ASSESSMENT OF PRESCRIPTION PATTERNS AND COSTS OF ONCOLOGY DRUGS USED IN THE PAEDIATRIC UNIT OF QUEEN ELIZABETH CENTRAL HOSPITAL, MALAWI

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DEDICATION

To my mother, Esther Mateyu, this success is a product of your unceasing prayers and sacrifices. Zikomo for always believing in me.

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LIST OF ABBREVIATIONS AND ACRONYMS

ABBREVIATIONS	FULL TERM
ADRs	Adverse Drug Reactions
AE	Adverse Events
AIDS	Acquired Immune Deficiency Syndrome
ART	Antiretroviral Therapy
BL	Burkitt's Lymphoma
BSA	Body Surface Area
COG	Children's Oncology Group
COMREC	College of Medicine Research and Ethics Committee
CMST	Central Medical Stores Trust
DALY	Disability-Adjusted Life-Year
DRPs	Drug Related Problems
DUR	Drug Utilization Research
DMARDS	Disease Modifying Anti-Rheumatic Drugs
DNA	Deoxyribonucleic Acid
DLBCL	Diffuse Large B-cell Lymphoma
EBV	Epstein-Bar Virus
EML	Essential Medicines List
GDP	Gross Domestic Product
HICs	High Income Countries
HHV-8	Human Herpes Virus-8
HIV	Human Immunodeficiency Virus
IV	Intravenous Injection
KS	Kaposi's Sarcoma
LDH	Lactate Dehydrogenase
LMICs	Low- and Middle-Income Countries
LPGW	Lowest Paid Government Worker
MWK	Malawi Kwacha
MSH	Management Sciences for Health
MPR	Median Price Ratio
NHL	Non-Hodgkin's Lymphoma

PODC	Pediatric Oncology for Developing Countries
SIOP	International Society for Paediatric Oncology
USD	United States of America Dollar
WHO	World Health Organization
WHO/HAI	World Health Organization and Health Action International
WHO-CHOICE	WHO Choosing Interventions That Are Cost-Effective

OPERATIONAL DEFINITIONS

Affordability: The number of days' wages the lowest paid unskilled government worker (LPGW) needs to spend to procure a course of treatment of a particular medicine.

Chemotherapy: It is the therapeutic use of one or more cytotoxic drugs to destroy or inhibit the growth and division of malignant cells in treatment of cancer.

Chemotherapy prescription: It is a written order from a prescriber to a dispenser to prepare and give chemotherapy drugs to a patient with sufficient information on how to use the drugs. In context of this study, complete prescription means number of drugs prescribed and dispensed for a full chemotherapy course

Essential medicine list: It is the list of medicines that satisfy the priority health care needs of the population.

Fractional expenditure: Amount of money spent on a medicine as a proportion of total medicine expenditure

Patient encounter: Entails an interaction between a patient and a prescriber that result in issuance of a prescription

Prescription pattern: The extent and profile of drug use, trends, quality of drugs, and compliance with regional, state or national guidelines like standard treatment guidelines, usage of drugs from essential medicine list and use of generic drugs.

Rational medicine use: Is a process that ensures that patients receive medications appropriate to their clinical needs, in doses that meet their own individual requirements of an adequate period of time, at the lowest cost to them and their community.

ABSTRACT

Background

Cancer is one of the global leading causes of childhood morbidity and mortality. High childhood cancer mortality rates in developing countries have been linked to chemotherapy prescribing patterns that fails to conform to good standards of treatment which leads to ineffective treatment, occurrence of adverse events, prolonged hospitalization and increased economic burden to patients. Children are more vulnerable to effects of irrational prescribing owing to their underdeveloped pharmacokinetic and pharmacodynamics profiles. Malawi has a paucity of data on prescribing patterns and cost of pediatric anticancer drugs.

Objectives

The study assessed prescribing patterns and costs of anticancer drugs used in the paediatric cancer unit of Queen Elizabeth Central Hospital in Blantyre, Malawi.

Methodology

A retrospective cohort study was conducted in the pediatric oncology unit at Queen Elizabeth Central Hospital (QECH). Data was abstracted from 293 files of children aged 0-18 years and diagnosed with cancer between January 2017 and December 2020. Prescribing pattern was assessed by comparing prescription patterns with the established QECH pediatric Oncology guidelines, and the WHO rational prescribing indicators. Dispensed quantity of drugs was used to compute a cost of chemotherapy prescription using current market prices obtained from Central Medical Stores catalogue and private wholesale suppliers. The local currency was converted to US dollar using reserve Bank of Malawi conversion rates to allow comparison. Data analysis was done using Microsoft Excel (2016) and STATA (version 13.1). Continuous variables were summarized as median and interquartile range (IQR) while categorical variables were summarized as frequencies and percentages.

Results

Majority of the participants were children aged between 0 to 5 years (45.4%). More males (60.4%) were affected by childhood cancer disease than females (39.6%). Over 75% of the participants were from rural areas. About 13% of the children were malnourished. Over half of the children had no comorbidities while 19.7% had malaria and/or HIV/AIDS. Burkitt's lymphoma (24.9%) was the most prevalent childhood cancer followed by retinoblastoma

(18.4%), non-Hodgkin's lymphoma (10.6%), and Kaposi's sarcoma (10.6%). Close to 30% of the participants died at the end of the review period. Twenty eight percent of the children recovered while 17.5% were discharged to receive palliative care. Vincristine (25.5%) was the most frequently prescribed anticancer agent while morphine was prescribed for 92.5% of the patients. Rituximab (USD36 442.25) was the most expensive anticancer drug at the oncology unit. Prescribing error of omission of height (47%) was the most prevalent. Majority of prescriptions (48.1%) had three drugs. The mean number of drugs per encounter was 3.5 (n=1028). The proportion of drugs prescribed from formulary, and by generic name was 100% and 99.2% respectively. Low grade glioma and Burkitt's lymphoma were the costliest anticancer prescriptions followed by Hodgkin's lymphoma and germ cell tumor. Evaluation of Median Price Ratio showed that anticancer drugs are priced within the acceptable range as recommended by World Health Organization. Despite anticancer drugs being priced fairly, many Malawians cannot afford a chemotherapy prescription.

Conclusion

Although the average number of drugs per encounter surpassed the WHO recommended standard, the utilization of anticancer drugs was largely found to be rational. However, many Malawians on minimum government wage cannot afford to pay for a chemotherapy prescription despite fair anticancer drug prices. Deliberate efforts and strategies should be put in place to make anticancer prescription affordable to Malawians on minimum wage.

1

1 CHAPTER ONE: INTRODUCTION

1.1 BACKGROUND

Cancer is the global second leading cause of death (1). In 2018, it was estimated that 9.6 million people died due to cancer, and the accompanying deleterious economic consequences were estimated to be US$1.16 trillion (2). Notably, 70% of cancer related deaths occur in low and middle income countries (LMICs) (2). Children living in LMICs have a higher risk of developing of developing cancer each year compared to those in high income countries (1). Childhood cancer survival rates in LMICs, especially in Africa, are low because of irrational prescribing, delayed diagnosis, misdiagnosis, death from the toxic effects of chemotherapy, and lack of life-style risk reduction strategies (1). Irrational prescribing of medicines leads to ineffective treatment, occurrence of adverse drug reactions, prolonged hospitalization and increased economic burden on patients and their families (4). Children, unlike adults, are more vulnerable to negative effects of irrational prescribing of medicines due to their varying and underdeveloped pharmacokinetic and pharmacodynamics profiles (3).

Irrational prescribing refers to prescribing that does not conform to set standards of treatment in a healthcare system (4). Irrational prescribing may manifest in different ways, namely: under- and over prescribing, and incorrect drug selection (4). Under-prescribing exists where medicines required by a patient are not prescribed or an insufficient dosage or treatment duration is issued (5). Under-prescribing and under dosing are often common in children because of inaccurate weight-based dosing calculations. On the other hand, over-prescribing are situations where medicines that are not indicated are prescribed, or if indicated, the quantity or duration is not appropriate (6). Incorrect prescribing occurs where medicines are given for a wrong diagnosis while extravagant prescribing refers to prescribing of expensive medicines in presence of cheaper options (7). These forms of irrational prescribing can harm patients as well lead to wastefulness. In this study, irrational prescribing was examined in spheres of incorrect prescribing.

Globally, irrational prescribing is a common problem especially in LMIC. It is estimated that 50% of all medicines are prescribed, dispensed or sold inappropriately and half of the patients fail to take them as required (8). Multiple treatment options and increased number of medicines which is common in cancer therapy contributes to irrational prescribing (9). Prescribing pattern analysis is a tool that can ascertain whether drugs are being used rationally or not. It involves evaluating whether patients receive medications appropriate for their clinical needs, in doses

that meet their own individual requirements, for an adequate period of time, and at lowest cost to them and their community (9). Therefore, in developing countries, where irrational prescribing is common, prescription pattern and cost analysis of medicines is indispensable.

In Malawi, childhood cancer is a big burden. It is estimated that 1000 incident cases of childhood cancer are diagnosed every year (10). Queen Elizabeth Central Hospital (QECH) alone reports about 280 cases of childhood cancer annually with burkitt's lymphoma (BL) being the most prevalent malignancy (11). Over the years, childhood cancer care and management has improved; however, challenges in supply of key chemotherapy drugs, few numbers of trained pediatric oncology specialists, and use of less intensive chemotherapy protocols still remain. In view of these challenges, it is likely that prescribing of anticancer drugs may be irrational and costly.

Data from few studies done in Malawi in childhood cancer has informed policy and strategies in management of cancer cases. However, there is paucity of data to ascertain if the limited and costly available anticancer drugs are prescribed rationally or not in the childhood cancer management. Therefore, there was an urgent need to conduct a study on prescription pattern and cost analysis to address irrational use of medicines. Hopefully, the findings of this study will be used to improve clinical management, and rational prescribing of childhood anticancer agents in Malawi.

1.2 PROBLEM STATEMENT

Cancer is one of the leading causes of childhood mortality and morbidity (1). It is estimated that about 300,000 children aged 0 to 19 are diagnosed with cancer annually in the world (12). Treatment options in childhood cancer include surgery, radiotherapy and chemotherapy. In many African countries, chemotherapy is an integral component of cancer treatment in children. The chemotherapeutic agents are used either alone or in combination with other treatment modalities such as radiotherapy or surgery (2). Chemotherapy is complex, costly and quite toxic especially in children; hence challenges of irrational prescribing and medicine use are common. Irrational prescribing is a major cause for irrational medicine use (8). Bad prescribing habits leads to ineffective and unsafe treatment, exacerbation of illnesses, distress and high costs to the patient which is counter-productive in cancer therapy (8).

In Malawi, the available treatment modalities for management of childhood cancers do not include radiotherapy. However, 55 to 60% of cancer patients require radiotherapy as it is cost

effective, and a life-saving intervention (13). The limited treatment options in Malawi have prompted healthcare workers to rely almost exclusively on use of chemotherapy agents in management of childhood cancer. The challenges of limited treatment options are compounded by; frequent drug stock outs, use of less intensive treatment protocols, few trained specialists in paediatric oncology, and the high cost of cancer therapy. It is therefore probable that childhood cancer therapy is not rational and optimal in Malawi.

In many referral hospitals, chemotherapy agents account for a large proportion of healthcare budget expenditure. Hence, data on the cost burden, pattern and quality of use is required. In Malawi, the cost and prescription patterns of chemotherapy agents is not well-known. Lack of data on cost burden and prescription patterns of chemotherapy agents may lead to unwarranted expenditure on sub-optimal therapy and under funding for cancer treatments. It is probably that there is greater expenditure on less effective therapies. In addition, high costs of medicines increase burden to healthcare system which may compromise provision of other life-saving services (14). High costs reduce access to medicines, and reduces adherence to treatments because patients tend not to take medicines that they cannot afford.

This justifies the need for prescription patterns and cost analysis studies that generate baseline data to inform policy and clinical interventions in childhood cancer management. It is against this background that this study aimed to assess prescription patterns and costs of chemotherapy agents used in the paediatric oncology unit at QECH. The findings will be used to promote rational drug use in management of childhood cancer.

1.3 RESEARCH QUESTIONS

The study sought to answer the following research questions:

i. What is the prevalence of commonly diagnosed types of childhood cancers?

ii. What are the prescribing patterns of anticancer and adjunct drugs in the paediatric patients?

iii. Do prescribers adhere to national treatment guidelines for management of childhood cancers in Malawi.

iv. What is the estimated average cost and affordability of anticancer prescriptions?

1.4 RESEARCH OBJECTIVES

1.4.1 MAIN OBJECTIVE

The main objective of the study was to assess prescription patterns, costs and affordability of anticancer drugs used in the paediatric cancer patients at Queen Elizabeth Central Hospital in Blantyre, Malawi.

1.4.2 SPECIFIC OBJECTIVES

The specific objectives were to:

i. Determine the prevalence of commonly diagnosed types of childhood cancer.

ii. Determine the prescribing patterns of anticancer and adjunct drugs in paediatric cancer patients.

iii. Estimate the average cost and affordability of anticancer prescriptions.

1.5 SIGNIFICANCE OF THE STUDY

The study examined if the prescribing of anticancer drugs in the paediatric unit of Queen Elizabeth Central Hospital is rational or not. The study findings may be used to make a case for routine monitoring of rational medicine use and improve childhood cancer treatment outcomes. The findings will also assist in improving and strengthening local treatment protocols at QECH. Furthermore, the review of costs through ABC analysis identified which few agents take up large percentage of the budget. These agents in class A need to be closely monitored and controlled to reduce economic waste.

The findings of this study can potentially contribute to national childhood cancer policy and clinical interventions. The practice of oncology in Malawi is still in its early stages, as such results of this study provides preliminary data that can be used in the development of national chemotherapy treatment and care plans. It is argued that a well-informed national childhood cancer policy promotes evidence based cancer prevention, early diagnosis, curative and palliative therapy (15). The results of this study may be used to develop interventions that improve medication selection, dosing and reduce costs to the patients and the facilities thereby improving treatment outcomes.

The study also benefits individual childhood cancer patients by ensuring their access to rational cancer treatments. The findings of the cost analysis can guide in the identification of suitable affordable alternative generic medicines. Available and affordable medicines reduce levels of non-adherence and abandonment of therapy which improves individual child clinical outcomes.

2 CHAPTER TWO: LITERATURE REVIEW

2.1 PRESCRIPTION PATTERN MONITORING STUDIES

A prescription pattern is defined as the extent and profile of drug use, trends, quality of drugs, and compliance with regional, state or national guidelines like standard treatment guidelines, use of drugs from essential medicine list and use of generic drugs (16). Globally, drugs form a core part of every conventional healthcare system. Drugs are used for diagnosis, management and treatment of diseases in all age groups. Hence, to obtain optimal benefits, medicines are required to be rationally used (16).

Prescription pattern monitoring studies form an integral part of drug utilisation studies. These studies focus on prescribing, dispensing and administration of drugs to patients. They are aimed at facilitating the rational use of drugs in defined populations (16). Many prescription patterns monitoring studies have been conducted especially on antibiotics, antidiabetics, antihypertensive, antiepileptics and a handful in anticancer agents (17). Evaluation of prescription patterns of anticancer drugs is important due to availability of different regimens, the variable response rate to different drugs and intolerability of combination regimens (18).

A prescription pattern study done in India using the World Health Organisation rational prescribing indicators found that 82% of anticancer agents were rationally prescribed (19). On the other hand, a study done in Ethiopia found that majority of medicines in six major referral hospitals were irrationally prescribed. This agrees with findings of many studies that found medicine use in many developing countries to be irrational (20). Irrational medicine use has deleterious consequences in management of cancer**.**

2.2 PRESCRIPTION PATTERN MONITORING OF ANTICANCER DRUGS

Anticancer agents form a vital part of cancer management. The global prescription patterns of anticancer agents have changed over time due to discovery of new and better drugs as well as improved understanding of pathophysiology of cancer (21). It is important to conduct periodical prescription pattern monitoring studies especially in childhood cancer management to ensure provision of rational chemotherapy.

