EVALUATION OF ADEQUACY OF CONTROL OF CHEMOTHERAPY INDUCED VOMITING IN PAEDIATRIC PATIENTS WITH CANCER AT KENYATTA NATIONAL HOSPITAL

MANGHE ZEPHANIAH KIAMBI

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DECLARATION OF ORIGINALITY

Name:	Manghe Zephaniah Kiambi
Registration number:	U56/82680/2015
College:	College of Health Sciences
School:	School of Pharmacy
Department:	Pharmaceutics and pharmacy practice
Course name:	Masters of Pharmacy (Clinical Pharmacy)
Title of the study:	Evaluation of adequacy of contr ol of chemotherapy induced vomiting in paediatric patients with cancer at KNH

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1. DR. PETER NDIRANGU KARIMI, M. Pharm., Msc.MBA
   Department of Pharmaceutics and Pharmacy Practice, University of Nairobi

   Signature_____ Date_____

2. DR. DAVID ETALE WATA, M. Pharm.
   Clinical Pharmacist, Kenyatta National Hospital

   Signature_____ Date_____

ABSTRACT

Background

Chemotherapy-induced nausea and vomiting (CINV) is a common side effect associated with various chemotherapy regimens. To mitigate this phenomenon, several classes of antiemetics are recommended for use before and after chemotherapy administration. This includes agents like serotonin type 3 receptor antagonists (5-HT_3RA's), corticosteroids and neurokinin type 1 receptor antagonists (NK_1RA's). There is scanty information on CINV prophylaxis and level of control of vomiting in children with cancer in Kenyatta National Hospital.

Objective

The main aim was to assess the adequacy of control of vomiting in paediatric patients with cancer at Kenyatta National Hospital.

Methodology

A longitudinal study design was adopted. Universal sampling technique was used. Patients who satisfied the inclusion criteria were followed up prospectively up to 120 hours post chemotherapy to assess the incidence of vomiting. Complete response was used as the primary endpoint in assessing adequacy of control of emesis in the acute, delayed and overall follow up period. A structured questionnaire was used as the data collection and entry tool during the study period. Data was then analyzed using STATA version 13.0 software. Univariate analysis was done and presented as frequency tables. Bivariate analysis was done using Fisher's exact as a test of significance. Binary logistic regression was done to assess the strengths of the association. The level of significance adopted in the analysis was 0.05.

Results

The study population age ranged from 5 to 12 years with a mean age of 8.4±2.3 years. There was male predominance 58 (65.9%). Overall, 86 (97.7%) study participants got acute emesis prophylaxis. In the acute vomiting phase 77 (87.5%) got ondansetron monotherapy as prophylaxis, 6 (6.8%) got granisetron monotherapy while 3 (3.4%) got ondansetron and dexamethasone combination. Two (2.3%) patients did not receive prophylaxis in the acute phase. In the delayed emesis phase 10 (11.4%) study participants got prophylaxis. Out of those, 3 (3.4%) got ondansetron and dexamethasone combination while 7 (8%) got ondansetron monotherapy. Rescue treatment was given to 13 (14.77%) out of 58 (65.9%)

patients who had at least one episode of emesis. Complete response in the acute, delayed and overall follow up period was 47 (53.41%), 49 (55.7%) and 30 (34.09%) respectively. Peak emesis was reported on the first day 41 (46.6%) and reduced gradually over the follow up period. Duration of chemotherapy was found to increase the risk of delayed emesis (OR 4.91 95%CI (1.66 – 14.57), p=0.004). Chemotherapy regimen composition affected risk of emesis; platinum based regimens increased the risk of emesis (OR 20.36 95%CI (1.52 – 272.98), p=0.023) while presence of a steroid in the chemotherapy regimen decreased risk of vomiting (OR 0.26 95%CI (0.09 – 0.75), p = 0.012). High emetogenic chemotherapy increased the risk of emesis (OR 3.30 95%CI (1.22 – 8.88), p = 0.018) compared with moderately and low emetogenic chemotherapy.

Conclusion

Management of acute and delayed emesis in children still remains a big challenge. There was poor compliance with local and international guideline recommendations for management of chemotherapy induced vomiting.

Recommendations

Further studies can should assess the reasons for poor adherence to current CINV management guidelines and address the challenges and gaps in practice.

DEDICATION

This dissertation is dedicated to children; especially those with cancer.

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ABBREVIATIONS AND ACRONYMS

5-HT$_3$ RA - 5-hydroxytryptamine-3 receptor antagonists

95%CI – 95% Confidence interval

AC – Anthracycline Cyclophosphamide chemotherapy combinations

ALL – Acute Lymphoblastic Leukemia

AML – Acute Myeloid Leukemia

AOR – Adjusted Odds Ratio

APPHON - Atlantic Provinces Paediatric Hematology Oncology Network

BD – Twice daily (given 12 hourly)

CARB – Carboplatin

Chemo - Chmotherapy

CINV - Chemotherapy Induced Nausea and Vomiting

CIS – Cisplatin

CML – Chronic Myeloid Leukemia

CNS - Central Nervous System

COR – Crude Odds Ratio

CPM – Chlorphenamine

CPP – Cyclophosphamide based regimen

CR – Complete response

CTZ - Chemoreceptor Trigger Zone

DEX – Dexamethasone

ERC - Ethics and Research Committee

ESMO - European Society of Medical Oncologists

HEC - High Emetogenic Chemotherapy

HEPATO – Hepatoblastoma

HL – Hodgkins Lymphoma

IFOS – Ifosfamide

IV - Intravenous

KNH - Kenyatta National Hospital

LEC - Low Emetogenic Chemotherapy

LZP – Lorazepam

MASCC - Multinational Association of Supportive Care in Cancer

MEC - Moderate Emetogenic Chemotherapy

MTC – Metoclopromide

NEPA – Netupitant and Palonosetron combination

NEURO – Neuroblastoma

NHL – Non-Hodgkins Lymphoma

NK_1 RA - Neurokinin-1 Receptor Antagonist

OD – Once daily (given 24 hourly)

OND – Ondansetron

OR – Odds ratio

Osteo – Osteosarcoma

PLT – Platinum based regimen

PNS - Peripheral Nervous system

PO - Per os (taken orally)

