FACTORS ASSOCIATED WITH DRUG THERAPY PROBLEMS IN THE MANAGEMENT OF PEDIATRIC WILMS TUMOR PATIENTS AT KENYATTA NATIONAL HOSPITAL

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UNIVERSITY OF NAIROBI DECLARATION OF ORIGINALITY

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Title of work:	Factors associated with drug therapy problems in the management of pediatric Wilms tumor patients at Kenyatta National Hospital

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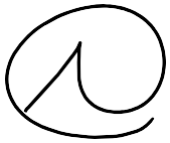

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SUPERVISOR'S APPROVAL

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ABBREVIATIONS AND ACRONYMS

ADR	Averse Drug Reaction
AOR	Adjusted Odds Ratio
BMI	Body Mass Index
BSA	Body Surface Area
CI	Confidence Interval
COR	Crude Odds Ratio
CT	Computed Tomography
DRP	Drug Related Problems
DTP	Drug Therapy Problems
GCSF	Granulocyte Colony Stimulating Factor
IV	Intravenously
Kg	Kilogram
KNH	Kenyatta National Hospital
MRI	Magnetic Resonance Imaging
NCCN	National Comprehensive Cancer Network
NHIF	National Health Insurance Fund
OR	Odds Ratio
PCNE	Pharmaceutical Care Network Europe Association
RG	Regimen
SD	Standard Deviation
SIOP	The International Society of Pediatric Oncology
UoN	University of Nairobi
WBC	White Blood Cells
WHO	World Health Organization
WT	Wilms Tumor

ABSTRACT

Background

Drug therapy problems are a common issue during the therapeutic management of pediatric cases of Wilms tumor. These drug therapy problems lead to events which require further medical attention therefore complicating the therapy process and lead to a consequent increased cost of treatment. This study sought to assess the drug therapy problems observed during management of Wilms tumor and their associated factors among pediatric patients in Kenyatta National Hospital.

Methodology

This was a hospital based cross sectional study where the patients and their guardians were interviewed, and data collected using a questionnaire and all other required data abstracted from patient files using a data abstraction tool. The patients included were pediatric patients between 0 and 15 years of age who received treatment within the study period of February 2023 to August 2023. Chi square test for independence and multivariate regression analysis were used to determine presence of significant association between drug therapy problems and associated factors.

Results

Out of a sample size of 66 pediatric Wilm's tumor patients assessed, the median age was 4 years (IQR 2 – 6). There were 35 female and 31 male patients with Vincristine as a single drug and Cyclophosphamide/ Doxorubicin combination the most common drugs used. The drug therapy problems found were the need for additional therapy which was the most prevalent, followed by adverse drug reactions and unnecessary drug therapy. In this study, stage I of Wilms tumor was associated with unnecessary drug therapy (p-value=0.003).

Conclusion and Recommendations

The drug therapy problems found in this study were the need for additional therapy, adverse drug reactions and unnecessary drug use which was associated with stage 1 of disease. Continuous review and education of patients during therapy would be beneficial to reduce occurrence of drug therapy problems.

CHAPTER ONE INTRODUCTION

1.1 Background

A drug therapy problem (DTP) is defined as an event that patients experience, which is not desirable, that involves or is suspected to involve therapy with medications and that interferes with achieving the goals of therapy and requires medical intervention (1). Similarly, a DTP may be defined as a detrimental event which impedes attainment of desired goals, and which have a negative effect on the patient's health in the absence of appropriate management. DTPs present a challenge as they affect the patient's outcomes which result in longer hospital stays, increased cost of treatment, increased morbidity and mortality (2). In management of cancer patients, there is a great risk of DTP occurrence due to the toxic nature of chemotherapeutic agents (3). Chemotherapeutic agents also have a high probability of causing adverse reactions due to their narrow therapeutic range and their potential to cause serious adverse effects even at therapeutic doses (4). These patients therefore have a high incidence of problems arising due to therapy and provide a major hurdle to achieving the goals of treatment. DTPs are classified into several categories including unmanaged indication, medication use without indication, sub therapeutic dose, overdose of medication, adverse drug reaction, inappropriate drug selection, and failure to receive the prescribed medication (1). Modalities that may be used to reduce the effects of these drug therapy problems of chemotherapeutic agents include dose reduction, use of cyto-protective agents, use of growth factors and use of alternative agents or drug analogues (5).

Drug therapy problems result in healthcare costs worth billions of dollars annually in America (1). DTPs occur worldwide with studies conducted in specific countries showing a prevalence of 3.2% in France, 6.2% in Germany, 1.8% in India among hospitalized patients (6). A study on DTPs among cervical cancer patients at KNH showed a prevalence of 93.8% with adverse drug reactions being the most prevalent at 69% and drug interactions at 47% (7).

Wilms tumor accounts for more than 90% of primary renal tumors in the pediatric population and is therefore the most prevalent primary renal tumor (8). Among all

childhood cancers, WT accounts for about 5% of childhood cancers worldwide (9). Failure to compete therapy as prescribed and difficulty in accessing healthcare facilities are the most frequent factors that are associated with unfavorable outcomes. Financial support, establishment of networks and multidisciplinary teams has improved overall survival in some countries although the effects of therapy and consequently, incomplete therapy remains a challenge (10). In Kenya, WT occurs in about 8% of pediatric cancers, mostly between 1 and 5 years of age with its highest frequency among 3-year-old children (1). The outcome of therapy depend on timely diagnosis, access to treatment, therapy, occurrence and management of therapy related adverse effects and comorbidities (10).

DTPs led to a sub optimal health related quality of life as observed by Abegaz *et al.* Patient treatment outcomes improve as a result of identification of DTPs and management of therapy related events. Therefore, this study investigates the effects of drug therapy on the patient, the issues encountered during therapy and the associated factors of therapy problems in the process of disease resolution.

1.2 Problem Statement

Treatment with chemotherapeutic agents are associated with development of DTPs due to toxicity and the complex nature of the drugs and regimens used while cancer patients also carry a greater potential of having comorbidities which further complicates their treatment (11). Patients with oncology related issues also require multiple drug therapy in order to address the cancer, manage comorbidities and also the adverse effects of this medication therefore predisposing them to a great risk of developing DTPs (12). In management of cancer in Kenya, DTPs are experienced mostly as drug-drug interactions due to polypharmacy, ADRs and need for additional therapy due to failure to receive medications or an untreated indication (7).

In Kenya, the incidence of WT has risen from 5% in 2001 to 8.5% in 2021 (7). Although outcomes of Wilms tumor therapy have improved over the past few decades, important therapy issues still remain, including the efficacy of therapy, drug therapy problems and side effects of medications used in management. This study will therefore investigate the medications used in therapeutic management of Wilms tumor among pediatric patients,

identify the drug therapy problems among these pediatric patients and outline the factors of problems in therapeutic management of Wilms tumor in pediatric patients.

1.3 Research questions

i. What are the medications used in therapeutic management of Wilms tumor in pediatric patients?

ii. What are the DTPs among pediatric patients with Wilms tumor?

iii. What are the factors associated with DTPs in therapeutic management of Wilms tumor in pediatric patients?

1.4 Objectives

1.4.1 Main objective

To assess DTPs and the associated factors among pediatric patients with Wilms tumor at KNH

1.4.2 Specific objectives

i. To determine the medications used in management of Wilms tumor among pediatric patients.

ii. To determine DTPs among pediatric patients with Wilms tumor

iii. To determine the associated factors of DTPs in therapeutic management of Wilms tumor in pediatric patients

1.5 Significance of the study

In order to achieve high quality health care, DTPs should be identified and managed (13). Conducting research on the drug therapy and treatment outcomes is crucial in identification, prevention and management of adverse events in therapeutic management of Wilms tumor and therefore improve the quality of life during treatment among children receiving therapy. Based on the results obtained from this study, recommendations will be made to improve therapy for Wilms tumor patients.

CHAPTER TWO LITERATURE REVIEW

2.1 Introduction

A drug related problem is defined as an event that is, or might be wrong in drug therapy, that may or may not be anticipated (14). Drug related problems are classified in order to ease the identification of the most common DTPs and the appropriate course of action in order to mitigate these problems. DTPs, which are estimated to occur in about 20% of patients, involve an event which potentially interferes with the patient's therapy and prevents the patient from achieving an optimum outcome of medication therapy (14). A study in America showed that 28% of hospital visits are related to use of medication and DRPs and of those, 70% are preventable (15). In another study conducted in Australia, up to 3% of admissions in hospitals are attributable to adverse drug reactions (16).

A systematic review of classification of medication related problems conducted in 2014 provided guidance on the classification of DTPs for use in research and in the pharmaceutical therapy process. 14 classification systems were developed for identifying and consequently grouping the DTPs identified in patients in order to ease the therapy process. Furthermore, different terminologies have been used to allude to therapy related issues such as medication errors (17), medication related problems (18), treatment related problems (19) and drug related problems (16). Manley *et al.* argued that drug therapy problem should replace other terms when referring to therapy related issues as it views these issues from a patient's perspective which should be the scope of pharmaceutical care (20).

In a meta-analysis of therapy challenges and outcome of WT therapy in Africa, 22% of cases in one group reported treatment related issues as the cause of mortality while in another group, mortality due to treatment related issues was at 17.3% (21). Another study showed that 54% of WT patients experienced DTPs during

the study period with adverse drug reactions being most prevalent at 38.5% (22). Different studies therefore have different prevalence and patterns of DTPs.

The Cipolle, Morley, Strand classification system provides a rational, comprehensive and systematic process of identifying and managing drug related problems. It provides a

hierarchical structure to the problem resolution process unlike the other classification systems for example the PCNE classification system (1,23). The Hepler and Strand classification system will be employed in this study for classification of DTPs among pediatric WT patients.