There is paucity of data especially in African countries on the prescription pattern of anticancer drugs used in children. Several studies have focused on prescription patterns of anticancer drugs used in management of adult carcinomas such as breast, prostate and lung cancer. This

knowledge gap coupled with already existing rational prescribing challenges in children probably compromises provision of effective and rational therapy. A study done by Damani et al (2016) observed irrational prescribing and use of medicines in specialist palliative care clinic for children (22). Another study conducted in Sierra Leone also reported that medicine use in children was irrational especially in government facilities (23). Therefore, in view of high prevalence of irrational medicine use in children and injurious consequences of irrational therapy, it is important to conduct prescription pattern monitoring study.

2.3 SELECTED DRUG USE PROBLEMS IN CHILDHOOD CANCERS

Cancer management and care is a multifaceted process, and it is associated with medicine (drug) use related problems. A drug related problem (DRPs) is defined as an event or circumstance involving drug therapy that actually or potentially interferes with desired health outcomes (24). Drug related problems can be classified into the following categories: unnecessary drug therapy, need for additional drug therapy, ineffective drug, dosage too low, adverse drug reaction (ADR), dosage too high and non-adherence (24).

Drug related problems have significant negative medical and health economics consequences. These include reduced quality of life, increased duration of hospital stay, increase in mortality and morbidity, and increased substantial cost implications (25). A study done in United States of America (USA) estimated the economic burden arising from drug-related morbidity and mortality to be between £17.3 and £75 billion annually (26). A similar study done in Australia, reported that 4.3% of paediatric admissions were due to DRPs, and direct costs alone were estimated to be £100,707 (24). Many studies have reported that 50 -80% of DRPs are preventable (25).

2.3.1 UNNECESSARY THERAPY IN CHILDHOOD CANCER

A study done in Ethiopia reported that 9.7% of all DRPs observed in paediatric oncology ward, resulted from unnecessary therapy (24). Unnecessary therapy is caused by duplication of therapy or dispensing of medicine without any indication. Antibiotics are commonly linked to this DRPs. Yismaw et al in a study done in Ethiopia in 2020 found that ceftriaxone antibiotic was commonly prescribed for children with cancer without any indication (24). Unnecessary therapy may harm the patient by causing ADRs and may affect adherence to life-saving chemotherapy drugs thereby interfering with the desired health outcome.

2.3.2 INAPPROPRIATE DOSING OF ANTICANCER DRUGS

Dosage problems cover wide areas ranging from inaccurate doses to unavailability of appropriate dosage forms. Inappropriate dosage (either high or low) is the most frequently reported DRPs followed by need for additional therapy, and non-adherence to prescribed medication (24). Inappropriate dosage accounts for between 34.9 to 61.8% of DRPs (24). Inappropriate dosages may cause ADRs, and toxicity which increases treatment related mortality and morbidity. Scarcity of child-specific dosage forms may force healthcare workers to use adult formulations in children which increases chances of administering an inappropriate dose (27).

Inappropriate dosage can take several forms such as; ineffective dose, inappropriate frequency and duration, high dose, frequency too short or too long, and need for additional monitoring (24). In oncology, dosing problems are related to use of an out-of-date calculation of body surface area, exceeding cumulative doses or missing dose adjustment in abnormal laboratory results such as low creatinine clearance (28). In Ethiopia, Yismaw et al. (2020) in a study of identification and resolution of DRPs in childhood cancer, reported that vincristine and doxorubicin are associated with dosage problems in children (24).

2.3.3 NEED FOR ADDITIONAL THERAPY

Additional therapy may be required for untreated conditions, preventative therapy or to provide synergistic effect. Need for additional therapy accounted for 8.2% of total drug related problems in a study done by Sisay et al in Ethiopia in 2015 (28). Need for addition premedication before chemotherapy and initiation of treatment of medical conditions such as dyslipidaemia and atopic dermatitis were some of the areas where cancer patients experience great need for additional therapy (28). Lack of needed therapy affects quality of life, adherence, and desired therapeutic goals for childhood cancer.

2.3.4 INEFFECTIVE DRUGS IN CANCER MANAGEMENT

The presence of ineffective drugs in healthcare facilities is a global problem. Administration of ineffective therapy prolongs disease conditions, affects quality of life, and also triggers loss of trust in conventional healthcare systems. Ineffective therapy also includes administration of inappropriate dosage forms, or recommending less-effective drugs when the most effective therapies are available. A study conducted in Spain identified ineffective therapy as one of the common DRPs in health care system (29). In Ethiopia, a study reported the incidence of ineffective therapy among paediatric cancer patients to be 4.3% (24). Therefore, healthcare workers must recommend the most effective, safe and affordable therapy available to childhood cancer patients.

2.4 OVERVIEW OF PEADIATRIC CANCERS

The categories of childhood cancers include leukaemia, brain cancers, lymphomas and solid tumours such as neuroblastoma and Wilms tumour (12). There are two distinctive distribution of childhood cancers in Africa. In North Africa, the most common cancers are: leukaemia, brain tumours and solid tumours (30). On the other hand, in sub-Saharan countries, the most commonly diagnosed childhood cancers are: burkitt's lymphoma (BL), nephroblastoma, retinoblastoma, non-Hodgkin's lymphoma, rhabdomyosarcoma and malignant germ cell tumours (30). This literature review will focus on common childhood cancers in sub-Saharan Africa.

2.5 EPIDEMIOLOGY AND MANAGEMENT OF PEADIATRIC CANCERS

2.5.1 BURKITT'S LYMPHOMA

Burkitt's lymphoma (BL) is a common type of paediatric cancer in sub-Saharan Africa region. It is the malignancy of the lymphoid tissue occurring mostly in the jaw and abdominal area. This mature B-cell neoplasm has an incidence of 50-100 cases per million during the first 15 years of life (30). World Health Organisation classifies BL into three clinical groups namely: endemic, sporadic and immunodeficiency-related BL (31). The endemic form is common in malaria infested areas, and it is associated with Epstein-Barr virus. The immunodeficiency-related variant is linked with HIV and to some extent organ transplantation (31). The sporadic form occurs outside the endemic equatorial belt and South Africa and usually attacks the abdomen and affects primarily the gastrointestinal tract (30).

Children with BL commonly present with a mass in the jaw, orbital socket, or abdomen (11). Sometimes the tumour may press on the spinal cord and children may present with weaknesses in the legs, paraplegia, and urinary incontinence (11). In cases of children with primary gut lymphoma, the localised abdominal mass without any other specific symptoms adds confusion to clinical practice and it delays diagnosis (30). The clinical biochemistry in BL includes elevated lactate dehydrogenase (LDH), and uric acid levels because of tumour rapid doubling time (31). In HICs, children presenting with BL are able to recover with a one-year survival of greater than 90% when managed with intense protocols (11).

The staging of BL is very crucial in diagnosis and management. Three staging systems include: St. Jude, Ann Arbor and Murphy (31). In childhood cancer, St. Jude or Murphy staging systems for children are preferred. The St. Jude system classifies BL in four stages where stage one is a single tumour or involves a single anatomical area excluding mediastinum or abdomen or extra nodal tumour on the same side of the diaphragm (31). The fourth stage under the St Jude classification entails any of the three stages with initial central nervous system (CNS) or bone marrow involvement (only if less than 25% of the marrow is composed of BL cells) (31).

Children from HIC have a 90% recovery rate from BL which is attributed to timely diagnosis and intensified treatment protocols (32). Low- and middle-income countries, have limited resources and supportive care. Hence, simplified and country specific protocols are used where about 50% cure rate is achieved (33). Burkitt's Lymphoma accounts for about 40% of childhood cancers in Malawi (34). Limited resources precludes the use of newer chemotherapy agents and high intensity protocols which cures greater than 80% of children presenting with stage three of BL (32).

Treatment protocols for BL depend on the presenting cancer stage. Early stages of endemic BL are managed by high doses of cyclophosphamide (40-60mg/kg), intra-thecal administration of methotrexate (12.5mg) and hydrocortisone (12.5mg) (34). Burkitt's lymphoma is a rapidly dividing tumour hence, allopurinol (5mg/kg) is administered to manage tumour lysis syndrome (34). Metoclopramide (10mg) is also administered before and after chemotherapy to minimise nausea and vomiting associated with chemotherapy (34).

Children presenting with relapse endemic BL and non-Hodgkin's lymphoma (NHL) are managed with intensive protocols. Relapse is defined as a point where the lymphoma does not respond to treatment or when the response to treatment does not last very long (35). Children with relapsing BL and NHL are managed with cyclophosphamide (60mg/kg), vincristine

(1.5mg/m^2) and prednisolone (60mg/m^2) from day one (34). Methotrexate (1g/m^2) and doxorubicin (60mg/m^2) are introduced on day eight of the therapy (34). Etoposide (150mg/m^2) is introduced on day 22 and 23 (34). Intrathecal methotrexate and hydrocortisone (12.5/12.5mg) are also administered while nausea and vomiting is managed using metoclopramide (10mg) (34).

2.5.2 NEPHROBLASTOMA OR WILMS' TUMOR

Wilms tumour is relatively common as it accounts for 5 to 7% of all childhood cancers (36). It is a tumour that develops in the nephron of a kidney from specialised nephroblasts cells. Wilms tumour is the most prevalent primary malignant renal tumour in sub-Saharan Africa (30). It is also regarded as one of the most common abdominal paediatric cancers, and fourth most common paediatric cancer in the world (37). The real cause of Wilms tumour remains unknown. However, it is linked to the genetic mutations during embryonic development. Mutation of genes that code for the genital urinary tract are implicated, and it affects children aged 3-5 years. Girls are more susceptible to Wilms tumour than boys (37). Children with Wilms tumour present with a painless, firm mass in the flank (11). Other physical defining features include; abdominal pain, gross haematuria, urinary tract infections, varicocele, fever and anaemia (37). Unlike BL, laboratory findings for Wilms tumour are not specific.

Wilms tumour can be treated by nephrectomy followed by systemic chemotherapy agents (37). The recovery and survival rate from Wilms tumour can be as good as 40%. A study done in Malawi found that the survival rate was 40% at 8 months (30).

Wilms tumour is categorised into five stages. In stage one the tumour is completely contained in the kidney and does not spill outside the renal capsule (37). The fifth stage are those tumours where both kidneys are affected at the time of initial diagnosis (37). Many children in Africa present with the late stages of Wilm's tumour. A study done in Nigeria found that 72% of the children presented with stage three and four while in Sudan 78% were in stages three and four at the time of diagnosis (30).

Children presenting with Wilms tumour can be cured through early diagnosis and cancer care. In HICs, the survival rates of children with Wilms tumour exceed 85% (33). Wilms tumour can be treated through a multidisciplinary approach combining surgery, chemotherapy and radiotherapy. Globally, two treatment strategies are used in management of Wilms tumour. The first strategy practiced by Children's Oncology Group (COG) involves operating the tumour

upfront followed by chemotherapy (33). The second strategy, used by International Society for Paediatric Oncology (SIOP), starts with pre-operative chemotherapy, and for both strategies long term survival of children with cancer has been attained (33). Survival rates in LMICs are low especially in sub Saharan Africa where they range from 11-46% (38). Low survival rates have been attributed to delayed diagnosis, malnutrition, abandonment of treatment and poor supportive care (33).

In Malawi, an adapted treatment protocol for Wilms tumour was introduced in 2006 with an agenda of improving survival and standardizing cancer care. The treatment protocol includes pre-operative chemotherapy, supportive care, nutritional support and strategies to enable patients to complete the treatment schedule (38). Children presenting with localised wilm's tumour are put on vincristine (1.5mg/m^2) and actinomycin (45mcg/kg) while those with metastatic Wilms tumour, doxorubicin (30mg/m^2) is added as a pre-operative regimen (34). Post-operation, children with stage one, localised tumour and intermediate risk are put on vincristine (1.5mg/m^2) and actinomycin (45mcg/kg) for four weeks (34). Children presenting with high risk and advanced stages of Wilms tumour are put on doxorubicin (2.0mg/m^2) and actinomycin (45mcg/kg) for about 14 weeks and are continued on vincristine (2.0mg/m^2) post operatively (34). Chemotherapy, and surgery are complemented by nutritional and supportive care in all children with Wilm's tumour.

2.5.3 RETINOBLASTOMA

Retinoblastoma attacks the retinal part of the eye. It is initiated by mutation of the RB-1 genes which were the first described tumour suppressor genes (39). Retinoblastoma represents 3% of all childhood malignancies and it attacks the very young children between 0 to 5 years (40). The incidence of retinoblastoma is constant around the globe at one case per 15 000 – 20 000 live births translating to 9000 new cases per year (39). Populations with poverty, and high birth rates have a high prevalence of retinoblastoma. In Nigeria, retinoblastoma is one of the five most frequent malignancies diagnosed in children (39). Regions with high a prevalence of retinoblastoma also record high mortality rates.

The most common presenting symptom is leukocoria although some patients may also present with strabismus (40). The tumour remains intraocular and is curable 3-6 months after the first sign of leukocoria (39). In African populations, it presents frequently too late with extraocular dissemination and the prognosis is always poor (30). Retinoblastoma presents in two forms namely; the bilateral, heritable form (comprising of 25% of the cases and characterised by

germline mutation of RB-1 genes) and unilateral, (comprising of 75% of the cases) (40). The Heritable form of retinoblastoma is diagnosed early compared to the acquired form. Therefore, children with a positive family history of retinoblastoma may be screened in early life to detect, diagnose and treat the malignancy before it spreads (41).

Two-thirds of the cases are diagnosed before the age of two, and 90% of the cases are diagnosed before the age of five (33). Despite varying incidences around the globe, it is estimated that 8000 children develop retinoblastoma each year world-wide (33).

Treatment modalities are dependent on the severity and stage of the malignancy. However, chemotherapy, surgery, and specialised radiotherapy are the main treatment strategies. High income countries have registered over 95% survival rate from retinoblastoma. The high survival rate is due to availability of state-of-the-art equipment and expertise that are not available in LMICs (33). Low-middle-income countries almost exclusively rely on chemotherapy and enucleation, and in rare cases radiotherapy is used (33)

Retinoblastoma chemotherapy involves administration of carboplatin (600mg/m^2) for children weighing below 10 kg (34). Etoposide and vincristine are also recommended in children weighing below 10 kg (34). The doses are calculated depending on the stage of the disease. Children with advanced forms of retinoblastoma are managed through palliative care. Cyclophosphamide, administered orally at 40 mg/kg, is the drug of choice in retinoblastoma palliative care (34)

2.5.4 KAPOSI'S SARCOMA

Kaposi's sarcoma (KS) is an inflammatory endothelial malignancy caused by human herpes virus-8 (42). The HIV/AIDS epidemic has increased the incidence of KS by over ten times (43). In children, KS is grouped into four main types, namely; epidemic, endemic, iatrogenic and classic. Epidemic forms are relatively common affecting the mucosa and visceral organs (42). The cases from sub-Saharan African region are mostly endemic in nature. In endemic countries, such as South Africa, KS represents 2 to 10% of all childhood cancers (30). Endemic cases present clinically as generalised or localised lymphadenopathy with sparse mucosal or skin lesions on the feet, legs, nose and genitalia (42). Kaposi's sarcoma can also cause painful lesions in the oral cavity which disturb food intake and the nutritional status of a child (11).

The risk of developing KS in children is exacerbated by HIV infection, immunosuppression, and human herpes virus infection (30). In Malawi, KS is considered as an HIV/AIDS defining

illness in both adults and children (11). It is established that ART is a best treatment for KS; however additional therapy is required when it is extensively spread owing to poor management or delayed treatment (11). Globally, there are no established consensus group therapeutic guidelines for management of paediatric KS (42). Lack of consensus has been attributed to rarity and paucity of publications on paediatric KS. Administration of antiviral therapy such as ganciclovir and valaciclovir can be considered in the prevention of herpes virus related paediatric KS (42). Furthermore, cases of paediatric KS can be managed by systemic chemotherapy (42).

Availability and early access to ART in HICs reduces the incidence of HIV-related KS. In LMICs, despite provision of free ART, there is delay in diagnosis of HIV/AIDS and initiation of ART therapy (44). Neither HIV nor wide spread KS are curable; treatment is aimed at reducing disease progression and improving quality of life (45).