POGO - Paediatric Oncology Group of Ontario

QID – Four times daily (given 6 hourly)

Rhabdo – Rhabdomyosarcoma

STS – Soft Tissue Sarcoma

TID – Three times daily (given 8 hourly)

VC - Vomiting Center

OPERATIONAL DEFINITION OF TERMS

Acute CINV - Nausea and vomiting that occurs within 24 hours post chemotherapy

Anticipatory CINV - Nausea and vomiting occurring before chemotherapy due to conditioning after prior exposure

Breakthrough CINV - Vomiting and/or nausea within five days after chemotherapy despite use of guideline directed prophylaxis

Complete control - Defined as no nausea, emesis, or rescue therapy

Complete protection - Defined as no emesis, no rescue therapy and no significant nausea

Complete response - Defined as no emetic episodes and/or rescue therapy

Cyclophosphamide based chemotherapy– chemotherapy regimen with either cyclophosphamide or ifosfamide, among other agents, as part of the combination.

Delayed CINV - Nausea and vomiting that occurs twenty four hours after chemotherapy

Level 1 emetogenicity – Chemotherapy agents that cause <10% emesis if prophylaxis is not given

Level 2 emetogenicity – Chemotherapy agents that cause 10 - 30% emesis if prophylaxis is not given

Level 3 emetogenicity – Chemotherapy agents that cause 30 - 60% emesis if prophylaxis is not given

Level 4 emetogenicity – Chemotherapy agents that cause 60 - 90% emesis if prophylaxis is not given

Level 5 emetogenicity – Chemotherapy agents that cause >90% emesis if prophylaxis is not given

Mild vomiting – Presence of 1 – 2 episoses of emesis over the follow up period

Moderate vomiting – Presence of 3 – 5 episoses of emesis over the follow up period

Multiday chemotherapy – Chemotherapy given for more than one day consecutively

Nausea - A feeling of discomfort with an urge to vomit

Per guideline – Treatment or intervention that is based on guideline recommendations

Platinum based chemotherapy – Chemotherapy regimen with either cisplatin or carboplatin, among other agents, as part of the combination.

Prophylaxis - Refers to guideline directed therapy to prevent CINV after chemotherapy

Refractory CINV - Nausea/vomiting occurring in subsequent chemotherapy sessions after guideline directed prophylaxis failed in earlier cycles

Rescue therapy - Refers to therapy given when CINV does not respond to conventional or guideline directed therapy

Retching - Unsuccessful attempt to vomit

Severe vomiting – Presence of >5 episoses of emesis over the follow up period

Vomiting - Forcible expulsion of stomach contents through the mouth

CHAPTER ONE: INTRODUCTION

1.1 Background to the study

Chemotherapy is associated with a myriad of side effects such as nausea, vomiting and hair loss. Several studies have reported that chemotherapy-induced nausea and vomiting (CINV) still remains one of the most common chemotherapy related side effect in children (1). It is also reported to have negative implications on the quality of life, increased cost and poor adherence to treatment (2). Great advancements have been achieved in development of novel agents to control CINV. However, current studies still show that CINV is one of the main concerns for most patients receiving chemotherapy (2,3). This finding has been attributed to poor use or lack of clinical guidelines for CINV management, knowledge gaps on choice of prophylaxis (4) and underestimation of risk and incidence of CINV by physicians (5,6). The emetogenicity level of a particular chemotherapy regimen, age of more than three years, female gender, anxiety and inadequate control with previous chemotherapy are some of the risk factors that determine the incidence and severity of CINV (7,8).

There exists a variety of standardized international guidelines, like the Multinational Association of Supportive Care in Cancer / European Society of Medical Oncologists (MASCC/ESMO) and Paediatric Oncology Group of Ontario (POGO) that guide on the use of antiemetics in children (9,10). Due to limited data from the paediatric population, majority of recommendations on paediatric CINV management have been extrapolated from adult studies. Most countries/sites, including Kenya, have no standard clinical guidelines for CINV management and therefore current practice borrows heavily from published international guidelines. Management of paediatric patients with CINV at KNH paediatric wards is guided by recommendations made in Kasili's synopsis of the management of paediatric cancers in Kenya(11). Still there is inadequate information on the use of prophylaxis, adherence to recommendations and the adequacy of control of chemotherapy induced vomiting among paediatric patients at KNH.

1.1.1 Pathophysiology of vomiting

The pathophysiology of CINV is complicated. Emesis is controlled by three sites: the chemoreceptor trigger zone (CTZ), the vomiting centre (VC) and the vagal nerve afferents. The main neurotransmitters normally involved in that process are: serotonin, dopamine and substance P. The main receptors involved in the pathophysiology of CINV are 5-HT_3,

dopamine and NK_1 receptors. The others include the histamine (H_1), corticosteroid, gabaminergic, cannabinoid, opioid and acetylcholine receptors (Ach). The μ-opioid receptors play a role in anti-emesis. This understanding of the neurotransmitters-receptor systems forms the basis for the use of the drugs used for management of CINV (12). There are three systems that are involved in the development of CINV: the central nervous system (CNS), the gastrointestinal system (GIT) and the peripheral nervous system (PNS). The vomiting center is stimulated by signals from the CTZ, the central nervous system, the GIT, the limbic system and the vestibular system (13). In the gastrointestinal system radiation, mechanical injury, toxins and chemotherapeutic agents can cause considerable damage to the enterochromaffin cells in the gut mucosal wall. This damage leads to release of serotonin which binds and activates vagal afferents as well as directly activating the vomiting center in the CNS (13,14). In the central nervous system, the chemoreceptor trigger zone (CTZ) which is located in the area postrema and outside the blood brain barrier is able to sense noxious agents in the blood and the cerebral spinal fluid. When that occurs the CTZ releases neurotransmitters that travel to the VC and the Solitary Tract Nucleus of the Vagus nerve triggering emetic response. Chemotherapeutic agents are also able to directly stimulate $5HT_3$ receptors directly at the VC causing emesis (7). The main neurotransmitters receptors involved are serotonin, dopamine and Neurokinin. The cerebral cortex and the limbic systems are able to stimulate the VC as a result of emotional states like pain, anxiety and mental conditioning (14,15). This pathway is involved in the pathophysiology of anticipatory nausea. The neurotransmitters involved are less understood compared to the CNS and the GIT responses. The VC receives signals from these systems and sends efferent signals to the effector organs like the smooth muscle of the gut, the salivary glands, the vasomotor system and the respiratory system. The efferent signals cause contraction of the stomach muscles and the diaphragm, excessive salivation, halted breathing during emesis and relaxation of the oesophageal sphincter (16). The emetic response is either manifested as nausea, retching or vomiting. Serotonin is the main mediator in acute CINV whereas dopamine and histamine are the main mediators involved in delayed emesis. Inflammatory mediators like prostaglandins and substance P also contribute to delayed CINV (8).