2.2 Drug Therapy Problems

2.2.1 Needs additional drug/ indication not managed.

This DTP includes situations where an indication is identified but not managed, preventive therapy is required for a condition or synergy is required to manage a condition (1). In WT therapy, several conditions may arise in the course of therapy either due to the health status of the patient or due to the toxic nature of chemotherapeutic drugs. It may also be due to a problem or potential problem with the effect or lack thereof of pharmacotherapy (24). The expected progress or goals of therapy are therefore not met due to suboptimal effect of the drug given in the required dose, frequency and duration (15). A study of DTPs in a hospital in Jordan found that need for additional therapy had the highest prevalence among DTPs identified while another study by Koh *et al.* identified this DTP in 31.3% of admissions due to DTPs (12). Common indications reported that are not managed include cough, urinary tract infection ad anemia (25).

2.2.2 Medication use without indication.

This DTP is observed when there is no pathological need for which a given drug is required for at the point when it is prescribed (1). In a study of medication use among cancer patients receiving palliative care, polypharmacy with more than 5 drugs was found in 45.2% of patients while excessive polypharmacy with more than 10 drugs was found in 8.6% (26). Another study on patients on multiple therapy reported that 7.5% of the patients had medication that was unnecessary (27). Furthermore, in a study conducted in an oncology unit in Ethiopia, 16.9% of the patients had unnecessary drug therapy (28).

2.2.3 Incorrect dosage

Dosage issues present a therapy problem as an ineffective dose of a drug may not give the desired therapeutic response. In some cases, the dose may be too high thus resulting in toxicity. Reduced frequency and short duration of administration of a drug constitute a dosage lower than the required dose while a short dosing interval and a longer duration of drug use constitute a higher dosage than required (1). Sisay *et al.* observed that dosing was a key DTP among chemotherapy patients with 37.9% having an incorrect dose (29). In another study on DTPs among hospitalized cancer patients, dose selection problems were observed in 24.2%

of the patients and among them, the dose was too low in 62.5% of them (15). In Minnesota, the second most prevalent DTP was the need to alter the dose of patients' medication. The assessor noted that the medication was correctly prescribed, but the therapy was ineffective because the dose taken was insufficient to achieve the therapeutic goals. About 25% of these cases require an increase in the prescribed dose (29).

2.2.4 Failure to receive the prescribed medication.

This DTP may be because of a number of factors. Deviation from the regimen may be due to patient factors that render them unable to receive treatment, for example due to deranged hematological parameters or presence of an infection. In one study on hospital admissions as a result of drug therapy, DTPs were seen in 76.1% of the patients where deviation from the guideline regimen accounted for 42.2% (30). The cause of the DTP may also be associated to the dispensing process (31). The drug may or may not reach the patient in the required form and strength with the required instructions and therefore taken by the patient in the required manner for the desired therapeutic effect (32). A study in Africa showed that in 11.11% of studies conducted, lack of drugs was a barrier to effective management of the disease (23).

2.2.5 Adverse drug reactions

The WHO defines an ADR as an unintended drug response which is harmful and occurs in doses prescribed for therapy, prophylaxis or diagnosis (33). Adverse effects of chemotherapeutic agents are as a result of their therapeutic activity which targets all

rapidly dividing cells, not only the cancerous ones (34). Frequent adverse events of these agents include nausea and vomiting, alopecia, impaired renal function, fever, electrolyte imbalance and myelosuppression. A study by Lau *et al.* concluded that cancer patients experience at least one adverse reaction during the therapy process and over 40% experience more than 2 ADRs (35).

Chopra *et al.* observed that in a 2-year study period, the incidence of ADR was 58.6% with the most affected system being the gastrointestinal tract with 43.7% followed by the skin with 24.9% and hematological system with 23.2% (36). In a study on patterns of ADRs due to chemotherapy in Bangladesh, 58% had alopecia, 52% had nausea and vomiting, 20% experienced stomatitis and 16% had myelosuppression. The other ADRs observed were impaired renal function (16%), impaired hepatic function (6%), inflammation (20%), headache (10%) and constipation or diarrhea (20%) (37).

2.3 Associated factors of DTPs

The most common associated factors of DTPs cited are age and gender. The reason for increased susceptibility with age could be due to pathological and physiological changes with advancement in age which affect the pharmacokinetics of a drug (31). A study on pattern of ADRs due to chemotherapy showed that differences in age related to difference in prevalence of DTPs (39). However, the limitation of this study to pediatric patients serves as limitation to expression of the effect of age on the prevalence of DTPs.

A study conducted in Nepal showed that 60% of men developed DTPs compared to 40% of women (38) while Blacker et al. observed that DTPs occurred more commonly in female patients than male and further attributed this finding to different stages of female development like puberty and pregnancy (39). Different studies have therefore shown significant variations in prevalence of DTPs between male and female gender.

Other factors that are related to DTPs include polypharmacy, comorbidities, renal function, cancer stage and the treatment regimen used. Saini *et al.* observed that DTPs in oncology, were common in single drug regimens and were even more prevalent in combined drug regimens (40). A study on drug related problems in chemotherapy showed

that comorbidities (OR: 3.1, p<0.003), polypharmacy (OR: 1.4, p=0.028) and length of hospital stay (OR:2.6, p<0.00) were positively and significantly associated with occurrence of DTPs (29). Another study conducted in Florida showed that the number of medications, age were the factors associated with DTPs with the strongest association with DTP incidence being number of medications used (41).

2.4 Wilms tumor burden

Wilms tumor primarily affects children especially those between the ages of 3 and 5. It becomes much less prevalent as children move beyond that age bracket though it can still occur to the age of 9. Most cases of Wilms tumor occur sporadically (13). That is, they occur as a result of mutations in cells that usually happen after birth. But on rare occasions, a genetic defect can increase the risk of development of WT. After taking a complete medical history and examination, tests done to narrow down to WT disease include blood chemistry tests, renal and liver function tests, coagulation and complete blood test after which imaging is done. Abdominal ultrasound is usually done first as it does not require sedation and usually ascertains presence and origin of a mass. Abdominal CT or MRI is used to evaluate involvement and extent of the identified mass (42). Low survival rates are mostly attributed to high treatment abandonment. Abandonment of therapy contributes a great deal to poor outcomes in pediatric oncology. It mostly affects stages 2 and 3 (8). If the issue is dealt with adequately, the survival rates here could increase. Stage level is also important. Those at stage 1 and 2 have a better chance of survival than those at later stages. Stage-level issues are brought about both by patient delays and health care system delays (43). The latter is caused by the unavailability of qualified personnel or equipment required to make the right diagnoses. Staging is an important factor in deciding the appropriate treatment modality to be used and consequent outcome of therapy, where low stage of disease is associated with better treatment outcomes (23). However, high income countries like the United Kingdom still manage a high survival rate of up to 81% when treating patients at stage 4 (44). So, to improve outcomes, more should be done both on increasing awareness of childhood cancer as well as improving the standards of care.

2.5 Management of Wilms tumor in pediatrics

Management of WT may be done using different modalities. Treatment may involve surgery only, chemotherapy and surgery or it may also involve radiotherapy, depending on various factors like stage of disease, presence of metastases, patients age, tumor weight, whether it is unilateral or bilateral, histology and clinical response to therapy (8).

2.5.1 Staging

2.5.1.1 Stage one

The tumor is confined to the kidney and is excised completely, the tumor surface is intact and is not ruptured before or during surgery. It may also be beyond the kidney but is encapsulated by a fibrous pseudo capsule. The tumor may be located in the renal capsule, intra renal vessels or in the pelvic system (8).

2.5.1.2 Stage Two

The tumor extends beyond the kidney or the pseudo capsule but is completely excised. There is regional extension of tumor infiltrates into blood vessels, lymph nodes and adjacent organs. There is no residual tumor evident beyond the margins of excision (8).

2.5.1.3 Stage Three

Residual non-hematogenous tumor remains and is confined to the abdomen. There may be implants on the peritoneal surface, tumor extension beyond the surgical margins of excision or there is local infiltration of the tumor into vital structures therefore complete resection is not possible (8).

2.5.1.4 Stage Four

At this stage, there are hematogenous metastases and deposits beyond the abdominopelvic region for example to the lung, liver and brain (8).

2.5.1.5 Stage Five

There is bilateral renal involvement at the point of diagnosis (8).

2.5.2 Histological risk Stratification

Tumor histology further classifies the disease based on relative frequency of components within the tumor into low, intermediate and high-risk types. Low risk type involves completely necrotic and resected tumors where there is no evidence of tumor involvement beyond the margins of resection. Intermediate risk type may be regressive where chemotherapy induced changes make up more than two thirds of the tumor, mixed type where there are up to 3 components with none of them making up two thirds of the tumor, epithelial type where epithelial component comprises more than two thirds of the tumor and stromal type where stromal component makes up more than two thirds of the tumor. The high risk type includes the blastemal type where blastemal component comprises more than two thirds of the tumor and disuse anaplastic type where there is non-localized anaplasia in any tumor type regardless of necrosis extent (45).

2.5.3 Treatment

WT therapy follows management of the disease based on different guidelines used worldwide. The NCCN guideline provides for the management of WT with a systematic flow of the process from screening to diagnosis to staging to management with recommendations according to different conditions of the patient, with categories based on evidence and consensus (8). The SIOP guideline gives recommendations for low income setting where there are minimal requirements for management with a curative intent including general and supportive care and social support (46). KNH adopts its management from the SIOP guidelines.

2.5.3.1 Treatment of Localized disease

Two drugs are used for preoperative treatment of localized Wilms tumor. Vincristine 1.5mg/m^2 is used intravenously on days 1, 8, 15, 22 while Actinomycin D is used intravenously at a dose of 45 micrograms per kilogram on days 1 and 15. Post-operative treatment is not required of stage one disease with low risk histology while treatment for intermediate and high risk stage one disease and for stage two and three is as outlined in **table 1 and 2**.