In Malawi, KS is the most common cancer in adult males (50.7% of total cancer cases) and second most common cancer in women and children (45). The treatment options largely depend on local diagnostic and treatment facilities, skills and the experience of clinical team caring for the child (44). Children who present with focal or less-extensively spread cancer can be completely cured. Children who are HIV positive, and present with KS are put on ART as first line treatment(34). When additional chemotherapy is needed; an intravenous (IV) injection of vincristine (1.5mg/m^2), etoposide IV (100mg/m^2) and bleomycin (15 IU/m^2) are recommended (45) (34). The cases that require palliative care are put on thalidomide (3mg/kg) for 60 days (34)

2.5.5 OTHER CHILDHOOD CANCERS

Other solid tumour such as neuroblastoma are commonly seen in North African and developed countries (30). Malignant tumours, especially osteosarcomas are also commonly diagnosed in sub-Saharan region. Amputation of the concerned limb is still the only viable treatment option in cases of osteosarcoma because most children present at the hospital very late (30).

In developed countries, acute leukaemia is the commonly diagnosed cancer in children. However, in developing countries it is rarely diagnosed. Symptoms of acute leukaemia (fever and anaemia) resemble those of malaria; as such it is possible that the acute leukaemia diagnosis is missed by healthcare professionals (11). When left untreated patients may die

within few weeks or months (11). These childhood cancers are curable especially when children have access to early diagnosis and treatment.

2.6 COST OF CHILDHOOD CANCER THERAPY

Globally there are unacceptable inequalities in access to cancer prevention, treatment, mortality and survival (46). The burden of cancer mostly fall on LMICs where 80% of children with cancer dwell (47). Although LMICs account for 80% of the global burden of cancer, the survival rates are poor (5 to 40% compared to more than 80% in HICs), and financing of cancer care only amounts to 5% of the resources allocated to cancer care globally (46). The global disparities in mortality and survival hinge upon a number of factors: including frail health systems, scarce resources, and competing political interests (47). In LMICs, lack of resources and competing political interests are compounded by lack of costing and cost-effectiveness data of cancer treatment.

Very few studies have examined cost and cost-effectiveness of paediatric cancer treatment. One of the few studies that examined cost-effectiveness of childhood cancer therapy argued that, in LMICs, childhood cancer treatment is cost effective (46). However, the study did not use any real-world data to arrive at this conclusion. Furthermore, other economic or costing studies have adopted a narrow definition of cost. They either examined cost of chemotherapy alone or did not include cost of outpatient care and fixed direct costs (46). Until recently, only two methodologically sound micro-costing studies of childhood cancer therapy have been published, and one of the studies estimated direct cost of treating BL in Uganda to be $1,312 per patient (46).

The prevailing rarity of data on full economic cost, and cost-effectiveness of childhood cancer treatment warrants conducting of micro-costing studies to establish the cost of providing cancer therapy to children in LMICs. The data can provide evidence to inform policy agenda-setting, health system priority-setting, and development of national childhood cancer strategies specific to LMICs (48). Most methodologically rigorous and competitive studies adopt WHO guidelines for economic evaluation; evaluating a generic outcome measure, the disability-adjusted life-year (DALY), which facilitates comparison of results across a variety of diseases, interventions, and health system contexts (47).

Costing of childhood cancer therapy factors in variable, fixed and family costs. Variable cost refers to directly attributable episodes of care such as: chemotherapy, supportive care

medicines, laboratory tests, biopsy and specimen processing, blood products, and diagnostic imaging (47). Fixed costs comprise of program related costs that vary with time rather than episode of care and includes institution overhead and personnel cost (47). Lastly, the family cost of care captures the wider social costs incurred by families and these include food, lodging and transportation.

A study on cost and cost-effectiveness of interventions for childhood cancer in three LMICs (Ghana, Mexico, and El Salvador) reported that cost per DALY averted through cancer treatment in each centre was very cost effective (46). In Ghana, the cost was $1,034 (with GDP per capita of $1,513 in 2016), and in Mexico it was $3,039 (with GDP per capita of $8,208 in 2016) (46).

2.6.1 COST OF CANCER THERAPY IN MALAWI

Despite the high burden of childhood cancer in LMICs, the number of facilities offering dedicated childhood cancer treatment are distressingly low (49). Understanding the costs and economic value of paediatric cancer treatment may assist policy makers in children oncology units to maximize the value of investments in health with informed resource allocation decision (49). Few costing studies have been done in Malawi in the field of cancer. The studies have focused on a narrow definition of cost, and restricted to specific cancers such as diffuse large B-cell lymphoma (DLBCL). A micro-costing analysis of DLBCL in Malawi reported that it costs $1,844 to treat a patient over the course of two years of follow up with first line regimen chemotherapy (50). In Malawi where the annual gross national income per capita was $320 (in 2017), the cost of chemotherapy was arguably costly and unaffordable (50).

It is a common assumption that treating children with cancer in LMICs is not cost effective (51). Contrary to this assumption, a cost effectiveness pilot study done in Malawi reported that the cost of chemotherapy and supportive care was less than $50 per child (51). Cost-effectiveness findings from the BL study was attributed to use of a locally adapted treatment protocol. A similar study in Brazil reported that the cost of treating childhood cancer was $16,700 per patient representing 6% of the threshold of being cost effective according to WHO definition (51). However, the studies failed to account for per-incident fixed costs and variable costs which might have affected the estimated cost-effectiveness of the treatment (51).

Cost -effectiveness may change over time, as such it is necessary to institute costing studies as an on-going process. In paediatric cancer management, costing and cost-effectiveness studies

should form indispensable part of healthcare plan in order to reduce health economic waste. Cost-effectiveness does not imply affordability of treatment. A study in Nigeria reported that about one-fifth of the children did not receive chemotherapy because their families were unable to afford care despite availability of treatment (52). Although, cost-effectiveness does not imply affordability, it provides a foundation where policy makers can build strategies and policies on childhood cancer treatment and care.

2.7 CONCEPTUAL FRAMEWORK

A working conceptual framework for this study was developed following selected WHO/INRUD rational prescribing indicators (53). Prescribing patterns by healthcare professionals have direct impact on cost, rational medicine use and ultimate clinical outcomes of cancer therapy. The WHO/INRUD rational prescribing indicators that were of interest included: number of drugs prescribed per patient, percentage of drugs prescribed by generic name, number of anti-cancer drugs and adjuvants prescribed per patient, and percentage of drugs prescribed from national essential drug list

The conceptual framework presented in **Figure 1** depicts the main determinants of cost of cancer therapy in paediatric unit at QECH. Cost of chemotherapy is determined by the type of drug selection, quantity dispensed, market price of drugs, and the formulation (IV or oral dosage forms) used. The drug selection process during chemotherapy is dictated by the type and stage of cancer, presence of adverse drug reactions, comorbidities and prescribing habits. Therefore, assessment of factors affecting prescribing patterns and cost provide direct evidence of rational chemotherapy use in paediatric unit of quality of QECH.

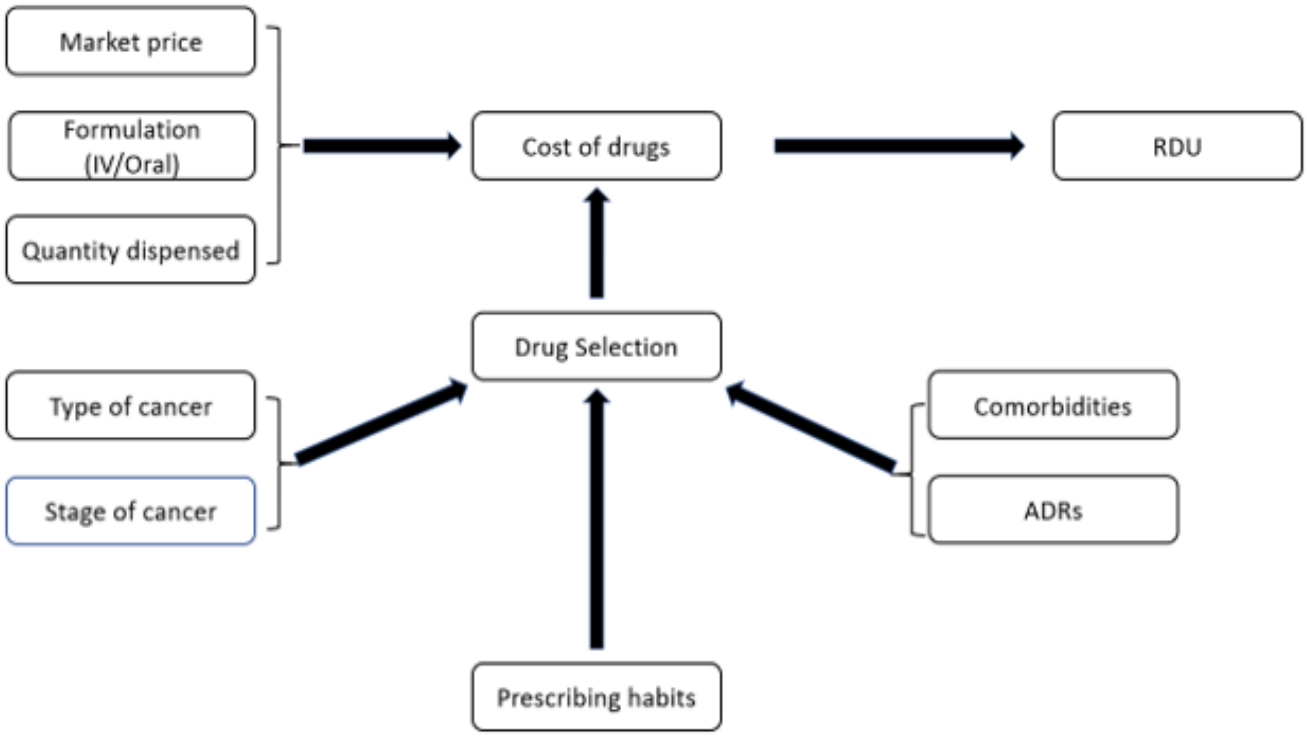

Figure 2.1:The conceptual framework for factors that influence prescribing patterns and costs of drugs

Note: **RDU**: Rational drug use

ADR: adverse drug reaction respectively

3 CHAPTER THREE: METHODOLOGY

3.1 STUDY DESIGN

To address the objectives of the present study, a retrospective quantitative cohort study was conducted. It involved the review and abstraction of data from patient prescription records. Standard and pre-tested data extraction forms were used for data collection.

3.2 STUDY SETTING

The study was conducted at Queen Elizabeth Central Hospital (QECH). Queen Elizabeth Central Hospital is Malawi's largest referral, and teaching hospital with an official bed capacity of 1,350 but usually the number of patients admitted exceeds the capacity (54). The dedicated paediatric oncology unit has an estimated inpatient bed capacity of about 30, and it receives 280 new cases of childhood cancer in Malawi annually. It receives patients from surrounding district hospitals, health centres and private healthcare facilities.

3.3 STUDY POPULATION AND PERIOD

The study targeted children (0-18 years) presenting with childhood cancer in Malawi. Paediatric cancer treatment is usually offered to children from birth to age 18 or 19 (55). However, Malawi defines a child as anyone below 18 years of age hence adoption of the age bracket for this study (56). The study population were children presenting with different types of cancers at QECH, paediatric oncology unit between January 2017 and December 2020.

Files of patients seen between January 2018 to December 2020 were reviewed. A four-year study duration was selected as one cycle of treatment typically lasts one to two years.

3.4 ELIGIBILITY CRITERIA

3.4.1 INCLUSION CRITERIA

Participants were included if they met all of the following criteria:

i. Were 0-18 years' old

ii. Had definite diagnosis of any childhood cancer

iii. Attended oncology paediatric unit at QECH between January 2017 to December 2020

iv. Were on at least one anticancer drug.

v. Completed at least 50% of the cycles of therapy

3.4.2 EXCLUSION CRETERIA

Patients with files having incomplete information were excluded from the study. Incomplete information referred to absence of chemotherapy and adjunct drug history as well as disease and diagnostic information of the paediatric malignancy.

3.5 SAMPLING METHOD

The present study used convenient sampling method to collect data due to unavailability sampling frame. In convenient sampling, all patient files that were accessible and satisfied the eligibility criteria (***Appendix 1***) were used to sample patient records data. If the sampled patient file did not satisfy the eligibility criteria, the next file was considered for the study. Daily, at least 30 files were requested from the records office, screened for eligibility and subsequently have data abstracted.

3.6 SAMPLE SIZE ESTIMATION

The following calculated sample size was deemed adequate for this study and it was computed using the Cochran formula presented in **Equation 3-2**.

Equation 3-1: Cochrane formula for sample size calculation

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

Where: n = the required sample size

z = standard normal value at confidence interval of 95%

p = estimate of proportion of inappropriate of dosing

d = margin of sampling error tolerated.

The value of Z at 95% confidence interval was 1.96, and value of p was set at 50% since there is no research finding related to estimated prescription pattern analysis of anticancer drugs in

LMICs. It is recommended that if there is no estimate of the expected prevalence of an outcome, one should assume a figure of 50% as this yields the largest computed sample size. The tolerated margin of sampling error (d) was set at 0.05 at 95% confidence interval. Hence applying the formulae yielded:

$$\mathbf{n = (z^2\, p\, (1\text{-}p)/\, d^2) = (1.96)^2\, (0.5)\, (1\text{-}0.5)/\, (0.05)^2 = 384}$$

The population of children at the paediatric unit was small and with it came a limited sampling frame. The paediatric oncology unit has a bed space of 25-30 and it is estimated that it treats 280 cases of childhood cancer each year. The small population and limited sampling frame necessitate the need to use Cochran correction formula for a finite population (**Equation 2**). (57)

Equation 2: Cochran correction formula for a finite population

$$\mathbf{nf = (n_o)/(1+n_o/N)}$$

Where: nf = desired sample when the population is less than 10,000

$\mathbf{n_o}$ = calculated sample size

N = population size (Number of incident case per year * duration of study: 280 * 3 = 840)

$$nf = (384)/\, (1+384/840) = 264$$

The corrected sample size was inflated by 10% in order to cater for non-response, missing records and poor-quality records. And 26 participants are added to 264 to compensate for missing information. Therefore, the minimum sample size adequate for this study was **290**.

3.7 DATA COLLECTION

Data was collected using pre-tested data collection forms (***Appendix 2*****).** The data collected included patient's demographics data: age, gender, height, weight, body surface area, Mid upper arm circumference and residential status. Data on the type of childhood cancer, cancer stage, outcome of the disease at the end of review period, and comorbidities were also collected. Additionally, variables that described the chemotherapy regimen were captured. These variables included prescribed adjunct medications, chemotherapeutic regimens, and dosing schedules. Adverse drug reactions were not collected because that was beyond the scope of this study. Drug prices were obtained from Central Medical Stores Trust (CMST) and private wholesaler supplier catalogues. Central Medical Stores Trust is a government agency that

supplies drugs and medical equipment to healthcare facilities. On the other hand, the study also explored current market prices from private wholesaler for comparison. Comparison of drug prices between the Central Medical Stores Trust and Private Wholesalers shaded light on the effect of government subsidy on the cost of chemotherapy. Both Central Medical Stores Trust and private wholesalers' prices are updated regularly to reflect current market prices.

3.8 OUTCOME DEFINITIONS

Paediatric anti-cancer drug prescribing patterns and cost analysis were the main outcome variables of interest. Prescription patterns were defined as the extent and profile of drug use, trends, quality of drugs, and compliance to regional, state or national guidelines, usage of drugs from essential medicines list and use of generic drugs (16). In this study, selected WHO prescribing indicators were used to assess prescribing patterns of anticancer drugs. The selected indicators included; number of drugs prescribed per encounter, percentage of drugs prescribed by generic name, number of anti-cancer drugs and adjuvants prescribed per patient, and percentage of drugs prescribed from national essential drug list (58). Other indicators such as percentage of injections prescribed were not significant since almost every cancer patient gets an injection. Each of these indicators were measured as described in the **Table 10** (***Appendix 3***).

Cost aspect of this study focused on the average cost of chemotherapy prescription. Average cost of prescription was calculated as a product of current market price of a drug and units of drugs used. Chemotherapy prescription accounted for oncology drugs that were prescribed, dispensed and administered to the children diagnosed with childhood cancer during the follow-up period. Non-medical costs, and other fixed costs were not considered because that was beyond the scope of this study.

3.9 QUALITY ASSURANCE AND DATA MANAGEMENT

A well-structured data collection tool was pre-tested before commencing the study. The data collection tool was reviewed and corrected as needed. A sample of 10 patient files were assessed to determine if the research question could be sufficiently answered using the collected data. One research assistant was recruited and trained in good data collection practices. The research assistant was continuously monitored throughout the data collection period to ensure only quality data was collected.