1.1.2 Classification of CINV

CINV is classified into three main types: acute, delayed and anticipatory based on the time that it develops vis-à-vis the time the chemotherapy is given. Other classifications include

breakthrough and refractory CINV. As discussed in the pathophysiology section, the difference in the neurotransmitters involved in each of the types informs the choice of prophylaxis.

Acute CINV

This is described as nausea and vomiting that occurs less than 24 hours after receiving chemotherapy. It begins most commonly 1 to 2 hours and peaks 4 to 6 hours post chemotherapy. It then resolves within 24 hours (7,17). It is mainly caused by a response to serotonin release and its binding effects on 5-HT3 receptors as well as activation of the vagal afferents that lead to the vomiting center (18,19).

Delayed CINV

This is nausea and vomiting that occurs after 24 hours up to 120 hours (5 days) post chemotherapy (17,20). However, delayed CINV may persist up to 7 days post chemotherapy (21). The main receptor systems involved here are the dopaminergic (D_2) and the Neurokinin-1 (NK_1) receptor systems in response to dopamine and substance P release respectively. Some studies have reported that the incidence in children is lower than in adults (22).

Anticipatory CINV

This is nausea and vomiting that occurs prior to administration of chemotherapy. It can occur hours and even days before chemotherapy is administered (7). Its development is influenced by the emetogenicity of the chemotherapy, history of motion sickness, adequacy control of CINV during the first chemotherapy session, anxiety and taste disturbances (23). This normally happens due to mental conditioning resulting from poor control of CINV during previous chemotherapy sessions (24). Studies have reported that about a quarter of paediatric patients suffer from this type of CINV (25). Due to the emotional and psychological factors involved in the development of CINV, incorporation of psychosocial and emotional support should be considered as adjunct therapies to conventional drugs (7).

Breakthrough CINV

This is where there is development of nausea and vomiting, within 5 days after chemotherapy, when the patient is already on CINV prophylaxis (17,20,26). This could be

due to lack of effectiveness of the prophylactic medications being used and often necessitates use of rescue medications (26).

Refractory CINV

This is nausea and vomiting that does not respond to subsequent conventional guideline directed CINV prophylaxis after it has failed in previous chemotherapy sessions. It can occur after a few or several chemotherapy sessions (21,26,27).

1.2 Problem statement

Most chemotherapy regimens used in management of malignancies in both adults and pediatric patients are associated with a variety of side effects. Nausea and vomiting, which is mostly dependent on the emetogenicity of the regimen being used (7), has been cited as one of the side effects that greatly affects the quality of life and medication adherence in most patients (3). From previous studies done in other countries CINV in children is not well documented (28). Despite prophylaxis of CINV in patients on MEC regimens, studies have shown that about 31% and 38% of the patients do not achieve complete response and complete protection respectively (3). There are no national or institutional guidelines on management of CINV in cancer patients in Kenya. Management of vomiting at KNH is mainly guided by recommendations made in Kasili's synopsis of the management of paediatric cancers. This lack of guidelines can lead to high variability (29) in the management of CINV in cancer patients. Some of the guideline recommended therapies for management of CINV like NK_1 receptor antagonists are not available for routine use in Kenyan public hospitals. Based on these factors, there is need to evaluate the patterns of CINV prophylaxis, adherence to guideline recommendations and the subsequent adequacy of control of CINV so as to inform on the gaps in management.

1.3 Purpose of the study

This study assessed prescribing patterns of antiemetics and the incidence of chemotherapy induced vomiting in the paediatric patients with cancer at KNH. In addition it assessed the dosing, frequency and duration appropriateness vis-à-vis local and international guidelines and recommendations. All this was done to inform on the current management of chemotherapy induced vomiting in paediactric cancer patients and identify gaps in practice that needs to be addressed.

1.4 Objectives

1.4.1 Main objective

i. To assess the adequacy of control of chemotherapy induced vomiting among paediatric patients with cancer at KNH

1.4.2 Specific objectives

i. To find out the complete response rates in paediatric cancer patients receiving prophylaxis for chemotherapy induced vomiting at Kenyatta National Hospital.

ii. To identify the type of drugs used for prophylaxis of chemotherapy induced vomiting in paediatric cancer patients at Kenyatta National Hospital.

iii. To determine whether doses of drugs used for prophylaxis of chemotherapy induced vomiting in paediatric cancer patients at Kenyatta National Hospital are appropriate.

1.5 Research Questions

i. What are the complete response rates in paediatric patients with cancer receiving CINV prophylaxis at KNH?

ii. Which types of drugs used for CINV prophylaxis in paediatric patients with cancer at KNH?

iii. How appropriate are therapies used for CINV prophylaxis in paediatric patients with cancer at KNH?

1.6 Significance and output

i. The study assessed the prescribing patterns of CINV prophylaxis among paediatric patients with cancer at KNH.

ii. The study identified gaps in practice with regards to CINV prophylaxis. This information will guide with the review of the current guidelines/protocols for management of CINV in paediatric patients with cancer at KNH.

iii. The study findings are meant to optimize CINV prophylaxis treatment outcomes in paediatric cancer patients at KNH. One of the findings was non adherence to guideline recommendations; guideline recommended prescribing would improve treatment outcomes.

