_\_\_\_
11. How many times has the patient received blood transfusions before the use of hydroxyurea? \_\_\_\_\_
12. How many times has the patient received blood transfusions in the last 1 year before the onset of Hydroxyurea use? \_\_\_\_\_

13. How many times has the patient received blood transfusions in the immediate 6months to 1 year after taking hydroxyurea for at least 6 months?

\_\_\_\_\_

14. How many times has the patient received blood transfusions after onset of hydroxyurea use? \_\_\_\_\_

15. What formulation is the patient currently on? Capsule/Liquid

16. Is the child on alternate day dosing? Yes / No

17. What dosage of hydroxyurea is the patient currently on in mg/day \_\_\_\_\_  
and in mg/kg/day \_\_\_\_\_

18. Is the child using any other medication apart from Hydroxyurea?

Folic Acid

Penicilin V

Anti- malarial drugs

None

Other

- If other please indicate the name of the Drug \_\_\_\_\_

19. What are the common side effects the child has experienced with the use of Hydroxyurea?

None

Nausea and Vomiting

Diarrhoea

Skin Changes

Other

-If other please indicate the adverse effects \_\_\_\_\_

20. Does the child take Hydroxyurea as prescribed? Yes /No

- If No please indicate the reason as to why not

It is costly

It is not available

It has unwanted side effects

I am not sure how to take it

No one is available to administer the drug

Other: \_\_\_\_\_

**Family History:**

21. Does the patient have other siblings? Yes/No

-if Yes have they ever done a Hb electrophoresis? Yes/No/Not known

22. Has the mother ever done Hb electrophoresis? Yes/No/Not known

23. Has the father ever done Hb electrophoresis? Yes/No/Not known

**The above information which shall be treated with uttermost confidentiality.**

## APPENDIX 8: DODOSO

### IMPACT OF HYDROXYUREA ON FREQUENCY OF BLOOD TRANSFUSION IN CHILDREN WITH SICKLE CELL ANAEMIA

DODOSO

Nambari Maalum: \_\_\_\_\_

#### MAELEKEZO

1. Tafadhali jibu maswali zote kwa umakinifu
2. Jibu kila swali kwenye nafasi iliyopewa na ambapo chaguzi umepewa tia alama pekee kwenye jibu lako
3. Dodoso hii itachukua takriban dakika 15 kuijaza
4. Tafadhali jibu maswali zote kwa ukweli
5. Unaweza kuulizia msaada wowote unapojaza dodoso hii

#### Habari za Jumla

Tafadhali andika taarifa zifuatazo kuhusu washiriki

Siku ya kuzaliwa: \_\_\_\_\_

Miaka: \_\_\_\_\_

Jinsia: \_\_\_\_\_

Uzito / Kilo: \_\_\_\_\_

Mahala pa kuishi: \_\_\_\_\_

Tarehe: \_\_\_\_\_

#### Taarifa kuhusu hali ya afya ya mshiriki

1. Umri kilichokuwa utambuzi wa Ugonjwa wa Selimundu ilipofanywa?

\_\_\_\_\_

2. Utambuzi uli thibitishwa na kipimo cha damu cha "Serum Electrophoresis"? Ndiyo / Hapana
3. Mshiriki alikuwa na umri gani alipoanza kutumia dawa ya hydroxyurea?  
\_\_\_\_\_
4. Mshiriki ametumia hydroxyurea kwa angalau miezi 6? Ndiyo / Hapana  
- Kama jibu hapo juu ni Ndiyo, ni mwezi / miaka ngapi mshirika amekuwa akiitumia hydroxyurea? \_\_\_\_\_
5. Mshiriki amelazwa kwa sababu ya matatizo ya kuhusiana na Ugonjwa wa Selimundu? Ndiyo / Hapana  
- Kama jibu hapo juu ni Ndiyo, wakati alipolazwa mara ya kwanza alikuwa na umri gani? \_\_\_\_\_
6. Mshiriki amelazwa kwa minajili wa kuongezewa damu? Ndiyo / Hapana  
- Kama jibu hapo juu ni Ndiyo, wakati alipopokea damu mara ya kwanza alikuwa na umri gani? \_\_\_\_\_
7. Ni mara ngapi mshiriki amelazwa kwa sababu ya matatizo ya kuhusiana na Ugonjwa wa Selimundu kabla ya matumizi ya dawa ya Hydroxyurea? \_\_\_\_\_
8. Ni mara ngapi mshiriki alikuwa amelazwa tukiangalia mwaka moja kabla ya mwanzo wa matumizi ya dawa ya Hydroxyurea? \_\_\_\_\_
9. Ni mara ngapi mshiriki amelazwa tukiangalia miezi sita hadi mwaka moja baada ya kuchukua Hydroxyurea kwa angalau miezi 6? \_\_\_\_\_
10. Ni mara ngapi kwa jumla mshiriki amelazwa kutokana na matatizo ya kuhusiana na Ugonjwa wa Selimundu baada ya mwanzo wa kutumia hydroxyurea?  
\_\_\_\_\_
11. Ni mara ngapi mshiriki amepokea damu kabla ya matumizi ya hydroxyurea?
12. Ni mara ngapi mshiriki amepokea damu tukiangalia mwaka moja kabla ya mwanzo wa matumizi ya dawa ya Hydroxyurea? \_\_\_\_\_
13. Ni mara ngapi mshiriki amepokea damu tukiangalia miezi sita hadi mwaka moja baada ya kuchukua Hydroxyurea kwa angalau miezi 6? \_\_\_\_\_
14. Ni mara ngapi kwa jumla mshiriki amepokea damu baada ya mwanzo wa kutumia hydroxyurea? \_\_\_\_\_
15. Ni nini uundaji wa dawa ya Hydroxyurea mshiriki anayochukua? Tembe / Majimaji