Table 1: Treatment of localized WT as per stage

	Low Risk	Intermediate Risk	High Risk
Stage 1	No	R G 1	R G 3
Stage 2	R G 2	R G 2	R G 4
Stage 3	R G 2	R G 2	R G 4

Table 2: Drugs used for regimens in treatment of WT.

Regimen	Drug	Dosing	Days/ Weeks
RG 1	Vincristine I.V.	1.5 mg/ m^2	Day 1, 8, 15, 22
	Actinomycin-D I. V	45 µg / kg	Day 8
RG 2	Vincristine I. V	1.5 mg/ m^2	Week 1, 2, 3, 4, 5, 6, 7, 8, 11, 12, 14, 15, 17, 18, 20, 21, 23, 24, 26, 27
	Actinomycin-D I. V	45 µg/kg	Week 2, 5, 8, 11, 14, 17,20, 23, 26
RG 3	Vincristine I. V	1.5 mg/ m^2	Week 1, 2, 3, 4, 5, 6,7, 8, 11, 12, 14, 15, 17, 18, 20, 21, 23, 24, 26, 27
	Actinomycin-D I. V	45 µg/kg	Week 2, 5, 8, 11, 14, 17, 20, 23, 26
	Doxorubicin I. V	50 mg/m²	Week 2, 8, 14, 20, 26
RG 4	Cyclophosphamide I. V	450 mg/m²	Day 1, 2, 3 on weeks 1,17, 19, 25, 31
	Doxorubicin I. V	50 mg/ m²	Day 1 on weeks 1, 7,13, 19, 25, 31
	Etoposide I. V	150mg/m^2	Given 21 days after the last course of above 2 drugs
			Day 1, 2, 3 of week 4,10, 16, 22, 28, 34
	Carboplatin I. V	200mg/m^2	Given 21 days after the last course of above. Day 1, 2, 3 of week 4,10, 16, 22, 28, 34
RG 5	Vincristine I. V	1.5 mg/m^2	Week 1, 2, 3, 4, 5, 6
	Actinomycin-D I. V	45 µg/kg	Week 1, 3, 5
	Doxorubicin I. V	50 mg/m²	Week 1, 5

2.5.3.2 Treatment of metastatic disease

Preoperative and postoperative treatment of Wilms tumor follows use of regimens as per **table 3.**

Table 3 Preoperative and postoperative treatment of metastatic WT

	Low risk	Intermediate	High risk
Preoperative	R G 5	R G 5	R G 5
Postoperative	R G 3	R G 3	R G 4
Postoperative Stage 4 With residual post-surgical metastasis	R G 3	R G 4	R G 4

2.5.3.3 Treatment of bilateral disease

Approach to preoperative treatment of bilateral disease follows **table 4.**

Table 4: Preoperative treatment of bilateral WT

	Drug	Dosing	Days/ Weeks
Bilateral WT	Vincristine I. V	1.5 mg/ m^2	Week 1, 2, 3,
	Actinomycin-D I. V	45 μg/ kg	Week 1, 3, 5
Progressive bilateral WT	Etoposide I. V	150mg/ m^2	Day 1, 2, 3 of week 1,4
	Carboplatin I. V	200mg/ m^2	Day 1, 2, 3 of week 1, 4

Postoperative treatment of bilateral disease involves chemotherapy according to stage and histology of individual tumors, with the option of radiotherapy (8).

2.6 Recurrent Wilms tumor

For WT that recurs, management depends on the initial treatment, histology, and location of the recurrent cancer cells. The usual treatment involves surgical removal, if possible, then administer chemotherapy that is different from the first regimen used. If the recurrent tumors are complicated, the children receive a very high dose and a stem cell or bone marrow transplant (32). However, these modalities are still under study.

2.7 Literature gap

As observed from the literature review, cancer patients and by extension WT patients carry a greater potential than other diseases of developing DTPs due to the toxic nature of chemotherapy and the rigorous course of treatment. This may be attributable to gender, age, polypharmacy and comorbidities. Although studies have been done on WT, there is a shortfall of data from Kenya and Africa as a whole concerning the DTPs and associated predictors in WT therapy. This study therefore investigates the prevalence of DTPs among pediatrics with WT as well as exploring the association of different variables to the DTPs identified. Furthermore, this study will provide information about the treatment of WT and identification and management of DTPs.

2.8 Conceptual framework

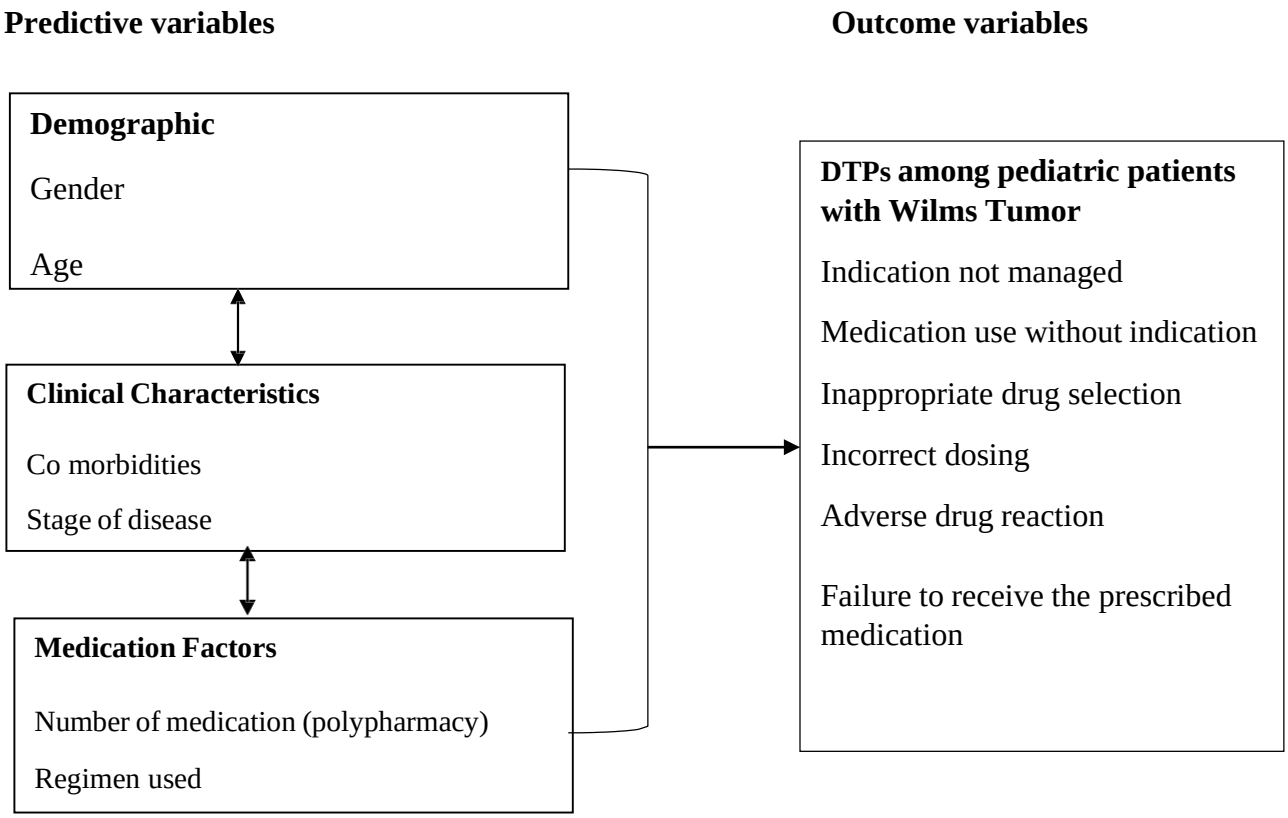

Figure 1: Conceptual Framework

CHAPTER THREE METHODOLOGY

3.1 Research Design

The study design was a hospital based cross- sectional study of pediatric patients with Wilms tumor, diagnosed and managed at KNH during the study period, February 2023 to August 2023. It involved interviewing the patients or guardians on DTPs; ADRs, need for additional therapy, incorrect dose, drug given with no indication or drug not administered as well as the possible factor for the drug therapy problems encountered and the data was collected using a questionnaire and a data abstraction tool. This data was collected from the patients within one week of receiving their chemotherapy medication and at any stage of treatment during the study period. The data was collected multiple times for patients who received multiple drug administrations during the study period. Further information such as red blood cell count, neutrophil count, drugs and dosages used was abstracted from the patient files.

This study design was used as it observed whether drug therapy problems were encountered during management of Wilms tumor and the possible associated factors associated with these DTPs. This study design was feasible as it observed all the intended parameters and due to the limitation of time required for follow up. This study design also had fewer ethical considerations as there was no intervention or interference with the patients' treatment.

The advantage of this design was that the patients were not deliberately treated, exposed or withheld from treatment as the study was carried out, while the selected design also provided a cost effective and efficient tool to meet the study objectives.

3.2 Research Site and Setting

The study area was KNH, which is a referral hospital near the capital of Kenya where majority of the pediatric patients in Kenya are referred for treatment. The hospital is located in Nairobi, the capital city of Kenya, about 3.5 kilometers from the central business district, along Hospital Road, off Ngong Road. It is one of the largest teaching

and referral hospitals with 2000 inpatient beds, 22 outpatient clinics, 24 theatres and 50 wards.

KNH offers comprehensive and affordable cancer treatment with subsidized costs, compared to other hospitals and facilities in the region and also accepts insurance cover from the national insurance body, NHIF, which is affordable and available to all including low- i n c o m e earners who cannot afford other private insurance packages. It therefore provided a good study site as most cancer patients are referred there, admitted and managed.

The study setting was the pediatric oncology ward, 3D, located among the pediatric wards on third floor, ward 1E, an isolated pediatric oncology ward and the outpatient oncology clinic.