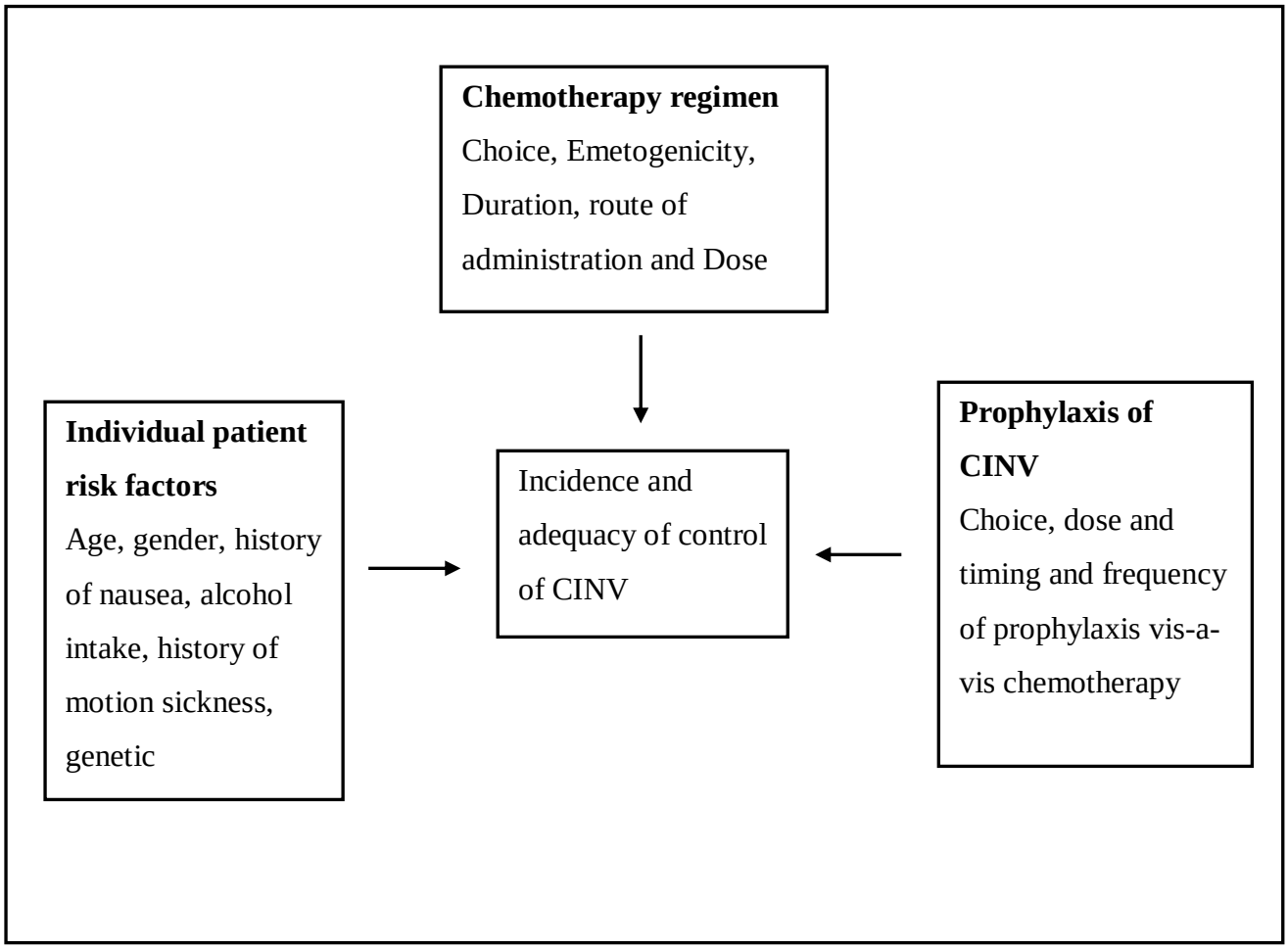
1.7 Study limitations

The study mainly focused on paediatric patients and therefore findings can be only be inferred to patients with characteristics similar to those in the study population. Communication barrier was encountered in a few patients as a result of the cancer. Both English and Swahili consent and assent forms were developed for the study participants. For those who could not read the data collection tools were read out to them and translated to the study participants in a simple and understandable way with options for clarification. Responses were then directly documented on the questionnaire. Delayed CINV can persist up to 7 days post chemotherapy (21). However follow up in this study was carried out over a period of 120 hours (5 days) and therefore may not have captured the actual incidence of delayed CINV if follow up period was to be extended. Anticipatory nausea has been reported to occur days to hours before chemotherapy (7). In this study anticipatory CINV was only assessed if it occurred within one hour to chemotherapy. Nausea as a result of chemotherapy was not assessed in the study group.

1.8 Conceptual Framework

The incidence and adequacy of control of CINV after chemotherapy is determined by several factors. The main determinant is the emetogenicity of chemotherapy. Studies have been done that have classified various chemotherapies into four levels of emetogenicity: high, moderate, low and minimal (30). The route, dose and combination of the chemotherapeutic agents contribute to the levels of emetogenicity. For instance, combination of two moderate emetogenic agents can make the combination a highly emetogenic one due to synergism (26,30,31). Patients on more emetogenic regimens would therefore require more aggressive prophylaxis as compared to those on less emetogenic regimen (32–34). In addition, patient individual factors like sex, genetic polymorphism, history of motion sickness and age of the patient are some of the factors that also determine the outcomes of chemotherapy induced nausea and vomiting (33). The clinician needs to consider these factors so as to individualize therapy (35). In mitigating the effects of chemotherapy, appropriate agents must be used as per the guidelines. Factors that may determine the effectiveness of the prophylaxis include: the choice of the agents to be used, the appropriateness of the dose, the timing of prophylaxis vis-à-vis the chemotherapy and to an extent the knowledge of the clinician/pharmacist on CINV prophylaxis (36,37)

Figure 1: Conceptual framework



CHAPTER TWO: LITERATURE REVIEW

2.1 Introduction

This chapter will highlight on the risk factors of CINV and review various studies that have been done to assess the adequacy of control of vomiting in children.

2.1.1 Risk factors for CINV

Several risk factors have been attributed to the incidence of CINV. These will be discussed below.

2.1.2 Emetogenicity of chemotherapy

Emetogenicity of the chemotherapy regimen is one of the main predictors of the incidence and severity of CINV (23,35). Chemotherapeutic agents are classified based on their potential to induce nausea and vomiting in the absence of prophylaxis (30). Various studies and recommendations have classified chemotherapeutic agents broadly into four main categories as listed in the table below. As per the most current published international guidelines (38) the choice of prophylaxis is mainly based on the emetogenic potential of the regimen that the patient is on (8). In cases where combination therapy is used, Hesketh's algorithm was used in determining the emetogenicity of the entire regimen.