Data entry was done using Microsoft Excel (2016). The data was cleaned, coded and stored safely in a password locked computer on a daily basis. The data was backed up on cloud storage after every two days and a separate copy was stored in an external drive. The external drive was password protected.

3.10 STATISTICAL DATA ANALYSIS

Statistical analysis was performed using STATA (version 13.1) software. Descriptive data analysis was conducted. Categorical variables were summarized as frequencies and percentages. To test if variables were normally distributed, Shapiro wilk test was used.

Normally distributed continuous variables were summarized as the mean and standard deviation of the mean. On the other hand, continuous variables that were not normally distributed were summarized as the median and interquartile range.

The selected WHO prescribing indicators (number of drugs prescribed per patient, percentage of drugs prescribed by generic name, number of anti-cancer drugs and adjuvants prescribed per patient, and percentage of drugs prescribed from national essential drug list) were calculated as described in Appendix 3.

ABC analysis was conducted to identify anticancer drugs which need stricter control by hospital top level management. ABC analysis is one of the most important tools used in inventory management and it is based on Pareto's Law which states that 80% of the total value will be consumed by 20% of the items (59). ABC analysis was done by calculating fractional expenditure of individual anticancer drugs and arranging the results in a descending order. The cumulative cost of all individual drugs was calculated. Percentage expenditure of individual drugs and cumulative percentage of the expenditure was calculated. Then, the list of the anticancer drugs was divided into three categories: A, B, C, based on the percentage of the cumulative cost of 70%, 20% and 10% respectively (59).

The cost of individual drug prices was calculated by multiplying the cost per unit (vial or tab) with the number of units used in treatment of the disease. Prices from both CMST and private wholesaler were used. The present study also computed Median Price Ratio (MPR) to check if patients or government are being charged fairly when purchasing anticancer drugs.

The Median Price Ratio was calculated for each anticancer drug by dividing the local consumer price in (USD) with International Reference Price, and multiplying the result by 100. The

reference prices used in this study were obtained from the 2015 Management Sciences for Health International Drug Price Indicator Guide (60).

Furthermore, cost analysis entailed evaluation of the estimated average cost of anticancer prescription for each cancer type. The estimated average cost of anticancer prescription was calculated by dividing the total cost of treating Cancer **X** by the number of prescriptions for cancer **X**. In this study, a prescription covered one full cycle of the cancer treatment.

In the present study, affordability was calculated for one full cycle of anticancer treatment. Affordability assessment used prices from Central Medical Stores Trust which supplies majority of drugs to Queen Elizabeth Central Hospital. The number of days' wages needed to pay for one full cycle of treatment was obtained by dividing the cost of one full cycle of anticancer treatment for each cancer type, by the daily minimum wage in Malawi. The daily minimum wage in Malawi is MWK1,928.08 which is equivalent to USD 2.37 (Reserve bank of Malawi exchange rate :1USD = MWK809.77).

3.11 ETHICAL CONSIDERATIONS

Permission to conduct this study was obtained from Kenyatta National Hospital-University of Nairobi Ethics and Research committee (KNH/UON-ERC) and the College of Medicine Research and Ethics Committee (COMREC) of Malawi. The scanned copies of the letter of approval (KNH-ERC/RR/285 and P.07/21/3363 respectively) can be found in Appendices 7.4 and 7.5. Management of Queen Elizabeth Central Hospital also authorized the study to take place at the paediatric oncology unit. Patient data confidentiality was safeguarded through the use of unique codes and password protected computer accessible only by the principal investigator.

4 CHAPTER FOUR: RESULTS

4.1 PARTICIPANTS INCLUDED AND REASONS FOR EXCLUSION

The study sought to determine the prescription pattern and cost analysis of anticancer drugs used in the paediatric unit of Queen Elizabeth Central Hospital in Malawi. A total of 400 patient files were reviewed, and 293 files met the set eligibility criteria. One hundred files were excluded because they had incomplete information on chemotherapy and adjunct drug history as well as disease and diagnostic information of the paediatric malignancy. Seven files were also excluded because the patients did not complete 50% of the chemotherapy. **Figure 4.2** summarises the number of files screened, reasons for exclusion and the final number of participants.

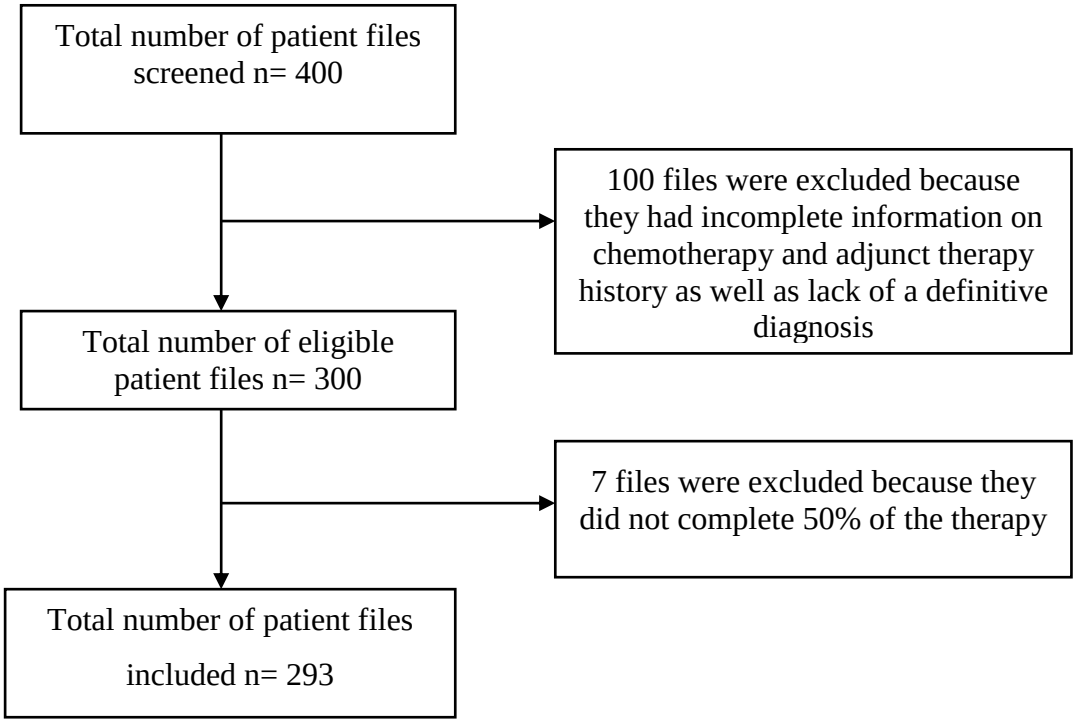

Figure 4.1: Number of participants included and reasons for exclusion

4.3 BASELINE SOCIAL DEMOGRAPHIC CHARACTERISTICS OF PARTICIPANTS

The study participants had a median age of 6 years [IQR 3, 11]. Those aged between zero and five accounted for 133 (45.4%) while 91 (31.1%) were between ages six and eleven. Children aged twelve and above were 69 (23.6%). Females were 116 (39.6%) while males were 177 (60.4%). The median weight and height of the participants was 17 kg [IQR 12, 26.2] and 110.7 cm [IQR 92, 135.5] respectively. The median body surface area was 0.71m^2 [IQR 0.56, 0.97].

The mid-upper arm circumference (MUAC) was measured at admission and the median was 14.9 cm [IQR 13.4, 16.4]. Majority of the children were well nourished 157 (72.4%) while 32 (14.8%) were at risk of malnutrition. Only 11 (5.1%) had severe acute malnutrition while 17 (7.8%) had moderate acute malnutrition according to MUAC screening tool (61). Majority of the participants came from rural areas 220 (75.0%) while 73 (24.9%) came from urban areas. **Table 4.1** summarizes the baseline-demographic characteristics of the study participants.

Table 4.1: Baseline social-demographic characteristics of the participants

Variable	Number	Percentage (%)
Age groups (Years)		
0-5	133	45.4%
6-11	39	31.1%
12 and above	23	23.5%
Gender		
Male	177	60.4%
Female	116	39.6%
	Median	**IQR**
Weight (kg)	17	(12, 26,2)
Height (cm)	110.7	(92, 135.5)
BSA (m^2)	0.71	(0.56, 0,97)
MUAC (cm)	14.9	(13.4, 16.4)
	Frequency	**Percentage (%)**
Mid-upper arm circumference (MUAC) groups		
Severe acute Malnutrition < 11.0cm	11	5.1%
Moderate Acute Malnutrition 11.0cm -12.5cm	17	7.8%
At risk for Malnutrition > 12.5cm- 13.5cm	32	14.8%
Child well-nourished > 13.5 cm	157	72.4%
Residence		
Rural	220	75.1%
Urban	73	24.9%

4.4 PREVALENCE OF VARIOUS TYPES OF CHILDHOOD CANCERS

The largest proportion of the patients were diagnosed with Burkitt's lymphoma (73, 24.9%) followed by retinoblastoma (54, 18.3%). Children with Wilm's tumour, Kaposi sarcoma, and non-Hodgkin's lymphoma accounted for (31, 10.6%) of the diagnosed cases.

There were 22 (7.5%) cases of acute lymphocytic leukaemia; 19 (4.5%) of rhabdomyosarcoma and very few cases of Hodgkin's lymphoma (9, 3.1%), germ cell tumour (5, 1.7%) and

hepatoblastoma (2, 0.7%). **Figure 4.3** depicts different types of childhood cancer, diagnosed among the study participants.

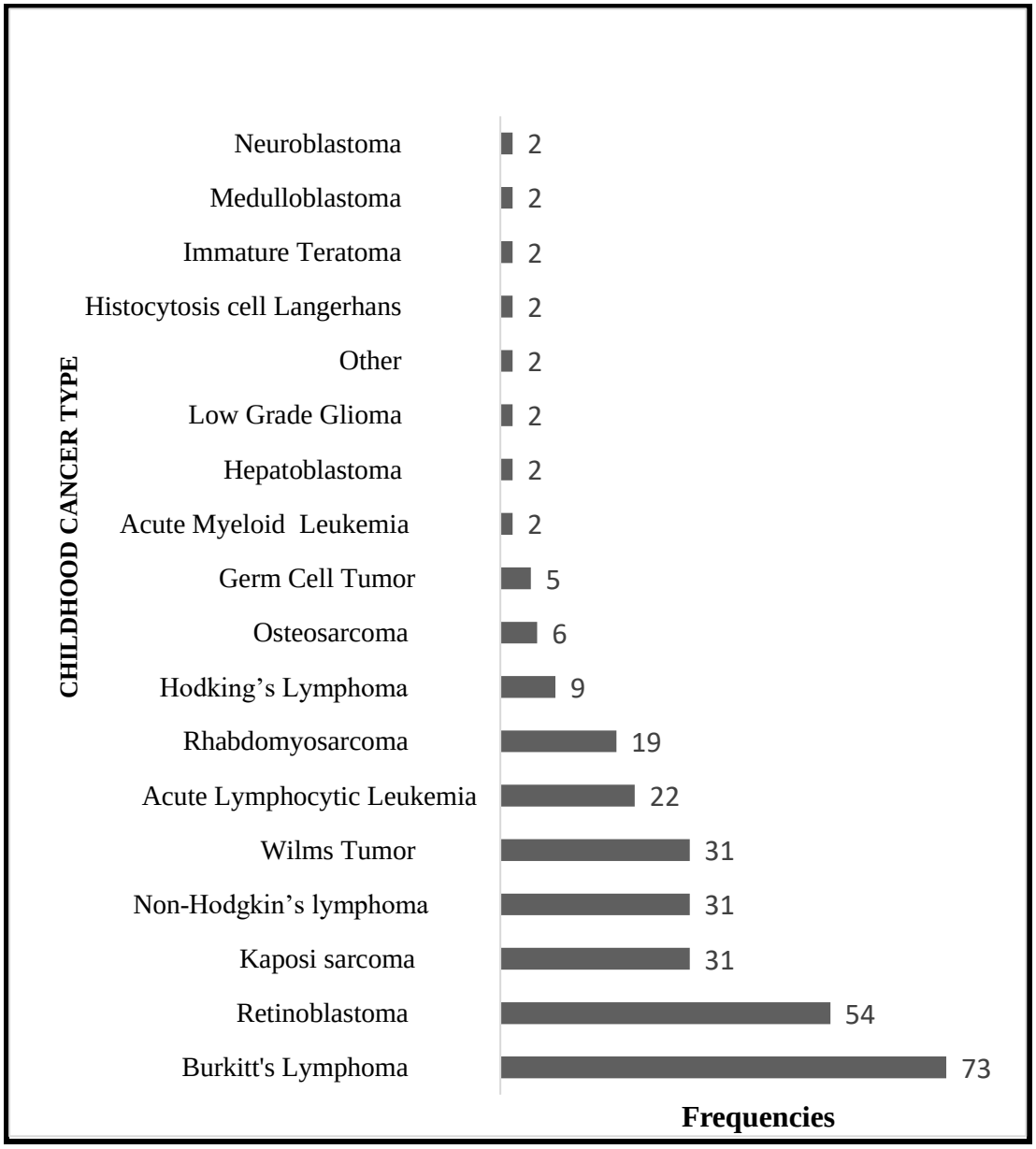

Figure 4.2: Prevalence of various diagnosed childhood cancers (n=293)

4.5 CANCER STAGES AT DIAGNOSIS

The largest proportion of children were diagnosed with cancer at stage I (196, 66.9%) followed by stage III (48, 16.4%). Those at stage II and IV were (27, 9.2%) and (22, 7.5%) respectively. **Table 4.2** summarises the stages of cancer at diagnosis.

Table 4.2: Cancer stages at diagnosis of the paediatric cancer patients

Tumour stage	Females	Males	Frequency	%
I	67	129	196	66.9%
II	15	12	27	9.2%
III	22	26	48	16.4%
IV	12	10	22	7.5%

4.6 PREVALENCE OF COMORBIDITIES AMONG PEDIATRIC CANCER PATIENTS

Malaria and HIV/AIDS were the most prevalent comorbidities among the participants (57, 19.66%). Tuberculosis was diagnosed in among 6 participants (2.1%) while 9 (3.1%) had other comorbidities such as malnutrition and anaemia. However, majority of the participants (161, 55.5%) did not present with any comorbidities. **Figure 4.4** depicts prevalence of comorbidities among the study participants.

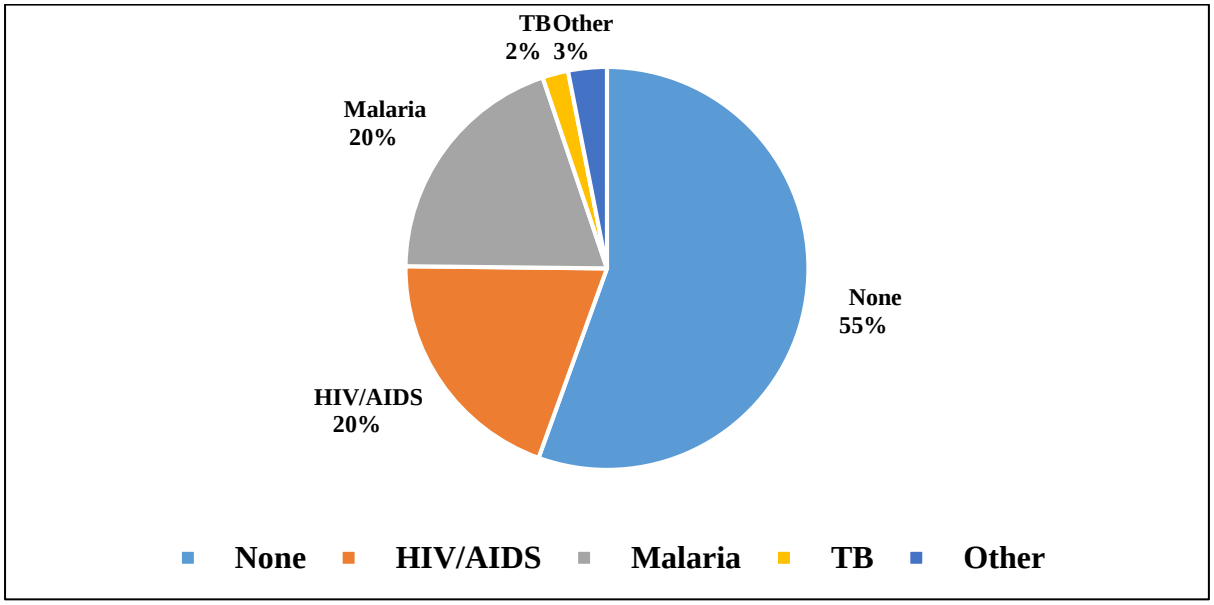

Figure 4.3: Prevalence of comorbidities among paediatric cancer patients

4.7 COMORBIDITIES OBSERVED FROM VARIOUS TYPES OF CHILDHOOD CANCERS

The childhood malignancies were stratified by comorbidities. Malaria was prevalent in children with Burkitt's Lymphoma (44, 77.2%), followed by acute lymphocytic leukaemia where (6, 10.5%) had malaria. Almost half of the children (28, 49.1%) with Kaposi sarcoma had HIV/AIDS. Children who presented with no comorbidity were mainly diagnosed with retinoblastoma (39, 24.2%) followed by Wilm's tumour (25, 15.5%). Tuberculosis was

reported in 6 children of whom 5 (83.3%) were diagnosed with Non-Hodgkin's lymphoma and 1 (16.7%) had Wilm's tumour. **Table 4.3** Presents comorbidities observed from various types of childhood cancers.