3.3 Study population

The study participants were pediatric Wilms tumor patients, between 0 – 15 years of age admitted in KNH for management of Wilms tumor within the study period, February 2023 to August 2023.

3.3.1 Eligibility criteria

3.3.1.1 Inclusion criteria

i. Patients with Wilms tumor

ii. Patients aged 15 years and below.

iii. Patients with informed consent from guardian or parent and informed assent for children over 5 years.

iv. Patients on at least one chemotherapeutic drug for management of WT which has been administered not more than one week prior.

3.3.1.2 Exclusion criteria

i. Psychologically challenged patients without a caregiver or guardian to fill the questionnaire.

ii. Patients with any acute condition that would limit their participation in the study.

iii. Patients under 10 years, without a guardian or caregiver.

3.3.2 Sampling

3.3.2.1 Sample size determination

A study of childhood cancers in referral hospitals in Kenya showed a prevalence of Wilms tumor of 8.5% (9). The Cochran formula was used to calculate sample size for the study. As per information obtained from the KNH statistics department, 213 admissions due to Wilms tumor among pediatric patients were reported between July 2019 and June 2022.

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

Where

N - sample size

Z - critical value associated with level of significance (1.96%)

P - Prevalence of Wilms tumor (8.5%)

d - Margin of error (acceptable random sampling error). Since the outcome variable is categorical, d is set at 0.05.

A standard normal distribution (Z=1.96) with a confidence interval (CI) of 95% was used. The margin of error (d) was set at 0.05 and a prevalence of 8.5% was used in the sample size calculation.

$$N = \frac{1.96^2 * 0.085(1 - 0.085)}{0.05^2}$$

= 119.512

≈120

$$\frac{120}{213} * 100$$

=56.33 %

Since the calculated sample was more than 5% of the known population size, the Cochran finite population correction factor was applied.

$$n = \frac{no * N}{no + (N - 1)}$$

Where,

N - adjusted sample size

No - calculated sample size.

N - Population size

$$n = \frac{120 * 213}{120 + (213 - 1)}$$

= 76.98

= 77

Therefore, the sample size was 77

3.3.2.2 Sampling Technique

Simple random sampling was used to obtain a representative sample. All patients who met the eligibility criteria had an equal chance of study participation. A patient list was obtained from the KNH dispensing record in oncology pharmacy and combined with information from the KNH health records information office. The patients who met the eligibility criteria were taken through the consent form and those willing to take part in the study were interviewed in line with the questionnaire.

For those between 5 to 15 years of age, consent was sought from their parents or guardians in addition to assent from the children themselves, while for those under 5 years, informed consent was sought from their guardians and these guardians were interviewed and the missing data abstracted from the patient files.

3.4 Data collection tool

A pre-tested, structured and modified questionnaire derived from review of different literature was used by the primary investigator to collect information from the patients and their records.

3.5 Pretesting

The forms and procedures were pretested by the principal researcher using 5% of the sample size at KNH one month preceding the study. This allowed for the detection of any inadequacy of the data collection tools. The records used during pretesting were not included in the main study.

3.6 Validity

The validity of this study was ensured by having a well-structured data extraction form which was relevant as per the objectives of the study and the form used simple, appropriate wording. The study site used had a good representation of Wilms tumor among pediatric patients in Kenya and the wider region.

3.7 Reliability

The data collection tool was pre-tested in a pilot study before carrying out the study to ensure no gaps and ambiguities and to improve precision of the tool.

3.8 Data collection techniques

Data was collected from patients using a pre-tested questionnaire by the primary investigator and trained study personnel. Data on drug therapy problems observed in patient management was noted and summarized using a pre-tested data collection tool by the primary investigator.

3.9 Data management

Completion of the data collection tool was assessed after every patient interview was completed and any form with missing information excluded from the study.

Data collected was entered and stored as key-coded data in a modified Microsoft Excel file in a password protected laptop where only the primary investigator had access to. The data was backed up every week using a hard drive, stored under lock and key. The data was cleaned and transferred to STATA version 15.0 for analysis.

3.10 Data analysis

The data was analyzed using STATA version 15.0. Descriptive statistics, frequency, median, mean and percentages was generated for continuous and categorical variables. Continuous data from patient demographics such as age, weight and BMI was summarized as means (SD), if normally distributed and medians [interquartile range] if not normally distributed. Graphs and frequency distribution tables were used to represent the outcomes of the study which are medications used, drug therapy problems and possible predictors. The independent variables were tested for statistically significant association with the probability of DTPs using binary logistic regression analysis to investigate for predictors of DTPs. Binary and multivariable logistic analyses were also used to assess associated factors of DTPs and to control for confounders which were age, gender, polypharmacy, drug regimen used, stage of disease and comorbidities. A p value of less than 0.05 was considered statistically significant for this association.

3.11 Ethical considerations

Approval was sought from the UoN and KNH Ethics and Research Committee before the study was done (KNH-ERC/A/151). Authorization to carry out the study was obtained from the KNH administration. Study serial numbers and codes were used in place of patient names and details as identifiers. The collected data was kept confidential and restricted only to the principal investigator using password protected laptop and locked back up hard drive. The data was used for the purposes of this research only.

CHAPTER FOUR: RESULTS

4.1 Introduction

This chapter describes the results obtained after descriptive and inferential analysis of the data collected. It includes socio demographic results, the regimens used in management and DTPs of the patients and analysis of the factors of the DTPs found.

Sixty-six children who were placed on treatment for Wilms tumor were studied for DTPs. The results are presented according to the study objectives.

4.2 Descriptive analysis

4.2.1 Socio demographic and clinical characteristics

The clinical and demographic characteristics of the 66 patients under study are summarized in **Table 5**.

There were more female (53%) than male (47%) patients. The median age was 4 years, with an interquartile range of 2 to 6 years. Most patients (72.7%) had a BMI below 18.5kg/m^2. Six patients were diagnosed at stage 1, three at stage 2, twenty-one at stage 3, twenty-eight at stage four disease, while among them, thirty-two had left sided disease, twenty-six with right sided disease and eight had bilateral disease. Most patients (56%) were on post-operative therapy.

Table 5: Summary table of clinical and demographic characteristics of Wilms tumor patients receiving treatment at KNH.

Variable	n (%)
Sex	
Female	35 (53)
Male	31 (47)
Age	
<5	46 (69.7)
>5	20 (30.3)
BMI	
<18.5	48 (72.7)
18.5 – 24.9	10 (15.2)
25 – 29.9	8 (12.1)
Stage of cancer	
1	6 (9.1)
2	3 (4.6)
3	21 (31.8)
4	28 (42.4)
5	8 (12.1)
Primary tumor site	
Left Kidney	32 (48.5)
Right Kidney	26 (39.4)
Bilateral	8 (12.1)
Adverse symptoms	
Yes	29 (43.9)
No	37 (56.1)
Treatment phase	
Post op	56 (84.9)
Pre op	10 (15.2)

4.2.2 Summary of symptoms reported by Wilms tumor patients at KNH.

When interviewed, twenty-nine participants reported symptoms that required additional therapy while thirty-seven were faring well without any complaints. The complaints expressed by the patients are shown in **Table 6** with the most prevalent being nausea and vomiting.

Table 6: Symptoms reported by Wilms tumor patients receiving treatment at KNH.

Symptom	Frequency (%)	Symptom	Frequency (%)
Poor appetite	27 (40.9)	Nausea & Vomiting	31 (47)
Weight Change	23 (34.8)	Diarrhea	7 (10.6)
Pain	14 (21.8)	Constipation	8 (12.1)
Dizziness	1 (1.5)	Rash	1 (1.5)
Tinnitus	1 (1.5)	Dehydration	1 (1.5)
Epistaxis	2 (3)	Hyponatremia	19 (28.8)
Hemoptysis	1 (1.5)	Hyperkalemia	23 (34.8)
Hypertension	6 (9.1)	Hematuria	2 (3)
Dyspnea	3 (4.5)	Anxiety	1 (1.5)
Wheezing	2 (3)		
Heart burn	10 (15.2)		

4.2.3 Drugs Used in management of Wilms tumor.

The most common drugs were Vincristine as a single drug in 39.4% of the patients and Cyclophosphamide/ Doxorubicin combination in 21.2% as shown in **Figure 2**.