Table 1: Hesketh's algorithm for determining the emetogenicity of combination regimens (31)

1. Determine the most emetogenic regimen based on Hesketh's table. This determines the emetogenicity of the entire regimen
2. Consider the following rules to determine the contribution of other additional agents • Addition of Level 1 agents does not affect the emetogenicity of the overall regimen. • Addition of one or more level 2 agents increases the emetogenicity of the entire regimen by one level above the most emetogenic agent. • Each additional level 3 or 4 agent increases the emetogenicity by one level per agent.

Table 2: Hesketh's table of emetogenicity potential of chemotherapeutic agents (31)

Emetogenicity /Level	**Frequency of emesis without prophylaxis (%)**	**Agent(s)**
High (level 5)	>90	Intravenous agents AC combinations, cyclophosphamide ≥1500mg/m^2, Cisplatin, Dacarbazine, Carmustine, Mechlorethamine, Steptozocin Oral Procarbazine, Hexamethylmelamine
Moderate (level 4)	60-90	Intravenous agents Carboplatin, cisplatin <50mg/m^2, carmustine <250mg/m2, Cyclophosphamide>750mg/m^2 to ≤1500mg/m^2, Cytarabine >1000mg/m^2, Doxorubicin >60mg/m^2, Epiribicin, Ifosfamide, Irinotecan, Thiotepa, Oxaliplatin, methotrexate> 1000mg/m^2 Oral agents Procarbazine
Moderate (level 3)	30-60	Cyclophosphamide <750mg/m^2, cyclophosphamide (oral), doxorubicin 20-60mg/m^2, epirubicin ≤90mg/m^2, methotrexate 250-1000mg/m^2, Ifosfamide, irinotecan
Low (level 2)	10-30	Intravenous agents Cytarabine <1000mg/m^2, Docetaxel, Etoposide, 5-fluorouracil <1000mg/m^2, Gemcitabine, Methotrexate 50mg to 250mg/m^2, Paclitaxel, Topotecan Oral agents Capecitabine, Etoposide, Fludarabine, Thalidomide
Minimal (Level 1)	<10	Intravenous agents Bleomycin, Vincristine, Vinblastine, Vinorelbine, Rituximab Oral agents Chlorambucil, Hydroxyurea, Melphalan, Methotrexate <50mg/m^2

2.1.3 Age

Young age has been reported as one of the risk factors of CINV (39). Incidence rates of CINV in children on prophylaxis vary with the age. Complete control in toddlers has been reported to be superior compared to the older children and adolescents (1). The reason for this is unclear but the findings in that particular study are supported by other previous studies (40).

2.1.4 Sex

Female gender has been reported as a risk factor in the development of CINV (35,39). Progesterone hormone, which is found in higher levels in females and produced during periods (41), is associated with induction of nausea and vomiting. Production of prostaglandins, especially during monthly periods, also increases the incidences of development of CINV (41). As discussed in the pathophysiology of CINV, prostaglandins play an important role in delayed emesis.

2.1.5 Genetic polymorphism

Differences in drug biotransformation can lead to differences in responses (42–44). There are differences in metabolism and encoding of the receptors involved in the pathogenesis of CINV therefore resulting in differences in antiemetic response. For instance one study (21) states that metabolism, transporters and receptor target pathways for 5-HT_3 receptor antagonists are polymorphic. This polymorphism has been shown to have an effect on their efficacy. The field of pharmacogenomics has not been fully exploited in management of cancer patients. However, increase in information on the racial genotypic variations can help in individualizing therapy, improve on the safety of chemotherapy and foster a better understanding of the etiology of CINV (45,46).

Other factors

Positive history of nausea of various etiologies (like motion sickness, pregnancy related or prior chemotherapy), the dose of the chemotherapy, anxiety disorders, concurrent opioid use and alcohol intake (less than 45ml /day) has been found to be a predictor of CINV (46,47).

2.2 Antiemetic therapies for CINV

The various antiemetic therapies used in management of CINV are discussed below

2.2.1 5-HT_3 receptor antagonists

This class of agents includes: ondansetron and granisetron which are first generation agents and Palonosetron, dolasetron and tropisetron which are second generation agents. The agents are effective in management of both acute and delayed CINV when combined with a corticosteroid, a NK_1 receptor antagonist or both (10,27). A study carried out at the Kenyatta National Hospital to assess the superiority of either granisetron compared to ondansetron in control of CINV in patients above 18 years on HEC (platinum based regimens) showed no differences in effectiveness and tolerability in both agents. It was further recommended that ondansetron is the more preferred agent due to its cost effectiveness as compared to granisetron (48). In a second paediatric study that assessed superiority of granisetron/dexamethasone (regimen 1) versus a cocktail containing granisetron/dexamethasone plus midazolam and diphenhydramine (regimen 2), it was found that regimen 2 was not superior to regimen 1 in controlling of both acute and delayed CINV. It was observed that regimen 2 had more side effects to the children (49). This finding is further supported by a study that assessed the control of CINV in a variety of MEC regimens using a 5-HT3RA and dexamethasone combination which reported that the combination is sufficient in the control of CINV in most MEC regimens (50).

2.2.2 Neurokinin receptor antagonists

NK_1 receptor antagonists which block the effects of substance P are used in combination with 5-HT_3RA and dexamethasone for delayed CINV prophylaxis. Aprepitant, fosaprepitant, rolapitant and Netupitant/Palonosetron (NEPA) have been approved for use (38,51). Other agents being studied include casopitant and rolapitant. Triple regimens containing a 5-HT_3RA, Dexamethasone and NK_1 receptor antagonist have been shown to be superior to two drug regimen containing a 5-HT_3RA and Dexamethasone in management of acute and delayed CINV (52). Use of NEPA, which is a combination of a 5-HT_3RA (Palonosetron) and a NK_1 receptor antagonist (netupitant), which has a long half life is given as a single dose prior to chemotherapy and is effective in management of both acute and delayed forms of CINV (53). In addition it reduces the need for hospital stay and adherence monitoring. The agents in this group are not available for routine use in management of CINV in Kenyatta National Hospital.