Table 4.3: Co-morbidities among paediatric patients with cancer

Cancer type	Co-morbidities				
	HIV/AIDS	Malaria	TB	Other	None
Burkitt's lymphoma	3	44	0	1	24
Retinoblastoma	10	2	0	3	39
Kaposi sarcoma	28	0	0	0	3
NHL	3	1	5	2	20
Wilm's tumour	2	1	1	0	25
ALL	5	6	0	0	11
Rhabdomyosarcoma	1	1	0	2	15
HL	3	1	0	0	5
Other cancers	2	1	0	1	19
Total	57	57	6	9	161

NHL: Non-Hodgkin's Lymphoma, **ALL**: Acute Lymphoblastic Leukaemia,

HL: Hodgkin's Lymphoma

4.8 OUTCOME OF CANCER TREATMENT

At the end of the review period 85 (29.1%) of the children died while 82 (28.1%) were discharged with no sign of malignancy. Some children (51, 17.5%) were discharged to receive palliative care, and 69 (23.6%) participants were still battling the disease at the end of the review period. Five (1.7%) defaulted or were lost to follow up. **Table 4.4** summarises the frequencies of each outcome of the disease.

Table 4.4: Outcomes of cancer treatment amongst paediatric cancer patients in Queen Elizabeth Hospital in Malawi

Outcome	Frequency	Percentage (%)
Death	85	29.1%
Resolved	82	28.1%
Progression	69	23.6%
Palliation	51	17.5%
Other	5	1.7%

4.9 DIFFERENCES IN TREATMENT OUTCOMES ACROSS STAGE OF CANCER AT DIAGNOSIS

Outcomes of the treatment at the end of the review period were stratified by cancer stage at diagnosis. More than half of children (15, 68.2%) who presented at stage IV died while (5, 22.7%) were discharged to receive palliative care. Of those who presented at stage III, (16,33.3%) died while (14, 29.2%) were on palliative care. Children who were diagnosed at stage I had a high recovery rate (68, 34.9%) followed by (54, 27.6%) who were still fighting cancer. Those diagnosed at stage I only 23.6% died at the end of the review period. **Table 4.5** shows treatment outcomes observed from various by cancer stage at diagnosis.

Table 4.5: Differences in treatment outcomes across stage of cancer at diagnosis

Cancer stage	Treatment outcomes				
	Death	**Other**	**Palliation**	**Progression**	**Resolved**
I	46	2	25	54	68
II	8	0	7	3	9
III	16	3	14	11	4
IV	15	0	5	1	1
Total	85	5	51	69	83

4.10 PRESCRIBING ERRORS (MISSING INFORMATION)

Omission of patient height was the most frequently occurring error of omission (80, 47.3%), followed by omission of the mid-upper arm circumference values (76, 45.0%). Only 7 prescriptions (4.1%) had omission of body surface area, a parameter necessary for calculation of chemotherapy dosage. **Table 4.6** depicts the types of error of omission observed from 169 prescriptions

Table 4.6: Types of missing information observed in chemotherapy prescriptions of children diagnosed with cancer at Queen Elizabeth Central hospital

Type of omitted information	Frequency	%
Patient weight	2	1.2
Patient height	80	47.3
MUAC	76	45.0
BSA	7	4.1
Outcome of treatment	1	0.6
Comorbidities	3	1.8

***BSA**: Body surface area**; MUAC**: Mid-upper arm circumference*

4.11 PRESCRIBING PATTERNS OF ADJUNCT DRUGS

In this study, analgesics were the commonly used class of adjunct therapy. Morphine was used in 271 patients while paracetamol was used in 79.5% of the children. To counter the constipating effects of narcotic analgesics, laxatives such as bisacodyl (60.4%) and liquid paraffin (47.4%) were used. Steroids such as prednisolone and dexamethasone were also used in 51.2% and 12.3% of the children respectively.

To prevent tumour lysis syndrome of solid tumours, 44.4% of the children were prescribed allopurinol. Metoclopramide was the antiemetic of choice as 34.4% of the children received the drug while 26.6% of the patients were put on ondansetron.

Peripheral neuropathy was mostly managed using gabapentin and pyridoxine. A few children; 5.1%were put on oral rehydration therapy (ORS). Omeprazole was the proton pump inhibitor of choice as 6.8% of the children were put on it to counter gastro-irritating effects of chemotherapy. Children with cases of anaemia were prescribed for folic acid and ferrous sulphate. **Table 4.7** shows prescribing patterns of adjunct drugs.

Table 4.7: Prescribing patterns of adjunct drugs used in management of childhood cancers

AGENTS USED		Number of patients	%
Anti-emetics	Metoclopramide	101	35.4
	Ondansetron	28	26.4
Opiates	Morphine	271	92.5%
	Pethidine	10	3.4%
Laxatives	Bisacodyl	177	60.4%
	Liquid paraffin	139	47.5%
	Lactulose	17	5.8%
Steroids	Prednisolone	150	51.2%
	Dexamethasone	36	12.3%
	Hydrocortisone	1	0.3%
Analgesics	Ibuprofen	89	30.4%
	Paracetamol	233	79.5%
Cytoprotectants	MESNA	1	0.3%
Rehydration salts	ORS	15	5.1%
Proton pump inhibitors	Omeprazole	20	6.8%
	Pantoprazole	2	0.7%
Vitamins	Folic acid	15	5.1%
	Pyridoxine	7	2.4%
	Ferrous sulphate	4	1.4%
Antidotes	Leucovorin	12	4.1%
Anticonvulsants	Gabapentin	7	2.4%
Alpha/beta adrenergic agonists	Adrenaline	3	1.0%
Xanthine oxidase inhibitors	Allopurinol	130	44.4%

ORS: oral rehydration salts:

4.12 CHEMOTHERAPEUTIC AGENTS PRESCRIBED IN THE PAEDIATRIC ONCOLOGY UNIT

Various therapeutic classes and individual chemotherapy agents were used to treat childhood cancers. Vincristine was the most commonly used drug across many childhood malignancies followed by doxorubicin. Intrathecal methotrexate and cyclophosphamide had comparable usage of 12.0% and 11.9% respectively. Rituximab was used in 29 patients as a part of a clinical trial study. Thalidomide was used in two patients as an immunomodulatory agent. **Table 4.8** depicts the prevalence of use of chemotherapeutic agents prescribed in paediatric oncology unit.

Table 4.8: Chemotherapeutic agents prescribed in the paediatric unit of Queen Elizabeth Central Hospital in Malawi

CHEMOTHERAPY AGENTS USED	Therapeutic class	Names of drugs	Frequency	(%)
Cytotoxic drugs	Alkylating agent	Cyclophosphamide	122	11.9%
		Carboplatin	58	5.6%
		Ifosfamide	1	0.1%
		Cisplatin	20	2.0%
		Dacarbazine	9	0.9%
	Antimetabolites	Methotrexate/HC	123	12.0%
		Methotrexate p.o	3	0.3%
		6-Mecaptopurine	14	1.4%
		5-fluorouracil	1	0.1%
		Cytarabine	8	0.8%
	Antibiotics	Doxorubicin	159	15.5%
		Actinomycin-D	38	3.7%
		Bleomycin	50	4.5%
	Vinca alkaloids	Vincristine	262	25.5%
		Vinblastine	10	1.0%
	Podophyllotoxins	Etoposide	111	10.8%
	Taxanes	Paclitaxel	2	0.2%
DMARDS	DMARDS	Rituximab	29	2.8%
Enzymes	Enzymes	Asparaginase	6	0.6%
Immunomodulatory agents	Immunomodulatory	Thalidomide	2	0.2%

DMARDS: Disease modifying anti-rheumatic drugs, **P.O: oral, HC/hydrocortisone**

4.13 ANTICANCER DRUG COMBINATIONS USED FOR DIFFERENT TYPES OF CHILDHOOD CANCERS

Various oncology drug combinations were used in management of childhood cancers. Children presenting with stage 1 burkitt's lymphoma were managed using a combination of cyclophosphamide and intrathecal methotrexate/hydrocortisone (IT MTX/HC). Advanced stages and relapse of burkitt's lymphoma and Non-Hodgkin's lymphoma were managed using a combination of cyclophosphamide, doxorubicin, vincristine, prednisolone, Methotrexate, and Etoposide. Retinoblastoma was treated using a combination of carboplatin, etoposide and vincristine. Patients with Kaposi sarcoma were put on a combination of vincristine, bleomycin and etoposide. Wilm's tumour was managed using a combination of actinomycin D, doxorubicin and vincristine. **Table 4.9** shows drug combinations that were used to manage five commonly diagnosed childhood cancers.

Table 4.9: Drug combinations used to manage different childhood cancers in the paediatric unit of Queen Elizabeth Central Hospital in Malawi

CHILDHOOD CANCER	DRUG COMBINATION
Burkitt's lymphoma-Stage 1	Cyclophosphamide, IT MTX/HC
Burkitt's lymphoma &Non-Hodgkin's lymphoma-other stages	Cyclophosphamide, Doxorubicin, Prednisolone, Vincristine, IT MTX/HC
Burkitt's lymphoma & Non-Hodgkin's lymphoma-Relapse	Cyclophosphamide, Doxorubicin, Prednisolone, Vincristine, Methotrexate, IT MTX/HC, Etoposide.
Retinoblastoma	Carboplatin, Etoposide and Vincristine
Kaposi sarcoma	Vincristine, Bleomycin and Etoposide
Wilm's tumour	Doxorubicin, Actinomycin D, Vincristine

IT MTX/HC: Intrathecal Methotrexate/hydrocortisone

4.14 NUMBER OF CHEMOTHERAPY DRUGS PER PRESCRIPTION

The number of chemotherapy drugs per prescription was assessed. Almost half of the prescriptions (141, 48.1%) had three drugs while 81 (27.7%) had four drugs. A small number of (6, 2.1%) of chemotherapy prescriptions had seven drugs and only (2, 0.7%) prescriptions had one drug. The mean number of chemotherapy drugs per prescription were 3.5 as shown in **Figure 4.5**

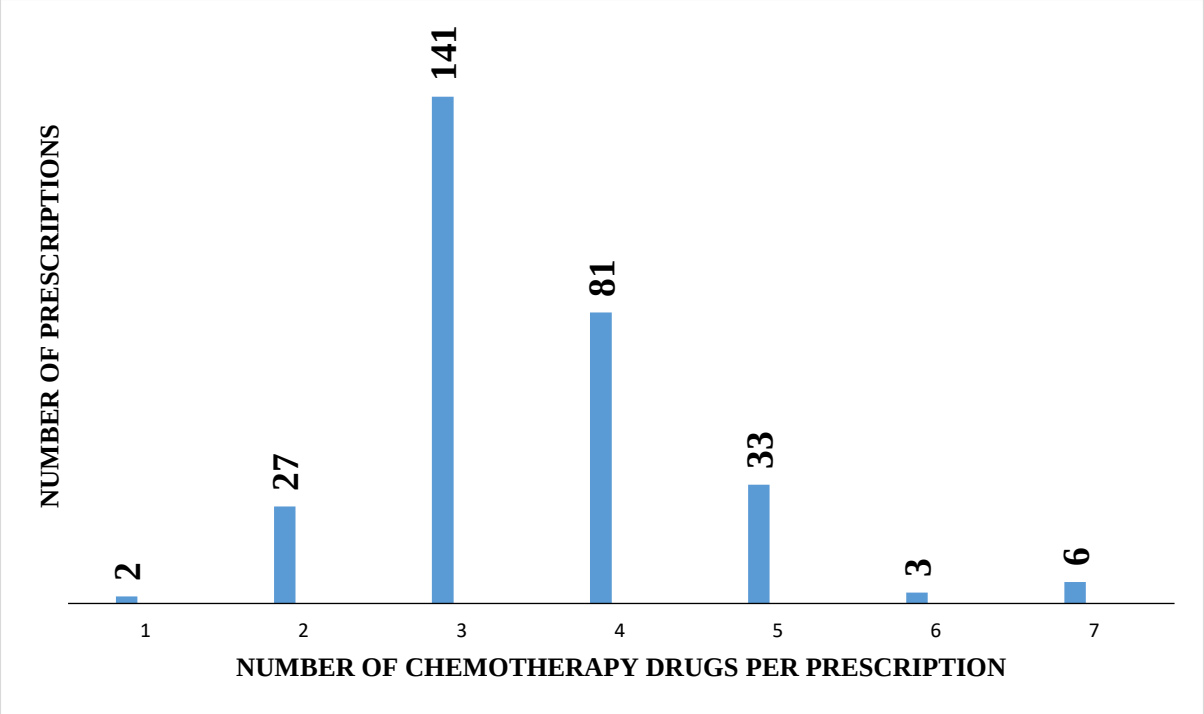

Figure 4.4: Number of chemotherapy drugs per prescription

4.15 COMPLIANCE OF PRESCRIBING PRACTICES TO THE PRESCRIBING INDICATORS

World Health Organisation (WHO) indicators are used to determine whether drugs are being used rationally or not. The mean number of chemotherapy drugs per encounter was 3.5 which was above the reference values. Percentage of drugs prescribed by generic name was 99.2% while the percentage of drugs prescribed from the essential formulary 100%. These two parameters were within the normal reference values. The QECH paediatric oncology formulary was adapted from International Society of Oncology (ISOP) essential formulary. **Table 4.10** depicts the calculated prescribing indicators.

Table 4.10: Compliance of prescribing practices to selected prescribing indicators

Assessed prescribing indicators	Total drugs/encounters	Average/ percent	Standard derived or ideal
Mean number of drugs per encounter	1028	3.5	(1.6-1.8)
Percentage of drugs prescribed by generic name	1020	99.2%	100%
Percentage of drugs prescribed from the essential formulary	1028	100%	100%

4.16 CUMULATIVE EXPENDITURE ON ANTICANCER DRUGS BETWEEN JANUARY 2017 TO DECEMBER 2020

The cost of anticancer drugs was calculated using prices of drugs from the Central Medical Stores Trust (CMST), and a major private wholesaler of anticancer drugs in Malawi. **Table 4.11** depicts the expenditure on anticancer drugs used in this study. Cumulatively, the entire spectrum of anticancer drugs used between January 2017 to December 2020 cost MWK 52,941,400.04 which is equivalent USD 65,400.12 at Central Medical Stores Trust.

When costing was repeated using the private sector prices, the total estimated cost using private wholesaler prices was MWK 95,717,360.00 equivalent to USD 118,242.57. The conversion between currencies was done using the Reserve Bank of Malawi rate (1USD = MWK 809.77). The difference in the cost between the government agency and the private supplier was MWK 42,775,960 equivalent to USD 52,824.83.

The fractional expenditure on rituximab was the highest (MWK 21,764,709.42), followed by etoposide at MWK 6,715,500. Carboplatin and Bleomycin contributed MWK 6,424, 000, and MWK 2,831,868 respectively to the expenditure at the Central Medical Store.

The fractional expenditure on the commonly prescribed anticancer drug, vincristine was MWK 2,825,680, and doxorubicin was MWK 2,667,833.90. The least costly drug was oral methotrexate (MWK 3,136), while the fractional expenditure on 6-Mecaptopurine was estimated at MWK 5,640.