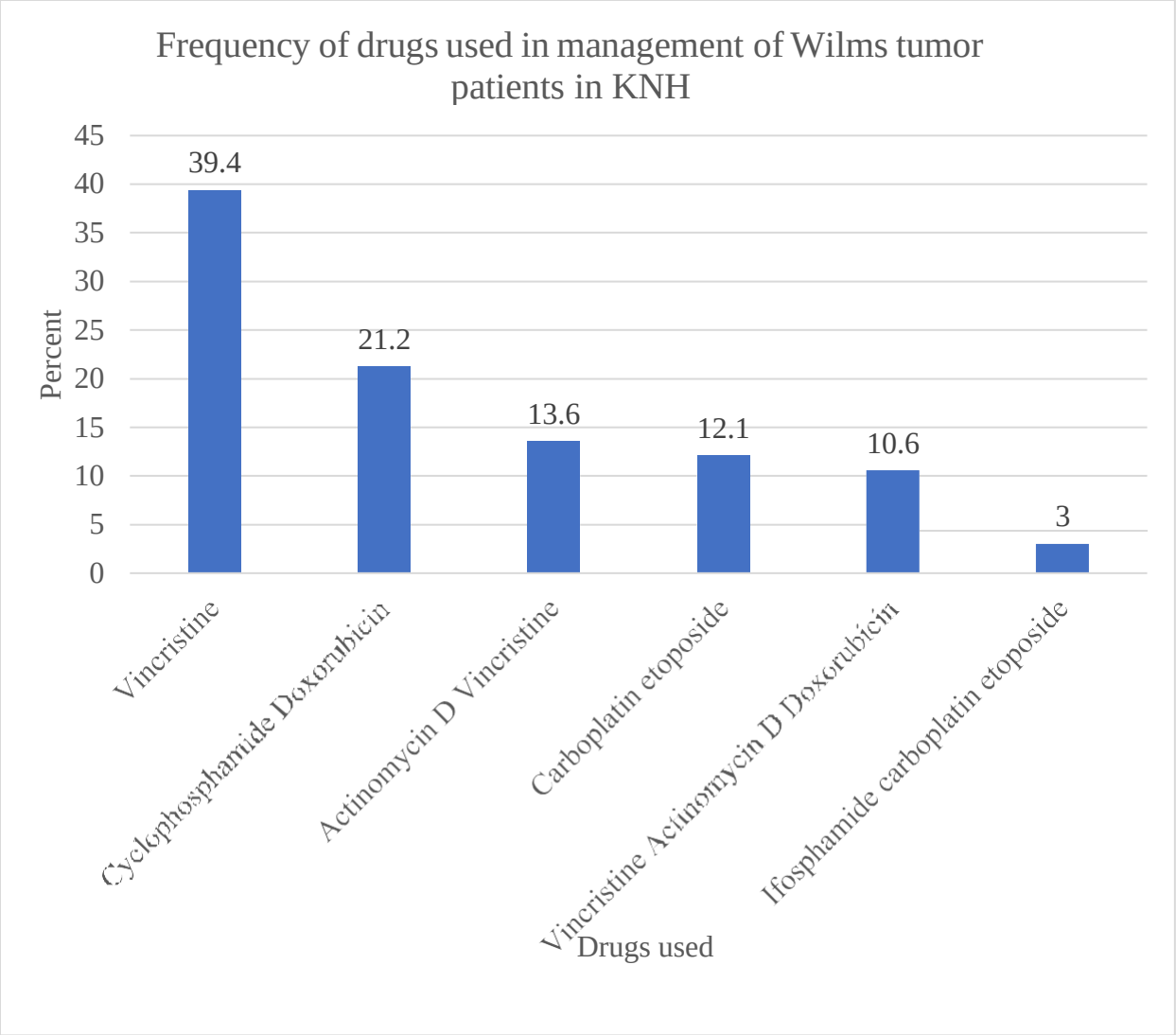

Figure 2: Chemotherapy regimens used in treatment of Wilms Tumor.

4.2.4 Drug therapy problems among pediatric patients with Wilms tumor

The majority of the study participants,55 (83.3%) needed additional drug therapy as summarized in **Figure 3**.

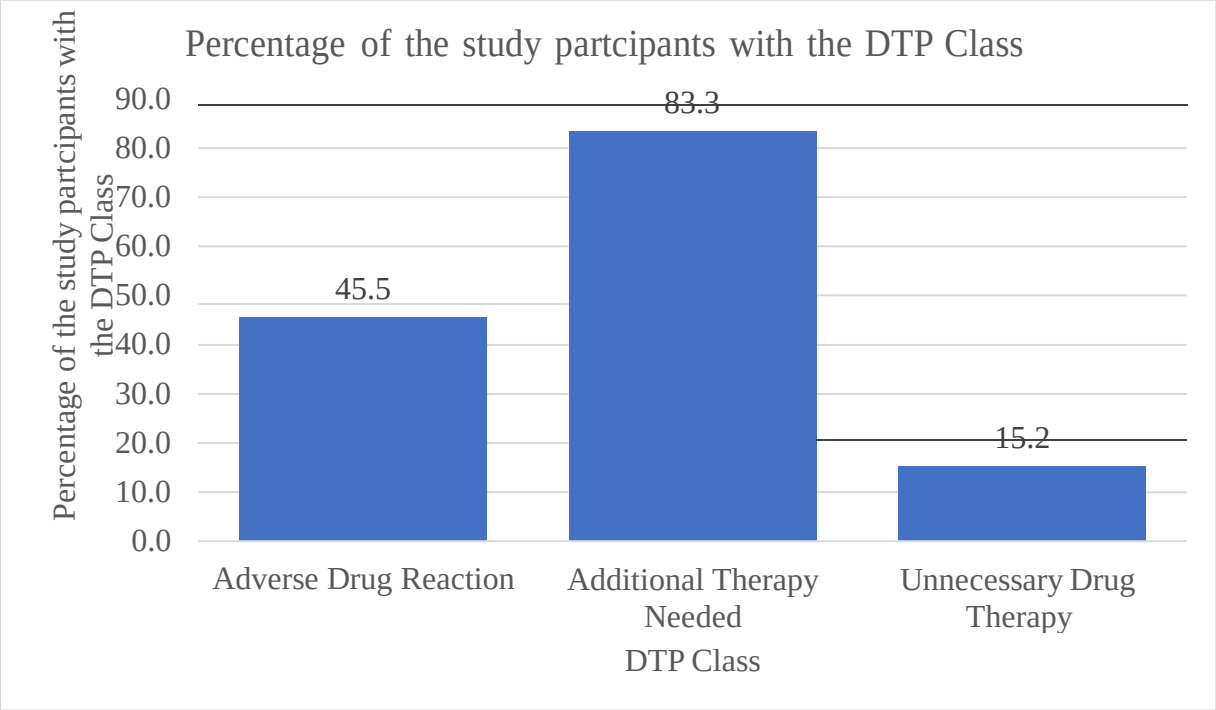

Figure 3: Summary of the DTPs experienced by pediatrics with Wilms tumor.

The specific DTPs found in each class are as shown in **Table 7.**

Table 7: Frequency of DTPs experienced by Wilms tumor patients receiving treatment at KNH.

ADR	n (%)	Needs Additional Therapy	n (%)	Unnecessary Drug Therapy	n (%)
Anemia	16 (19.75)	Hematinic drug	30 (19.61)	Anti-emetic	6 (50)
Leucopenia	15 (18.52)	Hyperkalemia medication	22 (14.38)	Prophylactic antibiotic	1 (8.33)
Pain	13 (16.05)	Analgesic	20 (13.07)		
Hyperkalemia	9 (11.11)	Sodium supplement	18 (11.76)		
Hyponatremia	8 (9.88)	Appetite medication	16 (10.46)		
Nausea	5 (6.17)	Prophylactic antibiotic	16 (10.46)		
Constipation	5 (6.17)	GCSF	7 (4.58)		
Diarrhea	4 (4.94)	Laxative	7 (4.58)		
Hyperacidity	2 (2.47)	Anti-diarrhea	6 (3.92)		
		Antihypertensive	5 (3.27)		
		Antiemetic	3 (1.96)		
		Bronchodilator	2 (1.31)		

4.3: Associated factors of DTPs among Wilms Tumor patients

Chi square test for independence was used to assess the presence of an association between DTPs and other variables. Bivariate and multivariate logistic regression were carried out for the variables with p-value of less than 0.25 to determine the association between the drug therapy problems and independent variables. A p value of <0.05 was used to indicate statistically significant association.

4.3.1 Relationship between various factors and ADRs

There was no significant relationship between sociodemographic and clinical characteristics and ADRs, **Table 8.**

Table 8: Relationship between Socio demographic and clinical characteristics and ADRs for Wilms tumor patients receiving treatment at KNH.

Variable		ADR		P-value
		No	Yes	
Age				
	≤ 5	25	21	0.961
	>5	11	9	
Gender				
	Male	16	15	0.652
	Female	20	15	
Regimen				
	Vincristine	19	21	0.154
		17	9	
	Vincristine/	32	25	0.721*
	Actinomycin-D	4	5	
	Cyclophosphamide/	29	23	0.7
	Doxorubicin	7	7	
	Carboplatin/	31	27	0.719*
	Etoposide	5	3	
	Ifosphamide/	35	29	1*
	Carboplatin/	1	1	
	Etoposide			
	Vincristine/	34	25	0.231*
	Actinomycin D/	2	5	
	Doxorubicin			
Stage				
	1	32	28	0.681*
		4	2	
	2	35	28	0.587*
		1	2	
	3	24	21	0.772
		12	9	
	4	22	16	0.524
		14	14	
	5	31	27	0.719*
		5	3	

Key: ***-** Fisher's Exact was used.

4.3.2 Relationship between various factors and need for additional drug therapy.

The need for additional therapy was significantly associated with use of Vincristine as a single drug and with cyclophosphamide and doxorubicin regimen, **Table 9.**

Table 9: Relationship between Sociodemographic and clinical characteristics and need for additional drug therapy.

Variable		Needs Additional Therapy		P-value
		No	Yes	
Age				
	≤ 5	6	40	0.231
	>5	5	15	
Gender				
	Male	7	24	0.324*
	Female	4	31	
Regimen				
	Vincristine	10	30	**0.040***
		1	25	
	Vincristine/	10	47	1*
	Actinomycin-D	1	8	
	Cyclophosphamide/	5	47	**0.003**
	Doxorubicin	6	8	
	Carboplatin/	9	49	0.611*
	Etoposide	2	6	
	Ifosphamide/	10	54	0.308*
	Carboplatin/	1	1	
	Etoposide			
	Vincristine/	11	48	0.591*
	Actinomycin D/	0	7	
	Doxorubicin			
Stage				
	1	9	51	0.260*
		2	4	
	2	11	52	1*
		0	3	
	3	9	36	0.480*
		2	19	
	4	4	34	0.182*
		7	21	
	5	11	47	0.334*
		0	8	

Key: **Bolded**: statistically significant, *- Fisher's Exact used.

4.3.3 Relationship between various factors and unnecessary drug therapy

There was a significant association between unnecessary drug therapy and stage 1 of Wilms tumor, **Table 10.**

Table 10: Relationship between sociodemographic and clinical characteristics and unnecessary drug therapy for Wilms tumor patients receiving treatment at KNH.