2.2.3 Corticosteroids

Corticosteroids, combined with other antiemetics, have a booster effect in antiemesis and are therefore recommended in management of CINV in both acute and delayed phases (38). The mode of action of corticosteroids is not well understood. Some studies postulate that corticosteroids have a direct inhibitory effect on 5-HT_3 receptors as well as central effect by activation of glucocorticoid receptors in the solitary tract nuclei (54,55).

Dexamethasone is the most commonly used agent. While there are no differences in the efficacy of different steroids, dexamethasone is commonly used due to guideline recommended dose, schedule and its availability in various formulations (38,56). Some studies have reported that the steroids are under prescribed in the management of delayed CINV (57). Use of corticosteroids is associated with side effects like insomnia, acne, dyspepsia and adrenal suppression (58,59). However use of corticosteroids has been shown to be safe in CINV prophylaxis and should be used as per guideline directed situations for optimal patient outcomes (60).

2.2.4 Dopamine receptor antagonists

These agents block dopamine (D_2) receptors at the gut, CTZ and the dorsal vagal complex. These agents can be broadly grouped as: butyropenones, phenothiazines atypical narcoleptics and substituted benzamides. In this group, by and large, olanzapine and metoclopromide have shown promise in management of CINV. Olanzapine, which is an atypical neuroleptic drug that has antiemetic effects, blocks a number of receptors which include: dopamine receptors, serotonin receptors, adrenergic receptors, muscarinic and histamine receptors. In one retrospective study, olanzapine was shown to be effective in management of CINV in prophylaxis and in breakthrough phases (61). In a second randomized double blind study in management of breakthrough CINV, 70% of the patients that received olanzapine as rescue therapy had no emesis as compared to 31% for patients that got metoclopromide. Based on the study findings olanzapine was superior to metoclopromide in management of breakthrough nausea (62). One of the shortcomings of olanzapine is the side effects like sedation which can be overcome by use of lower doses of 5 mg in prophylaxis (61,63). A study done in 1990 comparing high dose metoclopromide versus ondansetron in management of CINV it was concluded that: Ondansetron had better outcomes that metoclopromide in the acute phase (72% versus 41%) but had comparable outcomes in the delayed phase with metoclopromide having superior control of nausea (64). However at high doses like those used in CINV management occurrence of extrapyramidal side effects and galactorrhea due to

dopamine antagonism are major shortcomings especially in paediatric patients. Butyrophenones like phenothiazine, metopimazine and haloperidol have limited usage in delayed and breakthrough CINV. In one study comparing prochlorperazine, ondansetron and dexamethasone in management of delayed CINV in MEC and HEC regimens the following was noted: that patient on prochlorperazine had lowest average nausea scores whereas ondansetron had the highest score. There was no statistically significant difference in side effects and control of CINV in the three groups under study from day 2 to 5 (65). The use of haloperidol with 5-HT_3RAs has synergistic effect in the control of CINV and as such can be considered as rescue therapy (66).

2.2.5 Benzodiazepines

Anxiety has been linked with development of anticipatory nausea (15). The limbic system and the cerebral cortex can induce vomiting by sending of signals to the vomiting center in states like anxiety and pain. Benzodiazepines like alprazolam, lorazepam and midazolam have a role in reducing anxiety and thus reduce the incidence of anticipatory CINV (67,68). In management of acute and delayed CINV, studies have shown that addition of benzodiazepines to a 5-HT_3 receptor antagonist and dexamethasone regimen does not offer additional benefits to the regimen. In fact it increases the side effects like drowsiness and sedation (49).

2.2.6 Cannabinoids

As discussed earlier on pathophysiology of CINV μ-opioid receptors have a role in antiemesis. Dronabinol has been studied and found to be a viable option as an adjunct therapy in paediatric cancer patients. In the study 60% of the patients had a positive response to dronabinol (69). Since that study was done retrospectively, further prospective clinical trials are warranted to assess the dose, safety and efficacy of dronabinol.

2.2.7 Antihistamines

Dimenhydramine, diphenhydramine and meclizine have antiemetic, anticholinergic, CNS depressant, antihistamine and local anesthetic effects. Though the antiemetic effects are unclear, antihistamines are thought to act on the vestibular system which is a determinant in induction of nausea in motion sickness (21). A positive history of motion sickness is one of the predictors of incidence and severity of CINV. In such cases the antihistamines can be used as adjunct therapies in management of CINV. Addition into other regimens increases the side effects and does not significantly increase their effectiveness (49)

2.2.8 Herbal medicines/alternative therapies

Pharmacopuncture is an alternative therapy that has been used in management of conditions like pain and nausea (70). One metanalysis reported that there is no strong evidence available to support its use in management of CINV and recommended that further studies need to be done to evaluate the role of pharmacopuncture (71). Plants like *Zingiber officinale, Citrus aurantium, Hypericum perforatum, Achillea millefolium* are some of the plants that have been used commonly as adjunct antiemetics (72).

2.2.9 Principles of emesis control as per current guidelines

Current recommendations on the drugs to be used for prophylaxis are dictated by the level of emetogenicity of the regimen. To further reduce the incidence of CINV one has to consider other variables that are unique to the patient and factor them in decision making process. The following tables contain a summary of some of the guideline recommendations.