16. Mtoto anachuka dawa baada ya kuruka siku mmoja? Ndiyo / Hapana

17. Ni kipimo kipi cha hydroxyurea mshiriki anayotumia kwa sasa katika (mg / siku)

\_\_\_\_\_ na katika mg / kilo / siku \_\_\_\_\_

18. Mtoto ana tumia dawa yeyote isipokuwa Hydroxyurea?

Folic Acid

Penicilin V

Anti- malarial drugs

Hapana

Dawa nyingine

- Kama anatumia dawa nyingine ile tafadhali itambulisho hapa

\_\_\_\_\_

19. Kuna madhara lolote ambapo mtoto amewaipata kutokana na matumizi ya Hydroxyurea?

Hapana

Kutapika

Kuhara

Kubadilika ngozi

Madhara nyingine

-Kama amepata madhara nyingine ile tafadhali itambulisho

hapa\_\_\_\_\_

20. Mshiriki anatumia dawa alivyo elezwa? Ndiyo /Hapana

- Kama Jibu hapo juu ni hapana, tafadhali tueleze mbona hatumii dawa kwa namna inavyo faa

Ina bei ya juu

Haipatikani kwa urahisi

- Ina madhara kwa mtoto
- Sijui namna ya kuichukua
- Hamna anayeweza kumpea mtoto dawa
- Sababu nyingine ile: \_\_\_\_\_

**Historia ya Familia:**

21. Mshiriki ana ndugu wengine? Ndiyo / Hapana ikiwa ni ndiyo amefanyiwa / wamefanyiwa kipimo cha damu cha kupima Ugonjwa wa selimundu kinachotambulika kama "Serum Electrophoresis" Ndiyo / Hapana / Haijulikani

22. Je mama amefanyiwa kipimo cha Hb electrophoresis? Ndiyo / Hapana / Haijulikani

23. Je baba amefanyiwa kipimo cha Hb electrophoresis? Ndiyo / Hapana / Haijulikani

**Maarifa haya yatatumikiwa kwa usiri kabisa.**



## APENDIX 9. APPROVAL LETTER TO CONDUCT STUDY AT GERTRUDE'S CHILDREN HOSPITAL

Philip Nelson Olielo  
Reg No. H58/74771/14  
University of Nairobi  
College of Health Sciences  
P. O. Box 19676-00202  
Kenyatta National Hospital  
Nairobi Kenya  
Date:

Gertrude's Garden Children Hospital  
The ERC/ Director of Clinical services  
P. O. Box 42325  
Muthaiga Rd,  
Nairobi, Kenya

Dear Ms/Mr

### **RE: REQUEST FOR PERMISSION TO CONDUCT RESEARCH IN YOUR FACILITY**

I am Dr. Philip Olielo (student number H31/74771/14), a registered Master's student in the Department of Paediatrics and Child Health at the University of Nairobi.

I am hereby seeking your consent to conduct a study at your facility's Haematology Clinic in July and August. The proposed topic of my research is: **Impact of hydroxyurea in the frequency of blood transfusion in children with Sickle cell anaemia (SCA).**

The objectives of the study are:

- (a) To determine the effect of hydroxyurea use on the frequency of blood transfusion in children with SCA aged 1-18 years

- (b) To described the clinical characteristics of patients with SCA on hydroxyurea
- (c) To describe adherence to hydroxyurea & factors affecting adherence in children with SCA aged 1-18 years

To assist you in reaching a decision, I have attached to this letter:

- (a) A copy of an ethical clearance certificate issued by the University/Kenyatta National Hospital
- (b) 3 copies of the research proposal

My supervisors are Prof. Dalton Wamalwa, MB.ChB,M.Med (Paed), MPH an Associate Professor in the Department of Paediatrics and Child Health and a Consultant paediatrician and Dr. Nyambura Kariuki MB ChB M.Med (Paed); Paediatric Haematology & Oncology a Senior consultant at your Haematology Clinic.

Should you require any further information, please do not hesitate to contact me or my supervisor. Our contact details are as follows:

**Name: Dr Philip N Olielo**

**Mobile Number: 0721370746**

**Email: [polielo@yahoo.com](mailto:polielo@yahoo.com)**

**Name: Prof Dalton Wamalwa**

**Mobile Number: 0721239493**

**Email: [dalton@africaonline.co.ke](mailto:dalton@africaonline.co.ke)**

**Name: Dr Nyambura Kariuki**

**Mobile Number: 0722679119**

**Email: [kariukin1@yahoo.co.uk](mailto:kariukin1@yahoo.co.uk)**

Upon completion of the study, I undertake to provide you with a bound copy of the dissertation.

Your permission to conduct this study will be greatly appreciated.

Yours sincerely,

**Dr Philip Olielo**

**H58/74711/14**