Variable	**Unnecessary Drug Therapy**		**P-value**
	No	**Yes**	
Age			
≤ 5	39	7	1*
>5	17	3	
Gender			
Male	28	3	0.314*
Female	28	7	
Regimen			
Vincristine	35	5	0.456
	21	5	
Vincristine/	49	8	0.616*
Actinomycin-D	7	2	
Cyclophosphamide/	44	8	1*
Doxorubicin	12	2	
Carboplatin/	49	9	1*
Etoposide	7	1	
Ifosphamide/	54	10	1*
Carboplatin/ Etoposide	2	0	
Vincristine/	49	10	0.582*
Actinomycin D/ Doxorubicin	7	0	
Stage			
1	54	6	**0.004***
	2	4	
2	53	10	1*
	3	0	
3	37	8	0.483*
	19	2	
4	31	7	0.498*
	25	3	
5	49	9	1*
	7	1	

Key: **Bolded**: statistically significant, *- Fisher's Exact used.

4.3.4 The overall factors of various Drug Therapy Problems

Vincristine and a combination of cyclophosphamide and doxorubicin had significant association with the need for additional drug therapy at bivariate regression but lost significance at multivariate regression, **Table 11.**

Stage 1 of Wilms tumor was significantly associated with the use of unnecessary drug therapy at bivariate level but could not undergo multivariate analysis as it was the only statistically significant factor.

Table 11: Bivariate and multivariate logistic regression for the drug therapy problems

Type of DTP	Independent variable	Bivariate analysis		Multivariate analysis	
		COR (95% CI)	p-value	AOR (95% CI)	p-value
ADR	Vincristine (No/ Yes)	0.479 (0.173-1.327)	0.157	0.563 (0.195-1.620)	0.286
	Vincristine + Actinomycin D + Doxorubicin (No/Yes)	3.4 (0.609-18.972)	0.163	2.656 (0.45-15.69)	0.281
Need additional drug therapy	Age (≤ 5, >5)	0.45 (0.119-1.696)	0.238	0.587 (0.16-2.95)	0.518
	Vincristine (Yes, No)	8.333 (0.997-69.637)	**0.050**	5.244 (0.516-53.346)	0.161
	Cyclophosphamide + Doxorubicin (Yes, No)	0.142 (0.035-0.577)	**0.006**	0.326 (0.038- 2.773)	0.305
	Stage IV	0.353 (0.092-1.353)	0.129	0.916 (0.135-6.208)	0.929
Unnecessary drug therapy	Stage 1	18 (2.705-119.79)	**0.003**	N/A	

Key: **Bolded**- Statistically Significant

CHAPTER 5: DISCUSSION, CONCLUSION AND RECOMMENDATIONS

5.1: Introduction

This chapter discusses the findings, conclusion, and recommendations of the research.

5.2 Discussion

The chemotherapy regimens administered to pediatric Wilm's tumor patients in this study encompassed a variety of drug combinations. Vincristine was the most frequently used drug, followed by a combination of cyclophosphamide and doxorubicin. The DTP classes found were the need for additional therapy which was the most prevalent, followed by ADRs and unnecessary drug therapy. In this study, stage I Wilms tumor was associated with unnecessary drug therapy. However, ADRs and the need for additional drug therapy had no associated factors.

The use of vincristine for both localized and metastatic disease and combination of cyclophosphamide and doxorubicin for metastatic disease aligns with the SIOP guidelines from where the institutional protocol has been developed (70). This also agrees with findings by Breslow et al and Jesper et al, which found that use of vincristine alone or in combination therapy pre and post operatively was associated with better prognosis for Wilms tumor (47)

Among the DTP classes observed, the majority of the patients had unmet need that required additional drug therapy. The need for hematinics, potassium lowering agents and analgesics were highlighted in the study. A study conducted in pediatric population in Ethiopia reported that there is high prevalence of the need for additional drug therapy among the pediatric population (48). Unnecessary drug therapies were also reported in our study with the overuse of antiemetics and prophylactic antibiotics being highlighted. In concordance with our study, overtreatment of cancer patients has been reported in various studies especially on the overuse of antiemetics and prophylactic antibiotics (48–55). Schnipper et al also reported overuse of cytotoxic drugs in early cancer stages (56). In a general study on drug related problems in

pediatric population in Ethiopia, unnecessary drug therapies were also reported (48). Among the ADRs reported, anemia, leucopenia and pain were highly prevalent. In a study by Wahlang et al, anemia and leucopenia were reported as the most common toxicities though in the same study, vomiting, constipation, and anorexia were the most prevalent (57). Schulte et al found out that procedural and treatment related pain is common among pediatric cancer patients (58). In general, ADRs have been observed in other cancers such as colorectal cancer in adults where they accounted for 45% of the DTPs (71).

There was no association between age and DTPs. A study done in a pediatric ward of Southwestern Ethiopian hospital found out that being a neonate was significantly associated with high prevalence of medication related problems(48). However, in our study setting, pediatric Wilms tumor patients were reviewed by clinical pharmacists making it hard for the DTPs to go unnoticed. Our study also included both neonates and older children further explaining the difference in the study findings. Gender did not show any significant association with any of the documented DTP classes. Lavan et al equally reported that gender was not a predictor of ADRs in cancer patients (59). These findings are however inconsistent with other studies which have reported that the female gender is at an increased risk of developing serious ADRs which even at times may require hospital admission (36,60,61).

Chemotherapeutic regimens used in management of Wilms tumor were not significantly associated with DTPs. Even though the use of vincristine and combination of doxorubicin and cyclophosphamide were significantly associated with the need for additional therapy at a bivariate level, this relationship was lost at multivariate level. Combination therapy which would directly contribute to polypharmacy has been significantly associated with occurrence of DTPs in pediatrics (62). The difference in study findings was probably because even with the combination therapy, pediatrics rarely received five or more drugs that meet the threshold of polypharmacy as defined by Bjerrum et al and Erika et al (26).

Cancer stage was not significantly associated with both ADRs and need for additional drug

therapy. In a study done at a tertiary hospital in Kenya, advanced cancer stage was associated with adverse drug reactions (7). However, it is paramount to note that this relationship was observed in patients aged 50 years and above who in addition to the cancer itself may present with higher prevalence of comorbidities.

Stage I of Wilms tumor was significantly associated with unnecessary drug therapy at bivariate level and being the only significant factor, it was not subjected to multivariate analysis. This stage is associated with better prognosis and require less intensive therapy as described in SIOP protocol (45).

Our study was not without limitations, the main one being the small sample size used. The study however found a high prevalence of patients who require additional therapy, the drugs used which are deemed unnecessary and the ADRs experienced by the patients. This would greatly improve the patient therapy journey during management of Wilm's tumor.

5.3 Conclusion

Different regimens were used in line with SIOP protocol from which the KNH pediatric oncology treatment guidelines are developed. This emphasizes the need for patient centered approach in selection of the regimen to be used in management if Wilm's tumor both pre and post operatively. The study found that the majority of the patients need additional therapy, further supporting need for critical review of Wilm's tumor patients to address any unmet need. Stage 1 of WT was associated with unnecessary drug therapy supporting the fact that this category of patients is typically associated with better prognoses and may require less intensive therapy. Due to the small sample size of the study and the continuous review of treatment by the healthcare workers this study did not find other significant factors. This does not diminish the importance of vigilant monitoring and management of DTPs in pediatric oncology. Every patient is unique, and their response to treatment can vary widely.

5.4: Recommendations

5.4.1: Recommendation for practice

1. A clinical pharmacist should consistently be part of the multidisciplinary team involved in the care of Wilm's tumor patients in order to detect any DTPs.
2. Drug monitoring tools and drug interaction checkers should be developed and continuously used by the clinical pharmacists in the course of therapy.
3. Drug information services need to be well integrated into the care plan as most DTPs would be identified early and managed with correct information regarding drugs given to the healthcare worker and the patient.

5.4.2 Recommendations for future research

1. A prospective cohort study should be done to assess the prevalence and impact of DTPS on the treatment of patients and the associated factors.

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APPENDICES

APPENDIX I: ELIGIBILITY FORM

Subject name / ID …….

Study Number ……

CRITERIA	YES	NO
Inclusion Criteria		
Patients with Wilms tumor		
Patients aged 15 years and below		
Patients with informed consent from guardian or parent and assent from self for those between 5 and 15 years		
Patients on at least one chemotherapeutic drug for management of WT		
Exclusion criteria		
Psychologically challenged patients without a caregiver or guardian to fill the questionnaire		
Patients with any acute condition that would limit their participation in the study		
Patients under 10 years, without a guardian		

Statement of eligibility

The subject is Eligible [__] Not Eligible [_]

APPENDIX IIa: PARTICIPANT INFORMATION AND CONSENT FORM

Study title: Drug therapy problems in management of Wilms tumor among pediatric patients in KNH

Principal investigator

Dr. Andrew Muoria Ngaruiya- Master of Pharmacy, Clinical Pharmacy, University of Nairobi

Supervisors

Dr. G. Mugendi- Lecturer UoN, Dr. D. Wata- Pharmacist KNH Introduction

I, Andrew Muoria Ngaruiya, a postgraduate student at University of Nairobi, department of pharmacology, clinical pharmacy and pharmacy practice, would like to share information with you about a study. The purpose of this consent form is to give you the information you will need to help you decide whether or not to be a participant in the study. Feel free to ask any questions about the purpose of the research, what happens if you participate in the study, the possible risks and benefits, your rights as a volunteer, and anything else about the research or this form that is not clear. When we have answered all your questions to your satisfaction, you may decide to be in the study or not. This process is called 'informed consent'. Once you understand and agree to be in the study, I will request you to sign your name on this form. You should understand the general principles which apply to all participants in a medical research: Your decision to participate is entirely voluntary, you may withdraw from the study at any time without necessarily giving a reason for your withdrawal, refusal to participate in the research will not affect the services you are entitled to in this health facility or other facilities. We will give you a copy of this form for your records.