Table 3: MASCC/ESMO guideline (2016) recommendations on CINV prophylaxis in children (10)

Emetogenicity level	**5-HT_3 RA**	**Corticosteroid**	**NK_1 RA**
HEC	5-HT_3 RA	Dexamethasone	Aprepitant
	5-HT_3 RA	Dexamethasone	*Avoid if contraindicated
	5-HT_3 RA	*Avoid if contraindicated	Aprepitant
MEC	5-HT_3 RA	Dexamethasone	
	5-HT_3 RA	*Avoid if contraindicated	Aprepitant
LEC	5-HT_3 RA		
MINIMAL	No prophylaxis required		

Table 4: POGO (2015) guideline recommendations on CINV prophylaxis in children (26)

	Standard therapies			**Adjunct**
HEC	5-HT_3 RA	Steroid	NK_1RA*	
	5-HT_3 RA	DEX		
	5-HT_3 RA	DEX		
	5-HT_3 RA			CPZ, NBL
MEC	5-HT_3 RA	DEX		
	5-HT_3 RA			CPZ, NBL
LEC	5-HT_3 RA			
MINIMAL	No prophylaxis required			

Table 5: MASCC/ESMO recommended doses of 5-HT_3RA (10)

Agent	**Route**	**Dosing schedule**
Ondansetron	IV	8 mg or 0.15 mg/Kg
	Oral	16 mg* in two divided doses
Granisetron	IV	1 mg or 0.01 mg/Kg
	Oral	2 mg or 1 mg (preferred by most panelists)
Dolasetron	Oral	100 mg
Tropisetron	IV	5 mg
	Oral	5 mg
Palonosetron	IV	0.25mg
	Oral	0.5mg

Table 6: MASCC/ESMO dexamethasone dosing recommendations for CINV prophylaxis (10)

Risk of emesis	Phase of CINV	Dosing schedule
High	Acute emesis	20 mg once (12 mg when used with (fos)aprepitant or netupitant)
	Delayed emesis	8 mg bid for 3 - 4 days (8 mg once daily when used with (fos)aprepitant or netupitant)
Moderate	Acute emesis	8 mg once
	Delayed emesis	8 mg daily for 2 - 3 days (mostly given as 4 mg BD)
Low	Acute emesis	4 - 8 mg once

Table 7: MASCC/ESMO NK_1RA dosing recommendations for CINV prophylaxis (10)

Agent	Type of CINV	Dosing schedule
Aprepitant and Fosaprepitant	Acute Emesis	Aprepitant 125 mg or Fosaprepitant 150 mg IV. Both given once on the treatment day
Aprepitant and Fosaprepitant	Delayed Emesis	Aprepitant 80 mg orally OD for the 2 days post chemotherapy; none if Fosaprepitant was used.
Rolapitant	Acute and delayed CINV	180 mg orally OD on the day of chemotherapy
Netupitant	Acute and delayed CINV	300 mg netupitant/0.5 mg palonosetron orally once on the day of chemotherapy

Table 8: POGO dosing recommendations for CINV prophylaxis (26)

Agent	Emetogenicity	Route	Dosing schedule
Granisetron	HEC	IV	40mcg/kg/dose as a single daily dose
	MEC	IV	40mcg/kg/dose as a single daily dose
		oral	40mcg/kg/dose q12h
	LEC	IV	40mcg/kg/dose as a single daily dose
		Oral	40mcg/kg/dose q12h
Ondansetron	HEC and MEC	IV/PO	5 mg/m^2/dose or 0.15 mg/kg/dose IV/PO pre-therapy and then 8 hourly
	LEC	IV	10 mg/m^2/dose or 0.3 mg/kg/dose; maximum 16 mg/dose IV
		Oral	24 mg/dose PO) pre-therapy x 1
Aprepitant	HEC	≥12 years	Day 1: 125mg PO x 1; Days 2 and 3: 80mg PO once daily
Chlorpromazine		IV	0.5mg/kg/dose IV q6h
Dexamethasone	HEC	IV/PO	6 mg/m2/dose IV/PO q6h (half if combined with aprepitant)
	MEC	IV/PO	≤ 0.6m2: 2mg/dose IV/PO q12h > 0.6m2: 4mg/dose IV/PO q12h (Half the dose if combined with aprepitant)
Metoclopromide	MEC	IV/PO	1 mg/kg/dose IV pre-therapy x 1 then 0.0375 mg/kg/dose PO q6h
Nabilone			< 18 kg: 0.5 mg/dose PO twice daily 18 to 30 kg: 1 mg/dose PO twice daily > 30 kg: 1 mg/dose PO three times daily Maximum: 0.06 mg/kg/day

Table 9: APPHON guideline on breakthrough and refractory emesis management (26)

Variable	Options
Breakthrough emesis	Increase the doses of current medicines the patient is on without exceeding their maximum doses starting with $5HT_3RA$
	Incorporate an antiemetic from different class (if not included) to the regimen the patient is on.
	Add adjuncts like dimenhydrinate, lorazepam to the regimen the patient is on.
Refractory emesis	Use a different combination of antiemetics in the next cycle of chemotherapy
	Maximise antiemetic doses in subsequent chemotherapies (without exceeding maximum doses).
	Consider addition of dexamethasone in the next course of antiemetic if not contraindicated.
	Substitute ondansetron with more potent $5HT_3RA$'s if patient fails on two subsequent cycles.

Table 10: Kasili's synopsis recommendations on management of CINV(11)

Option	Agent	Agent	Dosing schedule
A	Acute emesis (HEC)	OND	0.15mg/kg IV 0.5 hours pre-therapy then 4 hours after chemotherapy (total of 3 doses)
		DEX	0.25mg/kg IV 40 minutes before chemotherapy
B	Acute emesis (High dose cisplatin)	OND	0.15mg/kg IV 30 – 45 minutes before chemotherapy
		DEX	0.25mg/kg IV 40 minutes before chemotherapy
		MTC	3mg/kg IV 30 minutes pre-therapy; second dose 90 minutes after chemotherapy
C	Acute emesis (moderate dose cisplatin, non-cisplatin regimens)	DEX	0.25mg/kg IV 40 minutes before chemotherapy
		LZP	$1.5mg/m^2$40 minutes before chemotherapy
		MTC	2mg/kg IV 30 minutes pre-therapy; second dose 90 minutes after chemotherapy
D		DEX	0.25mg/kg IV 40 minutes before chemotherapy
		CPM	0.35mg/kg or $10mg/m^2$ per 24 hours
E	Delayed emesis	MTC	0.5mg/kg PO on 1^{st} and 2^{nd} day post-chemotherapy the with bout of vomiting 3^{rd} and 4^{th} day
F	Delayed emesis	DEX	0.25mg/kg PO on 1^{st} to 4^{th} day post-chemotherapy

2.3 Incidences of nausea and vomiting

2.3.1 CINV incidences in HEC

One prospective study carried out in India assessed the efficacy, safety and cost benefit of olanzapine versus aprepitant inclusion into a triple regimen containing ondansetron and dexamethasone in patients receiving HEC (73). Complete response in the acute phase, delayed and overall period was 86%, 86% and 80% in the aprepitant/Palonosetron/dexamethasone arm and 84%, 88% and 78% in the olanzapine arm respectively. This showed that olanzapine is a viable alternative in management of CINV in patients on HEC. A more recent study carried out at Kenyatta national hospital to assess the efficacy and tolerability of ondansetron versus granisetron found out that complete response was 80% among adult patients receiving HEC (48). Use of triple therapy incorporating a NK_1 receptor antagonist in HEC supports the MASSC/ESMO recommendations (10).