The Disease modifying anti-rheumatic drug (DMARDS) was costly (MWK 21,764,709. 42), followed by alkylating agents estimated at MWK 8,821,000. Podophyllotoxins class cost MWK 6,715,500.

Vinca alkaloids were estimated at MWK 4,616,531.83, and antimetabolites took up MWK 2,593,876 of the total expenditure. The fractional expenditure on taxanes and enzymes were the least estimated at MWK 226,960.44, and MWK 659,101. 05) respectively.

The expenditure on adjuvant drugs was also estimated. Expenditure on antibiotics was MWK 6,375,145. 82 the total expenditure.

Table 4.11: Cumulative expenditure on Anticancer drugs in the Central Medical Stores Trust, Malawi between Jan 2017- Dec 2020

AGENTS USED	Therapeutic class	Names of drugs	Vials used	Cost/unit (MWK) (CMST)	Cost/unit (MWK) (PVT)	Total Cost (MWK) (CMST)	Total Cost (MWK) (PVT)	Total Cost (USD) (CMST)	Total Cost (USD) (PVT)
Cytotoxic Drugs	**Alkylating agent**	**Cyclophosphamide**	1105	1100	2500	1 215 500	2 762 500	1 501.54	3 412.60
		Carboplatin	292	22 000	70000	6 424 000	20 440 000	7 935.76	25 250.15
		Ifosfamide	4	15955.05	20000	63 820.20	80 000	78.84	98.83
		Cisplatin	139	8500	7000	1 181 500	973 000	1 459.54	1 201.98
		Dacarbazine	101	5249.61	13000	530 210.61	1 313 000	654.99	1 621.99
	Antimetabolites	**Methotrexate/HC**	451	5700	12000	2 570 700	5 412 000	3 175.66	6 685.61
		Methotrexate oral	98	32	120	3 136	11 760	3.87	14.53
		6-Mecaptopurine	47	120	300	5 640	14 100	6.97	17.42
		5-fluorouracil	12	1200	2500	14 400	30 000	17.79	37.06
		Cytarabine	107	5369.58	30000	574 545.06	3 210 000	709.75	3 965.41
	Antibiotics	**Doxorubicin**	515	5180.26	14000	2 667 833.90	7 210 000	3 295.66	8 906.73
		Actinomycin-D	156	5611.82	10000	875 443.92	1 560 000	1 081.46	1 927.12
		Bleomycin	351	8068	14000	2 831 868	4 914 000	3 498.29	6 070.41
	Vinca alkaloids	**Vincristine**	1672	1690	2500	2 825 680	4 180 000	3 490.65	5 163.68
		Vinblastine	291	6154.13	15000	1 790 851.83	4 365 000	2 212.29	5 392.22
	Podophyllotoxins	**Etoposide**	1221	5500	7000	6 715 500	8 547 000	8 295.86	10 558.37
	Taxanes	**Paclitaxel**	7	32422.92	55000	226 960.44	385 000	280.37	475.60
Enzymes	**Enzymes**	**Asparaginase**	27	24411.15	30000	659 101.05	810 000	814.21	1 000.62
DMARDS	**DMARDS**	**Rituximab**	59	368893.38	500000	21 764 709.42	29 500 000	26 886.61	36 442.25
		Grand total	**6655**			**52 941 400.40**	**95 717,360.00**	**65 400.12**	**118 242.57**

Table 4.12: ABC analysis of drugs used in Paediatric oncology unit of Queen Elizabeth Central hospital from Jan 2017-Dec 2020

Drug Name	Vials	Unit cost (CMST)(MWK)	Total cost (MWK)	% of total cost	Cumulative %	Classes
Rituximab	59	368893.38	21 764 709,42	41,11%	41,11%	
Etoposide	1221	5500	6 715 500,00	12,68%	53,80%	
Carboplatin	292	22 000	6 424 000,00	12,13%	65,93%	**A**
Bleomycin	351	8068	2 831 868,00	5,35%	71,28%	
Vincristine	1672	1690	2 825 680,00	5,34%	76,62%	
Doxorubicin	515	5180.26	2 667 833,90	5,04%	81,66%	
Methotrexate/HC	451	5700	2 570 700,00	4,86%	86,51%	
Vinblastine	291	6154.13	1 790 851,83	3,38%	89,89%	**B**
Cyclophosphamide	1105	1100	1 215 500,00	2,30%	92,19%	
Cisplatin	139	8500	1 181 500,00	2,23%	94,42%	
Actinomycin-D	156	5611.82	875 443,92	1,65%	96,08%	
Asparaginase	27	24411.15	659 101,05	1,24%	97,32%	
Cytarabine	107	5369.58	574 545,06	1,09%	98,41%	**C**
Dacarbazine	101	5249.61	530 210,61	1,00%	99,41%	
Paclitaxel	7	32422.92	226 960,44	0,43%	99,84%	
Ifosfamide	4	15955.05	63 820,20	0,12%	99,96%	
5-fluorouracil	12	1200	14 400,00	0,03%	99,98%	
6-Mecaptopurine	47	120	5 640,00	0,01%	99,99%	
Methotrexate oral	98	32	3 136,00	0,01%	100,00%	
			MWK 52 941 400,43	**100,00%**		

4.17 ABC ANALYSIS OF ANTICANCER DRUGS USED BETWEEN JANUARY 2017-DECEMBER 2020

Between January 2017 to December 2020, 19 different anticancer drugs which consumed MWK 52,941,400.43, were used in the paediatric oncology unit of Queen Elizabeth Central Hospital. ABC analysis showed that 4 (21.1%) drugs were categorised as class A and consumed about 71.3% of the total cumulative expenditure. Class B and C accounted for 5 (26.3%) and 10 (52.6%) drugs that consumed 20.9% and 7.8% of total cumulative expenditure respectively. **Table 4.12** shows the categorization of anticancer drugs on the basis of expenditure.

Of the overall expenses, Rituximab alone contributed 41.1% while Etoposide and Carboplatin contributed 12.7% and 12.1% respectively. **Figure 4.6** shows the top ten most expensive drugs in the paediatric oncology unit of Queen Elizabeth central hospital.

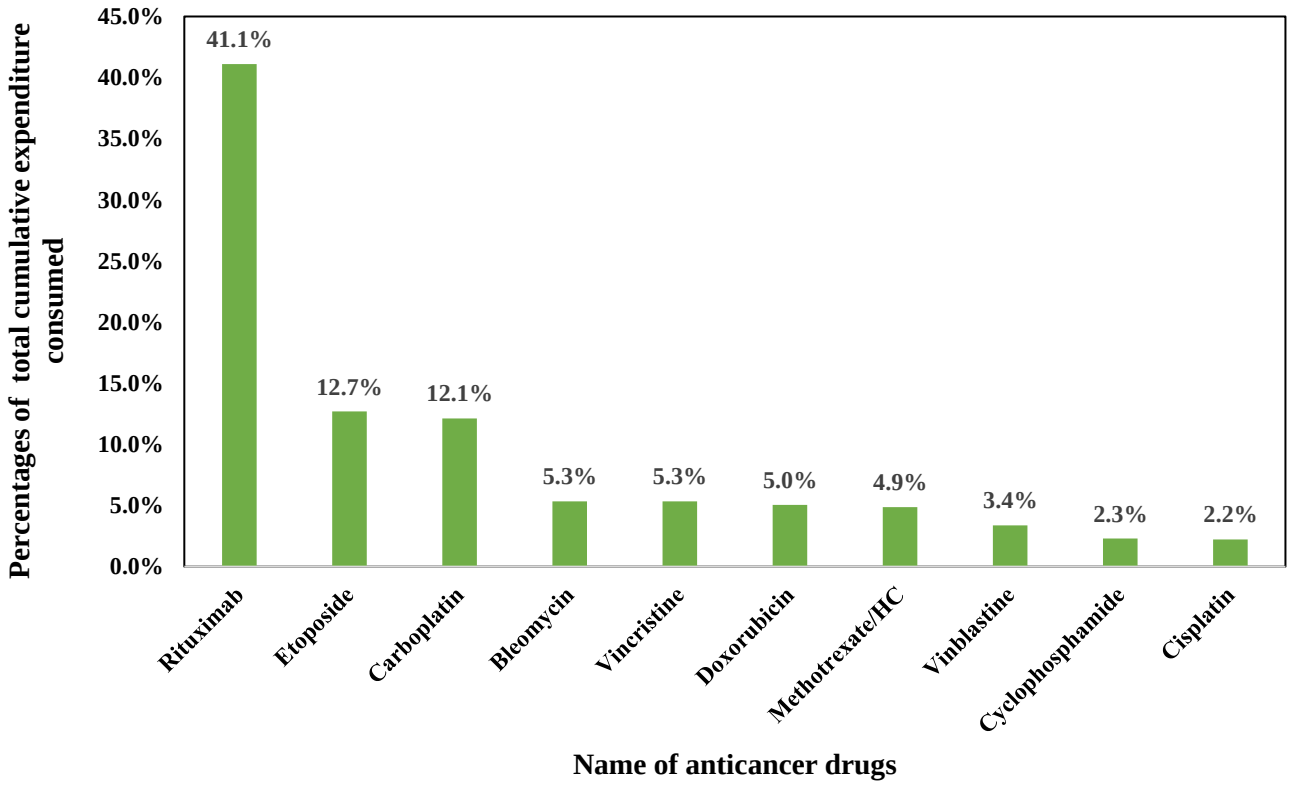

Figure 4.5: Top Ten Most costly anticancer drugs in paediatric oncology unit between January 201- Dec 2020

4.18 EVALUATION OF MEDIAN PRICE RATIO FOR ANTICANCER DRUGS USED IN PEDIATRIC ONCOLOGY UNIT AT QUEEN ELIZABETH CENTRAL HOSPITAL, MALAWI.

In computing the Median price ratio (MPR), the oral formulation prices were expressed per tablet while injectables were quoted per vial. The prices were converted from Malawian kwacha to US dollars using reserve bank of Malawi exchange rate (1USD = MWK809.77). **Table 4.13** shows the MPR of the anticancer drugs used to manage childhood cancer disease at Queen Elizabeth Central Hospital.

Table 4.13: Evaluation of Median price ratio (MPR) for anticancer drugs used at Queen Elizabeth Central Hospital in Malawi

DRUG NAME	MSH PRICES (USD)	CMST (USD)	MRP (%)
Cyclophosphamide*	5.24	1.36	**26.0**
Doxorubicin	5.41	6.40	119.0
Vincristine*	2.54	2.09	**82.3**
Etoposide	2.02	6.79	336.1
Bleomycin*	12.32	10.21	**82.0**
Cisplatin	7.25	10,5	144.8
Dactinomycin*	8.7	6.93	**79.7**
Vinblastine	4.98	7.60	152.6
Dacarbazine	6.81	7.35	107.9
IT Methotraxate/HC	2.63	7.04	267.7
Methotraxate/tab	0.02	0.04	200.0
6-Mecaptopurine/tab*	2.24	0.15	**6.7**
Asparaginase*	52.88	30.15	**57.1**
Cytarabine	3.48	6.63	190.5
Rituximab*	683.60	455.55	**66.6**
Carboplatin*	40.32	27.17	**67.4**
Paclitaxel	11.08	40.04	361.4
Ifosfamide*	21.55	19.70	**91.4**
5-Fluorouracil	0.26	1.48	569.2

Drug name*: drugs that were available at rates below the international reference price

The median price ratio for half of the drugs was below 100%. The other 50% of the anticancer drugs had an MPR value of above 100% with 5-fluorouracil reaching an MPR of 659.2%.

4.19 COST OF TREATMENT OF EACH TYPE OF CANCER

Burkitt's lymphoma was the costly cancer (MWK25,844,297.70) to treat followed by retinoblastoma (MWK8,079,360.00), Kaposi Sarcoma (MWK5,429,680.44) and Hodgkin's lymphoma at (MWK2,711,809.00). The least costly cancer was hepatoblastoma (MWK121,261.82). **Table 4.14** depicts the cost for treating each type of cancer.

Table 4.14: Total cost of each cancer type diagnosed at Queen Elizabeth Central Hospital, Malawi

CANCER TYPE	COST (MWK) (CMST)	COST (MWK) (PVT)
Burkitt's Lymphoma	25,844,297.70	37,980,500.00
Retinoblastoma	8,079,360.00	20,532,000.00
Kaposi sarcoma	5,429,680.44	7,857,000.00
Hodgkin's Lymphoma	2,711,809.00	6,458,100.00
Non-Hodgkin's lymphoma	2,203,906.62	4,796,500.00
Acute Lymphocytic Leukemia	1,824,105.69	3,916,260.00
Wilms Tumor	1,778,263.78	3,344,000.00
Germ Cell Tumor (GCT)	1,357,896.00	1,848,000.00
Low Grade Glioma	852,780.00	2,535,000.00
Osteosarcoma	672,594.56	1,099,000.00
Rhabdomyosarcoma (RMS)	619,210.72	1,289,000.00
Acute Myeloid Leukemia	325,840.50	1,686,000.00
Medulloblastoma	291,900.00	795,000.00
Histiocytosis cell Langerhans	259,073.46	631,500.00
Other	222,715.92	295,500.00
Neuroblastoma	173,592.22	255,000.00
Immature Teratoma	173,112.00	231,000.00
Hepatoblastoma	121,261.82	168,000.00
Total	**52,941,400.43**	**95,717,360.00**

4.20 ESTIMATED MEAN COST OF FULL COURSE OF TREATMENT

The estimated average cost for low-grade glioma was 526.55 USD while Burkitt's lymphoma course per patient was 437.20 USD. Acute lymphocytic leukaemia was estimated at 102.39 USD and Wilm's tumour was the least costly at 70.85 USD. The rates were converted using Reserve Bank of Malawi exchange rate of 1USD = MWK 809.77. **Table 4.15** below displays the estimated mean cost of full course of treatment per patient.

Table 4.15: Estimated mean cost of full course of treatment per patient

Type of cancer	Estimated mean cost of treatment per full course (MWK)	Estimated mean cost of treatment per full course (USD)
Low Grade Glioma	426,390.00	526.55
Burkitt's Lymphoma	354,031.47	437.20
Hodgkin's Lymphoma	301,312.11	372.10
Germ cell Tumour	271,599.20	335.37
Kaposi Sarcoma	175,150. 98	216.30
Acute Myeloid Leukemia	162,920.00	201.19
Retinoblastoma	149,615.77	184.76
Medulloblastoma	145,950.00	180.24
Histiocytosis cell Langerhans	129,536.73	159.94
Osteosarcoma	112,009.09	138.43
Other	111,357.96	137.52
Neuroblastoma	86,796.11	107.19
Immature Teratoma	86,556.00	106.89
Acute Lymphocytic Leukemia	82,913.90	102.39
Non-Hodgkin's Lymphoma	71,093.00	87.80
Hepatoblastoma	63,130.91	77.96
Wilms Tumor	57,363.35	70.85

(Reserve bank of Malawi exchange rate :1USD = MWK809.77)

4.21 EVALUATION OF AFFORDABILITY OF CHEMOTHERAPY TREATMENT

The affordability was measured from the patient's perspective. Although patients do not pay for these medications, it is important to examine if patients could afford to purchase a chemotherapy prescription in case of freezing of donor funding. According to World Health organisation/Health Action International method, affordability is measured by calculating for the cost of a month's supply of medicines for treating a given disease against the daily or monthly wages (62).

The affordability was calculated for the duration of therapy as stated in Queen Elizabeth central hospital (QECH) chemotherapy protocol. Thus, our affordability assessment used prices from Central Medical Stores Trust which supplies majority of drugs to QECH. The number of days' wages needed to pay for the total cost of treatment was obtained by dividing the cost of full course of treatment with anticancer drugs for each cancer type by the daily minimum wage in Malawi. The daily minimum wage in Malawi is MWK1,928.08 which is equivalent to USD 2.37.