May I continue? **YES** ☐ **NO** ☐

This study has approval by The Kenyatta National Hospital-University of Nairobi Ethics and Research Committee Protocol No.: __

WHAT IS THIS STUDY ABOUT?

Most patients with cancer are known to be disadvantaged when it comes to health care access, management, and treatment. They have drug therapy problems simply due to the severity of their conditions and multi-medications. In this study, we will ask you to state your experiences with medications and the issues you have with taking medications. Our purpose is to find out whether the medications you are prescribed are working for you or have any trouble, to find out whether they are safe and effective, to find out which drugs the patient is using and identify things the patient is doing or not doing that may be significantly increasing occurrences of Drug Therapy Problems. There will be approximately 77 participants in this study. We are asking for your consent to consider participating in this study.

WHAT WILL HAPPEN IF YOU DECIDE TO BE IN THIS RESEARCHSTUDY?

If you agree to participate in this study, you will be interviewed by a trained interviewer in a private area where you feel comfortable answering questions. Administration of the questionnaires will be at your own convenience, and you are free to skip questions that you do not wish to answer. The interview will last approximately twenty minutes. The interview will cover topics such as your medication history, biodata and medication experiences.

ARE THERE ANY RISKS, HARMS DISCOMFORTS ASSOCIATED WITHTHIS STUDY?

Psychological, emotional, social and physical factors are risks introduced by medical research. However, a concerted effort must be put in place to mitigate the risk. One of the risks that you may encounter is lack of privacy. Your information will be treated confidentially and will use a code number to identify you in a password protected database restricted for access using password protected electronically. Signed copies of your consent participation forms will be kept in a locked office file cabinet. Only the principal investigator and assistant researcher will access the documents. Additionally, during the administration of the questionnaires, this study will consume your personal time. However, we promise to observe time to avoid inconveniencing you as the study participant. Furthermore, this study does not involve any invasive procedures or taking additional medications and therefore does no harm to the

participants.

ARE THERE ANY BENEFITS?

The study findings will help us improve health outcomes especially prioritizing each drug therapy problem identified among pediatric patients with Wilms tumor. By so doing, it will help develop guidelines and protocols that will prevent drug therapy issues from occurring.

WILL BEING IN THIS STUDY COST YOU ANYTHING?

This study will cost you about twenty minutes of your time. ARE THERE ANY REIMBURSEMENTS?

There will be no payments in form of fiscal, gifts or incentives as a result of participation in the study. WHAT IF YOU HAVE QUESTIONS IN FUTURE?

If you have further questions or concerns about participating in this study, you are free to call or send a text message to the Principal Investigator before, during, and after the study. For more information about your rights as a research participant you may contact the Principal Investigator on Email: muoriajunior@gmail.com,and Telephone 0727795073. In addition, you may contact the Secretary/Chairperson, Kenyatta National Hospital-University of Nairobi Ethics and Research Committee Telephone No.: **2726300** Ext: **44102** Email:*uonknh_erc@uonbi.ac.ke.*

WHAT ARE YOUR OTHER CHOICES?

Your decision to participate in research is voluntary. You are free to decline participation in the study and you can withdraw from the study at any time without injustice or loss of any benefits.

Consent declaration form: Participant's Statement

I have read this consent form or had the information read to me. I have had the chance to discuss this research study with a study counselor. I have had my questions answered in a language that I understand. The risks and benefits have been explained to me. I understand that my participation in this study is voluntary and that I may choose to withdraw anytime. I freely agree to participate in this research study. I understand that all efforts will be made to keep information regarding my personal identity confidential. By signing this consent form, I have not given up any of the legal rights that I have as a participant in a research study.

I agree to participate in this research study: **YE** **N**

I agree to provide contact information for follow- **YE** **N**

Participant printed name:

Participant signature

Date

Witness: Date:

I, the undersigned, have fully explained the relevant details of this research study to the participant named above. The participant has understood and has freely given his/her consent.

Researcher's Name: Signature:

Date:

Role in the study:

APPENDIX IIb: PARTICIPANT INFORMATION AND CONSENT FORM (KISWAHILLI TRANSLATION)

Maelezo kuhusu kushiriki katika utafiti

Kichwa cha Uchunguzi: Kuchuguza matatizo ya dawa za tiba kwa wagonjwa ambao ni watoto wenye matatizo ya ugonjwa wa Wilms tumor.

Mchunguzi mkuu

Dkt Andrew Muoria Ngaruiya-mwanafunzi wa chuo kikuu cha Nairobi.

Wasimamizi: Dkt G. Mugendi, Mhadhiri, Chuo Kikuu cha Nairobi, Dkt D. Wata, Mfamasia, Hospitali ya kitaifa ya Kenyatta

Utangulizi

Mimi ni Andrew Muoria, mwanachuo katika chuo kikuu cha Nairobi, kitongocha shule ya pharmacia. Nafanya uchunguzi wa matatizo ya dawa za tiba kwa wagonjwa ambao ni watoto wenye matatizo ya ugonjwa wa Wilms tumor kwenye hospitali ya kitaifa ya Kenyatta

UMUHIMU WA MAFUNZO

Wagonjwa wengi wanajulikana kama wameathirika na magonjwa endapo wanamatatizo ya kiafya na matibabu ya magonjwa mbalimbali, pamoja na matatizo ya dawa ya tiba kutokana na hali zao mbaya. Katika mafunzo haya tutazungumzia utumiaji dawa na mambo unayopata unapotumia dawa.

Lengo letu ni kujua na kuelewa kivipi au nini wagonjwa watoto wanaoumwa kutokana na ugonjwa wa Wilms tumor, wanatatizwa na aina ya DTPs na kuchunguza yanayo sababisha matatizo na aina ya DTPs.

Haya yatachunguzwa kwa kutumia sehemu tatu ya maswali nitakayo kuuliza.

Tutafwata utaratibu ambapo unaweza ukakubali kushiriki kwenye mafunzo. Utatakiwa kujibu dodoso mbili ambalo litachukua makadirio ya dakika 20 na usimamizi wa dodoso utakuwa wako na utakuwa huru kuruka maswali ambayo hutaki kujibu. Taarifa zote zitakusanywa na mchunguzi mkuu na mtafiti msaindizi na zitakuwa ni za siri.

USHIRIKI WA KUJITOLEA

Katika mafunzo haya, kuchagua kushiriki ni kujitolea na unaonesha uhuru wako baada yakukubali kushiriki. Unaweza ukawa nje ya mafunzo kwa muda wote, kwa kufanya hivyo hutakosa faida ambazo utapewa.

HATARI NA MADHARA

Kisaikolojia, kihisia, kijamii na kimwili hizi ni hatari zilizo ndani ya utafiti. Vilevile juhudi halisi ziwepo kupelekea kupunguza hatari, moja wapo unayoweza kukutana nayo ni ukosefu wa usiri. Taarifa inayokusanywa itakuwa ni ya siri na italindwa kwa kutumia nywila inayolindwa na umeme wa mfumo wa taarifa ya madawa. Nakala zako zilizosahiniwa zenye mawazo yako za ushiriki wako zitafungiwa kwenye karatasi la kuhifadhi nyalaka ya kiofisi. Mchunguzi mkuu na mtafiti msaidizi pekee hao ndio watakao fanyia kazi taarifa yako. Kwa kuongezea, wakati wa ufanyaji wa dodoso, mafunzo yatachukua muda wako binafsi, tunaahidi kuangalia muda kuondoa mwingiliano ukiwa kama mshiriki wa mafunzo, zaidi mafunzo haya hayatahusisha au kutumia madawa

TAREJESHEWA PESA ZAKO?

Utafiti huu hautakugharimu pesa.

NA KAMA UTAKUWA NA MASWALI BAADAYE?

Kama una maswali zaidi au lolote ambalo hulielewi kuhusu utafiti huu, tafadhali usisite kuwasiliana nasi kupitia nambari ambazo zimeandikwa hapa chini.

Kwa maelezo zaidi kuhusu haki za mshiriki katika utafiti, wasiliana na Mtafiti Mkuu

Tovuti:muoriajunior@gmail.com Simu: 0727795073

au Kabitu/Mwenyekiti Simu.: **2726300** ongezo: **44102** Tovuti: *uonknh_erc@uonbi.ac.ke.*Utarudishiwa ada ya mazungumzo kupitia laini hizi kama mazungumzo yenyewe yanahusu utafiti huu.

Ridhaa (kukubali kushiriki)

Taarifa ya Mshiriki

Nimesoma au nimesomewa nakala hili. Nimepata kuzungumza kuhusu utafiti huu na mtafiti mwenyewe. Maswali yangu yamejibiwa kwa lugha ninayoielewa vizuri. Madhara na manufaa yameelezwa wazi. Ninaelewa kushiriki kwangu ni kwa hiari na kwamba ninao uhuru wa kutoshiriki wakati wowote. Ninakubali bila kushurutishwa kushiriki katika utafiti huu.
Ninaelewa kwamba bidii itatiwa kuhakikisha habari zangu zimewekwasiri. Kwa kutia sahihi kwa daftari hili, sijapeana haki zangu za kisheria ambazo ninazo kama mshiriki katika utafiti huu.

Nimekubali kushiriki katika utafiti huu: NDIO LA

Nimekubali kupeana nambari ya mawasilianao baadaye: NDIO LA

Jina la Mshiriki: Sahihi:
Tarehe:

Taarifa ya Mtafiti

Mimi, ninayetia sahihi hapo chini, nimeelezea maswala muhimu ya utafiti huu kwa mshiriki aliyetaja hapo juu na ninaamini ya kwamba ameyaelewa vilivyo na kwamba ameamua bila kushurutishwa kukubali kushiriki.

Jina la Mtafiti: Sahihi: Tarehe:
Kazi yangu kwa utafiti huu:

APPENDIX III: CHILD ASSENT FORM

Project Title:

_____

Investigator:

_____

We are doing a research study about the medicines you are being given and how they make you feel

Permission has been granted to undertake this study by the Kenyatta National Hospital-University of Nairobi Ethics and Research Committee (KNH-UoN ERC Protocol No.

_____

)

This research study is a way to learn more about people. Approximately 50 other children will be participating in this research study with you.

If you decide that you want to be part of this study, you will be asked to answer a few questions about how you are proceeding with your medication for about 20 minutes.

When we are finished with this study we will write a report about what was learned. This report will not include your name or that you were in the study.

You do not have to be in this study if you do not want to be. If you decide to stop after we begin, that's okay too. Your parents know about the study too.

If you decide you want to be in this study, please sign your name.

I,_____, want to be in this research study.

_____ _____

(Signature/Thumb stamp) (Date)

APPENDIX IV: QUESTIONNAIRE

Study title: Drug therapy problems and management outcomes of Wilms tumor among pediatric patients in KNH

Patient code: _____

Data collected by: _____

Designation: _____

Date of data collection: _____

Section 1: Demographic information

1.1. Age:years

1.2. Sex: Male ( ) Female ( )

1.3. Weight:_____Kgs

1.4. Height:_____meters

1.5. BMI: _____

1.6. BMI category

Category	Status	Mark
18.5 and below	Underweight	
18.5 to 24.9	Normal weight	
25 to 29.9	Overweight	
30 and above	Obese	

1.7. BSA:_____square meters

1.8. Residence: _____

Section 2: Clinical characteristics

a) For children above 10 years, to be filled by the participating child

2.1. Do you suffer from any other disease or medical problem apart from the one in the study topic?

Yes [_]

No [_]

If yes, which one(s)? _____

2.2. What is the duration since WT diagnosis?_____months

2.3. Do you have any concerns regarding your medication?

Yes [_]

No [_]

If yes, which one(s)? _____

2.4. Do you currently suffer from side effects?

Yes [_]

No [_]

If yes, which one(s)? _____

2.5. Review of systems

System	Sign and Symptom	Mark if Present
General	Poor appetite	

Systems	Weight change		
	Pain		
	Headache		
	Dizziness		
	Jaundice		
ENT	Change in vision		
	Loss of hearing		
	Ringing in the ears (tinnitus)		
	Bloody nose		
	Bloody sputum		
Cardiovascular	Chest Pain		
	Hypertension		
Pulmonary	Asthma		
	Shortness of breath		
	Wheezing		
Gastrointestinal	Heartburn		
	Abdominal pain		
	Nausea		
	Vomiting		

	Diarrhea		
	Constipation		
Skin	Eczema/Psoriasis		
	Itching (pruritus)		
	Rash		
Nutrition/Fluid/Electrolytes	Dehydration		
	Edema		
	Hypokalemia		
	Hyperkalemia		
	Blood urine (hematuria)		
Hematopoietic Symptoms	Excessive bruising		
	Bleeding		
Musculoskeletal	Back pain		
	Arthritis pain (osteo/rheumatoid)		
	Painful muscles		
Neuropsychiatric	Numb, tingling sensation		
	Tremor		
	Loss of Balance		
	Anxiety, nervousness		
	Inability to concentrate		
	Seizure		

	Memory loss		

b) For children below 10 years, to be filled by child's parent/guardian

2.6. Does your child suffer from any other disease or medical problem apart from the one in the study topic?

Yes [_]

No [_]

If yes, which one(s)? _____

2.7. What is the duration since WT diagnosis?_____months

2.8. Does your child have any concerns regarding your medication?

Yes [_]

No [_]

If yes, which one(s)? _____

2.9. Does your child currently suffer from side effects?

Yes [_]

No [_]

If yes, which one(s)? _____

2.10. Review of systems

System	**Sign and Symptom**	**Mark if Present**
General	Poor appetite	

Systems	Weight change		
	Pain		
	Headache		
	Dizziness		
	Jaundice		
ENT	Change in vision		
	Loss of hearing		
	Ringing in the ears (tinnitus)		
	Bloody nose		
	Bloody sputum		
Cardiovascular	Chest Pain		
	Hypertension		
Pulmonary	Asthma		
	Shortness of breath		
	Wheezing		
Gastrointestinal	Heartburn		
	Abdominal pain		
	Nausea		
	Vomiting		

	Diarrhea		
	Constipation		
Skin	Eczema/Psoriasis		
	Itching (pruritus)		
	Rash		
Nutrition/Fluid/Electrolytes	Dehydration		
	Edema		
	Hypokalemia		
	Hyperkalemia		
	Blood urine (hematuria)		
Hematopoietic Symptoms	Excessive bruising		
	Bleeding		
Musculoskeletal	Back pain		
	Arthritis pain (osteo/rheumatoid)		
	Painful muscles		
Neuropsychiatric	Numb, tingling sensation		
	Tremor		
	Loss of Balance		
	Anxiety, nervousness		
	Inability to concentrate		
	Seizure		

	Memory loss		

APPENDIX V: DATA ABSTRACTION FORM

SECTION A: Tumor characteristics and treatment

1. Cancer stage

   1 [_]

2 [_]

3 [_]

4 [_]

2. Primary tumor site

   Left kidney [_]

   Right kidney [_]

   Both kidneys [_]

3. Treatment stage

   Pre-operative [_]

   Post-operative [_]

4. Chemotherapy drugs used

Date	**Drug**	**Dose**

5. Was there schedule interruption

   Yes [_]

   No [_]

   If yes, specify reason: _____

SECTION B: Investigations and medication history

a. Investigations (WBC, Neut, Hb, RBC, UEC, Electrolytes)

Date	Test	Finding	Reference Range	Interpretation

b. Other current non chemotherapeutic drug regimens.

Date	Drug	Dose	Duration	Frequency	Route	Indication

c. Past medication history

Date	Drug	Dosage	Duration	Indication

d. DTP status

DTP	CAUSE	Mark if Present
Unnecessary drug therapy	No medical indication at this time	
	Duplicate therapy	
	Nondrug therapy more appropriate	
	Treating avoidable ADR	
	Addictive/recreational drug use causing the Problem	
Needs additional Drug Therapy	Untreated condition	
	Preventive/prophylactic therapy required to reduce risk of developing new condition	
	Synergistic/potentiating therapy	
	Drug not given	
Ineffective Drug	More effective drug available	
	Condition refractory to drug	
	Dosage form inappropriate	
	Drug not effective for condition	
Dosage too low	Ineffective dose	
	Frequency inappropriate	
	Drug interaction	
	Duration inappropriate	
ADR	Undesirable effect	
	Unsafe drug for patient	
	Drug interaction	
	Dosage administered or changed	

	too rapidly	
	Allergic reaction	
	Contraindications present	
Dosage too High	Dose too high	
	Frequency too short	
	Duration inappropriate	
	Drug interaction	
	Incorrect administration	

ERC APPROVAL DOCUMENTS

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Ref: KNH-ERC/A/151

13th April, 2023

KENYATTA NATIONAL HOSPITAL APPROVED 13 APR 2023 KNH/UoN-ERC P.O. Box 20723 NAIROBI

Andrew Muoria Ngaruiya
Reg.No.U56/37547/2020
Dept. of Pharmacy
Faculty of Health Sciences
University of Nairobi

Dear Andrew,

RESEARCH PROPOSAL: ASSESSMENT OF DRUG THERAPY PROBLEMS AND ASSOCIATED RISK FACTORS IN MANAGEMENT OF WILMS TUMOR AMONG PEDIATRIC PATIENTS IN KENYATTA NATIONAL HOSPITAL (P860/11/2022)

This is to inform you that KNH-UoN ERC has reviewed and approved your above research proposal. Your application approval number is **P860/11/2022.** The approval period is 13th April 2023 – 12th April 2024.

This approval is subject to compliance with the following requirements;

i. Only approved documents including (informed consents, study instruments, MTA) will be used.
ii. All changes including (amendments, deviations, and violations) are submitted for review and approval by KNH-UoN ERC.
iii. Death and life threatening problems and serious adverse events or unexpected adverse events whether related or unrelated to the study must be reported to KNH-UoN ERC 72 hours of notification.
iv. Any changes, anticipated or otherwise that may increase the risks or affected 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.
v. Clearance for export of biological specimens must be obtained from relevant institutions.
vi. 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.
vii. Submission of an executive summary report within 90 days upon completion of the study to KNH-UoN ERC.

KENYATTA NATIONAL HOSPITAL
P.O. BOX 20723, 00202 Nairobi

Tel.: 2726300/2726450/2726550
Fax: 2725272
Email: knhadmin@knh.or.ke

Ref: KNH/PAEDS-HOD/48 Vol.II

Date: 24th April 2023

Andrew Muoria Ngaruiya
Reg.No.U56/37547/2020
Dept. of Pharmacy
Faculty of Health Sciences
University of Nairobi

Dear Andrew

RE: AUTHORITY TO COLLECT DATA IN PAEDIATRICS DEPARTMENT

Following approval of your Research proposal by the KNH/UON-Ethics & Research Committee and subsequent filing of the Study Registration Certificate, this is to inform you that authority has been granted to collect data in ***Paediatrics Department***, on your study titled "***Assessment of drug therapy problems and associated risk factors in management of Wilms Tumor among paediatirc patients at Kenyatta National Hospital***". Kindly liaise with the Principal Nursing Officer, Paediatric Specialized Wards.

You will also be required to submit a report of your study findings to the office of the HOD, Paediatrics - KNH after completion of your study.

Dr. Esther Kimani
Ag. HOD Paediatrics

Copy to: Principal Nursing Officer, Paediatric Specialized Wards

PLAGIARISM REPORT 23/11/2023

27 November 2023

FACTORS ASSOCIATED WITH DRUG THERAPY PROBLEMS IN THE MANAGEMENT OF PEDIATRIC WILMS TUMOR PATIENTS AT KENYATTA NATIONAL HOSPITAL

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