A lowest paid government worker (LWPG) who earns USD 2.37 per day needs to work 222.17 days to afford a full course of anticancer treatment for low grade glioma. For the worker to

afford one full course of treatment for Burkitt's lymphoma, (commonly diagnosed childhood cancer) he/she needs to work for 184.47days. Hodgkin's lymphoma, germ cell tumour, Kaposi sarcoma and retinoblastoma will require the LPGW to work 157.1, 141.51, 91.27, and 77.74 days respectively. Less commonly diagnosed cancers such as Medulloblastoma required the lowest paid worker to work 76.05 days, Immature teratoma for 45.10 days while Hepatoblastoma requires 32.9 days of work. **Table 4.16** depicts the affordability assessment of each childhood cancer.

Table 4.16: Estimated affordability of full course of chemotherapy treatment

Type of cancer	Estimated mean price of full course (MWK)	Estimated mean price of full course (USD)	Days wages needed to pay for total Medicines treatment
Low Grade Glioma	426,390.00	526.55	222.17
Burkitt's Lymphoma	354,031.47	437.20	184.47
Hodgkin's Lymphoma	301,312.11	372.10	157.01
Germ cell Tumour	271,599.20	335.37	141.51
Kaposi Sarcoma	175,150. 98	216.30	91.27
Acute Myeloid Leukemia	162,920.00	201.19	84.89
Retinoblastoma	149,615.77	184.76	77.74
Medulloblastoma	145,950.00	180.24	76.05
Histocytosis cell Langerhans	129,536.73	159.94	67.49
Osteosarcoma	112,009.09	138.43	58.41
Other	111,357.96	137.52	58.02
Neuroblastoma	86,796.11	107.19	45.23
Immature Teratoma	86,556.00	106.89	45.10
Acute Lymphocytic Leukemia	82,913.90	102.39	43.20
Non-Hodgkin's Lymphoma	71,093.00	87.80	37.05
Hepatoblastoma	63,130.91	77.96	32.89
Wilms Tumor	57,363.35	70.85	29.89
Retinoblastoma	32,590.04	40.00	16.88

5 CHAPTER FIVE: DISCUSSION

The goal of prescription pattern analysis is to promote rational drug use. In this study, Burkitt's lymphoma was the most prevalent childhood cancer, cancer prescriptions were unaffordable while anticancer drugs were largely found to be rationally used.

Cancer affected more male children than females. This finding agrees with a study done in Ethiopia by Endalamaw et al (65). It is suggested that males are more predisposed to risk factors that are associated with childhood cancers including demographic, environmental, intrinsic and genetic factors (64). Childhood malignancies were more prevalent in children aged 0 to 5. This result is similar to the above-stated study done in Ethiopia (63). The similarity can be described by comparable cancer distribution factors in sub-Saharan African countries.

More than two-thirds of the participating children came from rural areas. This could be explained by the World Bank findings that about 82.6% of Malawian population resides in rural areas (65).

Thirteen percent of the children were malnourished, 14% at risk, while about two-thirds were well nourished. This finding disagrees with a study done by Israels et al in 2008, where it was reported that 55% of the children admitted at Queen Elizabeth Central Hospital were acutely malnourished (11). The dwindling malnutrition levels in children with cancer can be explained by the special feeding program at pediatric oncology unit. Children are given special diets during their hospital stay. Furthermore, early diagnosis and treatment of childhood cancer ensures that children are managed before their nutrition levels worsen. In 2011, the Malawi government joined the scaling up nutrition movement promoting multipronged approach in tackling malnutrition (66). It is also one of the few countries that abides by the African Union's Maputo declaration to spend over 10% of the national budget on agriculture (66). These strategies attest to the improved children nutrition levels in Malawi.

An Error of omission was evaluated from the total of 293 prescriptions. About 58% of the prescriptions were found to have an error of omission. This agrees with a study done in Mexico by Cornejo et al in who assessed 1762 chemotherapy prescriptions and found 58% of the patients to have an error of omission (67). Height (47%) was a parameter that was commonly omitted followed by MUAC (45%) and very few had missing patient weight and comorbidities. In India, Mathaiyan et al reported that 47% of errors in their study were due to omissions of age, weight and height which agrees with this study (68).

Height is an important variable in calculations of body surface area-based doses. Hence, omission of height from almost half of the prescriptions warrants further probe.

The largest proportion of the participants were diagnosed with Burkitt's lymphoma followed by retinoblastoma. This trend is different from developed countries. In United States of America (USA) and the United Kingdom (UK) the commonly diagnosed childhood cancer is leukemia (69). Similarly, In Australia the most commonly diagnosed childhood malignancy is leukemia, and it accounts for 33% of all cases (70). Unlike developed countries, lymphomas, retinoblastomas and Kaposi sarcoma are the most prevalent childhood cancers in various African regions (71). A study by Stefan et al in 2010, reported that in Kenya, Burkitt's lymphoma was common while in Western African countries Non-Hodgkin's lymphoma was prevalent, and Kaposi's sarcoma was widely reported in South Africa (71). In Malawi, a study by Israels et al in 2008, reported Burkitt's lymphoma as the most prevalent childhood cancer (11). Furthermore, Hesseling et al (2003) found that Burkitt's lymphoma accounts for half of the childhood cancers in Malawi (32). The regional and global differences in pattern of childhood cancer have been well studied and are attributed to genetic and demographic differences among study participants.

Retinoblastoma and Kaposi's sarcoma came as second and third prevalent childhood cancers respectively. Both Kaposi's sarcoma and Non-Hodgkin's had the same proportion of children. Unlike in developed countries, there were very few children who presented with neuroblastoma and leukemia.

In Nigeria, the findings by Ojesina et al (2002) and Onwasigwe et al (2002) were congruent to our findings that Burkitt's lymphoma followed by retinoblastoma are commonly diagnosed childhood cancers (72). He also noted a sharp decline of cases of Burkitt's lymphoma when he compared the incidence of Burkitt's lymphoma in a span of 10 years. The same concept explains why early studies of childhood cancers in Malawi reported high prevalence rates compared to this study. The decline in cases of Burkitt's lymphoma have been ascribed to improved living conditions, and greater control of malaria which is a major predisposing factor for Burkitt's lymphoma (72).

On cancer staging, 66.1% of the participants were diagnosed at stage I of the malignancy. In Africa, detailed information on the population distribution of childhood malignancy stage is often not available because of lack of resources to collect data as well as access to diagnostic imaging, and other diagnostic clinical data (73). However, comparison of stage data from low

income countries and high income countries reveals that the proportion of cases diagnosed at advanced stage was many times higher in Africa than Australia (73). The findings of this study on cancer staging disagrees with the commonly held belief that children in developing countries present late at the hospital when the malignancy is at an advanced stage. This disparity can be attributed to increased sensitization campaigns targeting early detection and treatment of childhood cancer as well as possibility of misclassification of the stages by health care workers.

The participants were assessed for presence of comorbidities. A large proportion of the children presented with no comorbidity while malaria and HIV/AIDS were reported in 144 participants. Infection with both Epstein Barr Virus (EBV) and plasmodium falciparum are regarded as co-factors in the etiology of endemic Burkitt's (eBL) lymphoma (74). This etiological relationship explains why children leaving in malaria holoendemic areas experience high incidence rates of endemic Burkitt's lymphoma. Nearly, 4 million people in Malawi are diagnosed with Malaria annually, and the cases account for 2% of malaria cases world-wide (75). Therefore, the high prevalence rate of malaria in Malawi justifies why Burkitt's lymphoma is a commonly diagnosed childhood cancer. The relationship between malaria and Burkitt's lymphoma also explains why 77.2% of children diagnosed with Burkitt's lymphoma had malaria.

HIV/AIDS was also a prevalent comorbidity besides Malaria. Subgroup analysis showed that about 50% of children diagnosed with Kaposi's sarcoma had HIV/AIDS. Chagaluka et al (2014) in a study done in Malawi observed that Kaposi's sarcoma is a common childhood cancer where HIV/AIDS is endemic (76). In addition, mortality from Kaposi's sarcoma in HIV-infected children remains significant in developing countries (77). Unlike developing countries, Mallawany et al (2018) reported that in USA and Europe barely 14 cases of childhood Kaposi's sarcoma were recorded over 20-year span of multiple HIV/AIDS cancer registries (78). The low prevalence of HIV/AIDS in developed countries as well as timely access to anti-retroviral therapy explains the low number of Kaposi's sarcoma cases. On the other hand, low-income countries report high prevalence of HIV/AIDS and Kaposi's sarcoma because it is one of the common opportunistic infections in HIV patients.

Outcome of the disease upon the end of the review period was one of the assessments done in this study. Proportion of children who were discharged with no sign of the disease was just about the same as the proportion of those who died. There is a significant difference in the incidence and survival outcomes of childhood cancers in sub-Saharan Africa compared to North America and Europe (79). In high income countries, survival rates of many childhood

cancers surpassed 80% while in LMIC it is estimated to be below 20% (80). A study done by Chikumatha et al (2020) in Malawi found that at the end of the review period 53% of the participants were discharged contrary to the 28% reported in the present study. Unlike in the contrasting studies, discharged patients in this study did not include those discharged to palliative care which explains the reported difference. Furthermore, the difference can be explained by the follow up period. This study had a 3-year follow up period (Jan 2017 to Dec 2020) while Chikumatha et al (2020) had a 2-year follow-up period. Longer follow-up period decreases survival rates (81). Death at the end of the review period claimed 29% of the participants. This is comparable to a study done at the same clinic by Chikumatha et al (2020) who reported 23% rate (81).

Another outcome of interest was proportion of patients discharged to palliative care. Palliative care aims to improve quality of life for cancer patients. Unlike in our study, where only 18% of the patients were discharged to palliative care, a systematic review study reported that 55% of pediatric patients in high income countries were discharged to palliative care (82). Another study done in China found that 65% of the children who had cancer were discharged to palliative care (83). The disparity in palliative care can be attributed to high childhood cancer mortality rates which means many children don't make it to the palliation stage. Furthermore, palliative care is rarely accessible in sub-Saharan Africa. Herce et al (2014) observed that in Sub Saharan Africa, only 5% of people in need of palliative care receive it (84).

Anticancer drugs cause many side effects and adverse drug reactions. In this study, adjunct therapy was used to counter side effects of anticancer agents ranging from severe vomiting to mutagenicity. Metoclopramide was the antiemetic of choice followed by ondansetron. Use of these agents is comparable to several studies including the one done by Ruggiero et al (2018) (85). In pain management, morphine was used in 93% of the children while paracetamol and ibuprofen were also used in majority of the participants. High utilization of opioids and non-opioid analgesics was reported in a study done by Wang et al (2003) (86). The similarity could be attributed to use of comparable standard treatment guidelines in pain management. Constipation induced by opioids was managed by laxatives such as bisacodyl, liquid paraffin and lactulose. Treatment of opioid induced constipation agrees with standard treatment protocols.

Other therapeutic agents such as steroids, proton pump inhibitors (PPI), vitamins and antidotes were also used in this study. Steroids are widely recommended in chemotherapy to reduce

inflammation, immune response and sickness during chemotherapy (87). Proton pump inhibitors were used in 7% of the study participants. A study done in France by Raoul et al (2021) reported that 26 % of the cancer subjects were treated with PPls (88). Another study done in Brazil by Uchiyama et al (2021) also reported that PPIs were used in 33% of the cancer patients (89). Most studies done on the use of PPIs in cancer patients included both adults and children in their sample. Older patients often have pre-existing factors that warrants use of PPIs unlike children. Hence, it is logical for this study done in children to report such lower proportions of PPIs use. Over 44% of the participants were treated with allopurinol, 8% with vitamins and supplements, while 4% were put on an antidote. These agents were used rationally according to the guiding treatment protocols.

Vincristine was used in 26% of the participants while doxorubicin and intrathecal Methotraxate was used by 16% and 12% respectively. Not many studies have been done in Sub-Saharan Africa that can be compared with utilization of vincristine, however a study done in India by Manjesh et al (2022) also reported that vincristine is a commonly prescribed drug in pediatric cancers (90). The similarity could be attributed to comparable childhood cancer disease pattern as well as prescribing practices. Rituximab was prescribed in 29 participants as part of clinical trial. Although, rituximab is commonly used in adult population, studies in children are limited and its safety not well researched (91). Thalidomide was used in 2 patients and several studies have recommended its use in cancer (92).

The oncology drugs were largely administered in combination. Close to half of the prescriptions (48%) had three drugs while 28% had four drugs and only six participants were prescribed up to seven drugs. Number of drugs per prescription is comparable to a study done in India by Beedimani et al (2019) who reported that 37% of the participants were put on combination therapy ranging from two to three drugs (93). The combination drugs used in management of all cases of childhood cancers were all prescribed according to the recommended International Society of Pediatric Oncology, Pediatric Oncology for Developing Countries (SIOP PODC) treatment guidelines (34). Combinations of drugs were dictated by the type and stage of the cancer, drug toxicity profile as well as stock availability.

Rational prescribing was evaluated by comparing the prescription pattern with QECH pediatric oncology formulary as well as selected World Health Organization (WHO) rational prescribing indicators. The average number of drugs per encounter was 3.5 against the ideal range of (1.6 to 1.8). The present study reported a figure of 3.5 which is many times higher than the ideal

range of (1.6-1.8) because the range in discussion is for out-patients. Unlike out- patients, in-patients are prescribed more drugs especially childhood cancer patients. Therefore, the figure of 3.5 could be ideal for an in-patient childhood cancer patient. Hogerzeil et al (1993) in a similar study in Nigeria reported an average number of drugs per encounter to be 3.8 and another study in in Brazil reported a figure of 2.4 (94). The average number of drugs per encounter in childhood cancer in Nigeria is comparable to the present study. The similarity can be attributed to comparable prescribing practices, treatment guidelines, and cancer stage at admission. In contrast, a study done by Mathew et al (2019) who reported the average number of drugs per prescription to be 9.6. Unlike in the present study, the contrasting study included adjuvant therapy such as anti-emetics, steroids, and supplements (95). Percentage of drugs prescribed by generic name and percentage of drugs prescribed from the formulary was 99.2% and 100% respectively against the ideal 100%. Both scores are within ideal range, and the health workers must be encouraged to continue this practice because generic drugs are as effective as branded ones and they are cost-effective.

Cost analysis studies provide an estimation of expenditure incurred during therapy. This study focused on costs associated with a chemotherapy prescription. In the present study, rituximab was the most expensive drug. Many studies have reported the high costs associated with rituximab as well its unaffordability in many resource constrained settings (91). A study done in South India by Babasahib et al (2014) reported that trastuzumab, similar monoclonal antibody, contributed to the major drug costs. Furthermore, Kimani et al (2021), in a study done in Malawi, noted that rituximab is not available in most public hospitals because of high cost (96). Rituximab is a fairly new drug with few biosimilar available on the market hence the high cost.

Alkylating agents were second to DMARDs (rituximab) in being costly. These agents are commonly used in most of the treatment protocols. A study done in India by Manichavasagam et al (2017) reported that majority of different drugs used in treatment protocols were alkylating agents (97). The lowest number of units of taxanes agents (n=7) were used, and they were least costly. Unlike in adult cancer treatment protocols, most childhood cancer protocols do not include taxanes.

The ABC analysis showed that out of 19 anticancer drugs used in the pediatric unit; 4 (21.1%) were in class A and consumed about 71.3% of the total cumulative expenditure while classes B and C had 5 (26.3%) and 10 (52.6%) consuming 20.9% and 7.8% of the total cumulative expenditure respectively. The drugs in class A require strict managerial control, accurate-data driven forecasting of demand, a close check on drug budget control, minimum safety stock, staggered purchase orders, frequent stock taking and judicious purchasing, stocking, issue and inspection policy (59).

Category B drugs require moderate control while category C require minimum control measures in inventory management. Drugs in class C can be maintained with looser control and with a high safety stock level.

There is paucity of studies on ABC analysis focusing pediatric anticancer drugs in the region. However, few studies done in Ethiopia and Kenya on general anticancer drugs have comparable results to the present study (59,(98).

Evaluation of prices was done to compare the local consumer price against the international reference price through median price ration (MPR). According to World Health Organisation, prices of medicines should not be more than four times the international reference (99). In the present study 50% of the medicines were available at prices below the international reference prices (median price ration < 100%). 5-Fluorouracil had a price that was more than four times the international reference price. The findings of this study show that anticancer drugs are priced fairly. The fair prices could be explained by government subsidies, removal of taxes on medicines, as well as favourable percentage mark-up on pharmaceuticals. The results of this study are congruent to a study done in Ghana by Mensah et al (2021) found who found the median price of anticancer medicines used in childhood cancer to be less than four (62). Several other studies from the globe also support the findings of this study (100).

In view of the favourable local consumer prices, Government of Malawi should be commended and encouraged to continuously pursue policies that ensure the prices of the generic anticancer medicines frequently used in management of childhood cancers are within acceptable ranges. The strategies should include continued pooled procurement, price negotiations and using international reference prices as tool to aid price negotiations (101). Furthermore, government should take an active role in dictating profit mark-up for pharmaceuticals and increase budgetary allocation towards procurement of anticancer drugs used in management of

childhood cancers. These strategies will guard the prices of anticancer medicines as well as ensure the prices are within ranges where most Malawians can afford.

The cost associated with each childhood cancer was also evaluated to determine which cancer was costly. Burkitt's lymphoma was the costly cancer followed by, retinoblastoma, kaposi's sarcoma, hodgkin's and non-Hodgkin's lymphoma. On the other hand, hepatoblastoma, immature teratoma and neuroblastoma were less costly. The high cost of burkitt's lymphoma in the present study is attributed to high prevalence of the disease in Malawi, and in the region. Hesseling et al (2003) observed that burkitt's lymphoma accounts for 50% of all childhood cancer (32). Therefore, high number of cases lead to high costs of treating the disease. In Uganda, Denburg et al (2019) observed similar results, however they also observed that treating burkitt's lymphoma with locally tailor made protocols was actually cost effective (47).

Further cost analysis was performed to establish the estimated average cost of chemotherapy prescription for each cancer type. Low grade glioma proved to be the most expensive cancer prescription (526.55USD), followed by burkitt's lymphoma (437.20USD), hodgkin's lymphoma (372.10) and germ cell tumor (335. 37USD). The least costly prescription was that of wilm's tumor and hepatoblastoma. There is deficit of literature on costs associated with management of low-grade gliomas in Africa. Furthermore, there is no universal consensus on treatment protocols although surgery is quite common. Despite lack of adequate literature Ooi et al (2022) confirmed that management of low grade gliomas is associated with high drug costs in low and middle income countries (102). The high drug cost stems from lack of access to neuroimaging facilities which limits timely diagnosis and treatment.

Assessment of cost associated with treatment of each type of childhood cancer showed that, most cancer treatment required less than 1000 USD. These results agree with a study done by Hesseling et al (2003) who found the costs of drug therapy in management of childhood cancer to be less than 1000 USD (32). Unlike the present study, the cost of management of retinoblastoma in Ivory Coast and Democratic Republic of Congo was nearly 2000 USD (103). Furthermore, a study done in 2018 in Mali found the cost of treating retinoblastoma to be 1700 USD (103). These two studies are in sharp contrast with the figures reported in this study because the contrasting studies conducted a full cost evaluation and not cost of chemotherapy prescription.

Given the estimated average cost of chemotherapy prescription for each cancer, further assessment was done to examine the affordability of chemotherapy prescription to patients and

their individual families. Affordability of medicines is considered reasonable if the cost of treating a disease is equal to or less than a day wage of the lowest paid government worker (62). In the present study, cancer treatments required more than one working day to pay for a day's treatment, which is considered unaffordable for most patients. For example, a lowest paid government worker in Malawi would need to work 184.47 and 91. 27 days to afford a burkitt's lymphoma and Kaposi's sarcoma prescriptions respectively. This study agrees with a study done in Tanzania by Yohana et al (2011) who found that cancer therapy was not affordable for most patients (104). Another study done in Pakistan by Sarwar et al (2018) agreed with our study that chemotherapy medicines are not affordable for most people (105). In view of these results, the Government of Malawi should make deliberate policies to make anticancer therapy affordable to many Malawians. Contingent plans must be devised on how the government and individual families can pay for chemotherapy prescriptions when there is lack of donor support. Currently, donors cover almost 100% of the cost of cancer treatment in children.

5.1 STUDY LIMITATIONS

The study was affected by poor patient records and missing data in the files which is an inherent problem in retrospective study designs. The study was done at a single site, Queen Elizabeth Central Hospital, hence the results can hardly be generalized. Cost analysis concentrated on the cost of chemotherapy prescription which does not give an accurate picture of the total costs incurred during cancer treatment.

6 CHAPTER SIX: CONCLUSION AND RECOMMENDATIONS

6.1 CONCLUSION

The selected prescribing indicators show that drugs are being used rationally in the oncology unit. Despite unaffordability of anticancer treatment, anticancer drugs are priced fairly in Malawi. Deliberate efforts and policies should continuously be pursued to ensure that prices of anticancer drugs should remain within the acceptable range as recommended by Malawi government as well as the World Health Organization.

6.2 RECOMMENDATIONS FOR FUTURE RESEARCH

A prospective prescription patterns and cost analysis study needs to be conducted at QECH oncology pediatric unit. Prospective studies generate quality data compared to retrospective studies. Similar study should also be conducted at the other three tertiary hospitals in Malawi to check if the results will be comparable. Furthermore, it will be more informative to conduct a full economic evaluation study. A full economic study will give a better picture of the cost and cost-effectiveness of the available cancer treatment options.

6.3 RECOMMENDATIONS FOR POLICY AND PRACTICE

The present study reported that chemotherapy drugs were rationally prescribed. Healthcare workers at Queen Elizabeth central hospital should be appreciated through recognition as well as recommending them for further studies. The Government of Malawi and all stakeholders should pursue deliberate policies and strategies to ensure prices of anticancer drugs continue to be within recommended range. The policies and strategies should include; pooled procurement, price negotiations and use of international reference price index as a tool to aid price negotiations. Furthermore, the government should take an active role in dictating profit mark-up for pharmaceuticals. These strategies would in turn address issues of unaffordability of cancer drugs in Malawi.

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8 APPENDICES

8.1 APPENDIX 1: ELIGIBILITY CRITERIA

ELIGIBILITY CRITERIA

- **All selected patient files that satisfy the following inclusion criteria will be eligible for this study**:

    1. Children aged from 0 to 18 ☐
    2. Have definite diagnosis of childhood cancer ☐
    3. Prescribed at least one anticancer drug ☐
    4. Should complete at least 75% of the therapy ☐
    5. Were on therapy between Jan 2017 to Dec 2020 ☐

- **Patient files that meet below exclusion criteria will be ineligible for this study**:

    Patient files with incomplete information. ☐

8.2 APPENDIX 2: DATA COLLECTION FORM

DATA COLLECTION FORM	
FORM NUMBER:	DATE FILLED:

1. BIO-DATA

i. Date of first appointment……

ii. Sex ☐ Female ☐ Male

iii. Age at first diagnosis (Years) ……

iv. Weight……. BSA……

v. Height……. MUAC……

vi. Resident

vii. Eligibility: ☐ Yes ☐ No

2. DISEASE AND DIAGNOSTIC INFORMATION

i. Type of childhood cancer:

☐ Burkitt's' Lymphoma ☐ Wilms Tumor

☐ Kaposi sarcoma ☐ Retinoblastoma

☐ Acute Leukemia ☐ Others (Specify)…….

ii. Cancer Stage at Diagnosis: ☐ Stage I ☐ Stage II

☐ Stage III ☐ Stage IV

iii. Other comorbidities: ☐None ☐ HIV/AIDS ☐ Malaria

☐ Malnutrition ☐ Tuberculosis

☐ Others (specify)……

3. ADJUNCT THERAPY USED

Drugs used	**Unit cost**	**Total units used**	**Total cost**

4. CHEMOTHERAPY TREATMENT INFORMATION

Drugs and drug regimen used	**Cost per regimen**	**Scheduled sessions**	**Total cost**

5. Outcome of childhood cancer treatment at the end of review period

☐ Remission

☐ Death

☐ Disease progression

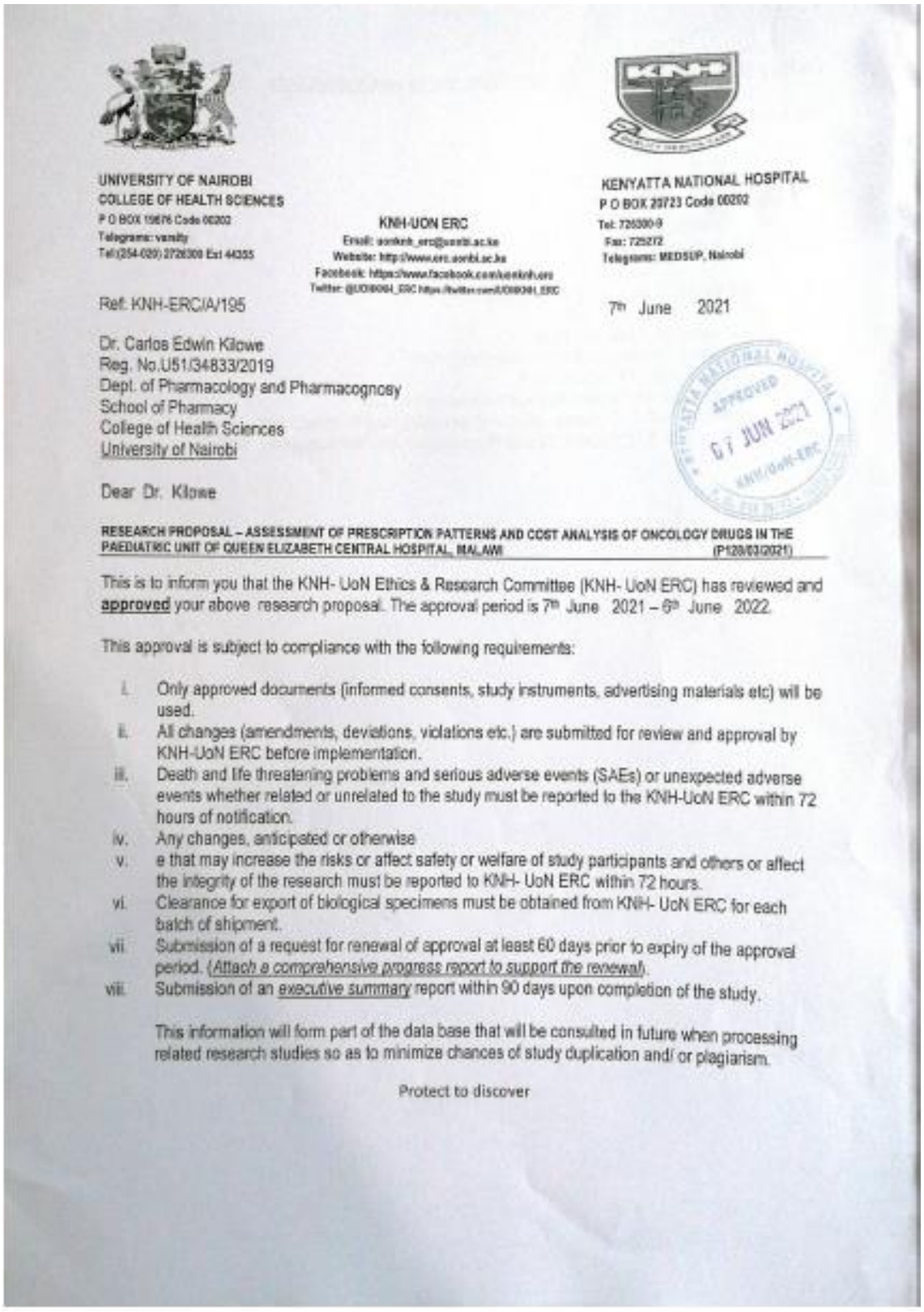
☐ Others (Specify)…….

8.3 APPENDIX 3: WHO RATIONAL DRUG USE PRESCRIBING INDICATORS

Table 8.1: WHO rational drug use prescribing indicators

Indicator	Purpose	Calculation
Average number of drugs per encounter.	To measure the degree of polypharmacy	Average: (Total number of different drug products prescribed) ---------- (Total number of encounters surveyed.)
Percentage of drugs prescribed by generic names.	To measure the tendency to prescribe by the generic names.	Percentage: (Number of drugs prescribed by generic names) ----------×100 (Total number of drugs prescribed)
Percentage of drugs prescribed from essential drug list or formulary.	To measure the degree to which practices confirms to a national drug policy as indicated by prescribing drugs from EML or formulary	Percentage: (Number of products prescribed which are listed on the essential drugs list or local formulary) ----------×100 (Total number of products prescribed, multiplied.)

8.4 APPENDIX 5: KNH-UON ETHICS APPROVAL



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7th June 2021

Dr. Carlos Edwin Kilowe
Reg. No.U51/34833/2019
Dept. of Pharmacology and Pharmacognosy
School of Pharmacy
College of Health Sciences
University of Nairobi

APPROVED 07 JUN 2021 KNH/UoN-ERC

Dear Dr. Kilowe

RESEARCH PROPOSAL – ASSESSMENT OF PRESCRIPTION PATTERNS AND COST ANALYSIS OF ONCOLOGY DRUGS IN THE PAEDIATRIC UNIT OF QUEEN ELIZABETH CENTRAL HOSPITAL, MALAWI (P128/03/2021)

This is to inform you that the KNH- UoN Ethics & Research Committee (KNH- UoN ERC) has reviewed and **approved** your above research proposal. The approval period is 7th June 2021 – 6th June 2022.

This approval is subject to compliance with the following requirements:

i. Only approved documents (informed consents, study instruments, advertising materials etc) will be used.
ii. All changes (amendments, deviations, violations etc.) are submitted for review and approval by KNH-UoN ERC before implementation.
iii. Death and life threatening problems and serious adverse events (SAEs) or unexpected adverse events whether related or unrelated to the study must be reported to the KNH-UoN ERC within 72 hours of notification.
iv. Any changes, anticipated or otherwise
v. e that may increase the risks or affect safety or welfare of study participants and others or affect the integrity of the research must be reported to KNH- UoN ERC within 72 hours.
vi. Clearance for export of biological specimens must be obtained from KNH- UoN ERC for each batch of shipment.
vii. Submission of a request for renewal of approval at least 60 days prior to expiry of the approval period. (*Attach a comprehensive progress report to support the renewal*).
viii. Submission of an executive summary report within 90 days upon completion of the study.

This information will form part of the data base that will be consulted in future when processing related research studies so as to minimize chances of study duplication and/ or plagiarism.

Protect to discover

8.5 COMREC ETHICS APPROVAL

CERTIFICATE OF ETHICS APPROVAL

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

P.07/21/3363 - Assessment of Prescription Patterns and Cost Analysis of Oncology Drugs Used In the Peadiatric Unit of Queen Elizabeth Central Hospital, Malawi by Carlos Edwin Kilowe

On 06-Sep-21

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

06-Sep-21

Prof. E. Umar-Chairperson (COMREC) — Date

Approved by College of Medicine 06-Sep-2021 (COMREC) Research and Ethics Committee

8.6 QECH-PAEDS LETTER OF SUPPORT FOR RESEARCH STUDY

QUEEN ELIZABETH CENTRAL HOSPITAL

COLLEGE OF MEDICINE

Department of Paediatrics and Child Health
Chichiri, Blantyre 3, Malawi

Date:

The Chairperson,

Dear Chairperson

SUBIECT: PERMISIOM TO SUMBMIT A STUDY PROPOSAL TO ETHICS COMITTEE

The department of Paediatrics and Child has agreed to grant permission to Carlos Edwin Kilowe to carry out a study titled **Prescription Patterns and Cost Analysis of Oncology Drugs Used In The Paediatric Unit of Queen Elizabeth Central Hospital, Malawi** in the Paediatrics and child Health department.

The study was presented the to the department and following the discussion by the department members, it was agreed that the study is relevant to the improvement of care of the Paediatric patients.

Yours sincerely,

Dr Jenala Njiramadzi-Maleta MBBS (MW), MMed Paeds (Mw,) FC Paeds (SA), Cert. Paed Critical care (SA)
Lecturer, Paediatrician and Paediatric Intensivist and Clinical Lead PICU,
Director of Research, Department of Paediatrics and Child Health
University of Malawi, College of Medicine.

Dr Yamikani Chimalizeni. MBBS (Mw), MMed Paeds (Mw), FC Paeds (SA), Cert. Paed. Cardiology (SA)
Senior Lecturer, Paediatrician and Paediatric Cardiologist,
Academic I-lead and Academic HOD, Department of Paediatric s and Child Health
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Dr George Chagaluka. MBBS (MW), MMed Peads (MW), Cert. Paed. Oncology (SA)
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