2.3.2 CINV incidences IN MEC

One prospective study assessed the incidence of nausea and vomiting in patients receiving MEC and on prophylaxis (3). In the acute phase 94.9% of the patients were on 5-HT_3RA and corticosteroid, 4.7% were on metoclopromide and corticosteroid and one patient had no prophylaxis. In the delayed phase 56.2% of the patients were not on any prophylaxis, 25.5% were on metoclopromide and dexamethasone, 17.7% were on 5-HT_3RA and corticosteroid and 1.3% on 5-HT_3RA alone. Despite this prophylaxis incidences of vomiting and nausea within 5 days of chemotherapy were 20.8% and 42% respectively. Complete response in the acute, delayed phase and the entire period was 84.2%, 77% and 68.9% respectively while complete protection in the acute and delayed phase and the entire period was 79.5%, 68.8% and 62.4% respectively. It was clear that management of delayed CINV was less aggressive compared to the acute phase. In a similar study where 201 patients on MEC and on prophylaxis with 5-HT_3RA on day 1 and a corticosteroid on day 1–3, complete inhibition of nausea and vomiting in the acute phase was 87.6% and 95.5% respectively and 68.2% and 92% in the delayed phase respectively (50). Nausea is less well controlled than vomiting in both phases. The improved control of CINV in the delayed phase, as compared to the study above, is attributable to the aggressiveness of prophylaxis with dexamethasone in the delayed phase. A second study assessing the incidence of anticipatory nausea found out the incidence before cycle 1, 2 and 3 was 4.8%, 7.9% and 8.3% respectively (74). Histories of significant

nausea and/or anxiety in previous chemotherapy were some of the predictors of developing anticipatory CINV in the subsequent cycles. This finding informs on the importance of adequately controlling CINV in the first cycle to prevent development of anticipatory CINV in the subsequent cycles.

CHAPTER THREE: MATERIALS AND METHOD

3.1 Research Design

Longitudinal prospective study design was adopted for this study. Children on various chemotherapy regimens and on prophylaxis at KNH were assessed prospectively for vomiting incidences up to 120 hours post chemotherapy.

3.2 Location of the Study

The study was carried out at Kenyatta National Hospital (KNH). KNH is located in Upper Hill along Hospital road around 3.5 kilometers from Nairobi central business district. KNH is a level 6 national referral hospital and doubles up as the University of Nairobi (UON) teaching hospital. It is an 1800 bed capacityhospital with 50 wards and 22 outpatient clinics. Out of the 50 wards, ward 1E is specifically for paediatric oncology cases. The facility is the major referral centre that manages adult and paediatric cancer patients referred from various parts of Kenya. Data from the statistics department estimate that there were 332 and 488 cancer patients aged below 12 years in 2015 and 2016 respectively. At KNH, paediatric patients are admitted through clinic 23 every Monday while others are managed as outpatients. Paediatric cancer patients are admitted in wards 1E, 3 A-D and 9D.

3.3 Target Population

The target population was all patients above 5 years and below 12 years of age with cancer and on chemotherapy at KNH.

3.4 Inclusion/Exclusion criteria

3.4.1 Inclusion criteria

- Patients aged from 5 to 12 years admitted for chemotherapy at KNH
- Patients who assented and whose parents/guardians consented for inclusion into the study

3.4.2 Exclusion criteria

The following patients were excluded from the study

- Patients/parents/guardians who did not consent/assent
- Patients with documented vomiting episodes within 24 hours prior to chemotherapy which was indicated on the patient's treatment sheet by the primary care giver.
- Patients undergoing concurrent radiation therapy.

3.5 Sample size determination

The formula used as described by A. S. Singh *et al*.(75)

$$sample = \frac{Z^2.p(1-p)}{e^2}$$

Interpretation and assumptions:

p = Prevalence of CINV with prophylaxis was estimated to be 20% based on previous study carried out at KNH(48).

e = Margin of error of 0.05

Z = standard normal variate at 5% type 1 error it is 1.96

$$sample = \frac{1.96^2.0.2(1-0.2)}{0.05^2}$$

Sample size = 246

Considering adjustments for finite population as described by A. S. Singh *et al* (75) over a period of 3 months based on annual admissions of 332 patients as per KNH statistics:

$$n = \frac{n_0.N}{n_0 + (N-1)}$$

$$n = \frac{246.332}{246 + (83-1)}$$

Adjusted sample size = 63 patients

To account for about 10% loss to follow up a sample size of 70 was considered. A total of 88 participants were recruited into the study.

3.5.1 Sampling technique

Universal sampling was used since the calculated sample size was close to the average number of patients likely to be admitted within the three months of data collection.

3.6 Research Instruments

A structured questionnaire to assess the adequacy of control of CINV was administered 24 hours after chemotherapy to assess acute CINV and from 25-120 hours post chemotherapy to

assess delayed CINV. Consent and assent was sought from the parent/guardian and the participant respectively before study participation. Independent and voluntary consent and assent given by the parent/guardian and the child respectively was a mandatory requirement before being included into the study (appendix II). The questionnaire was structured so as to capture the following information: patient biodata, chemotherapy regimen and dosing schedule, CINV prophylaxis regimen, CINV prophylaxis dosing and timing schedule and frequency of vomiting up to 120 hours post chemotherapy (Appendix I). Information on chemotherapy and prophylaxis regimen type, dosing and duration was extracted from individual patient files and corroborated with what was administered. For inpatients data on incidences of vomiting was collected directly from the patients in the cancer wards 1E, 3A-D and 9D. For patients who got discharged before 120 hours of follow up were over, data on incidence of vomiting was collected twice daily by use of mobile telephone call to the caregivers/parents with direct entry of information into the questionnaires.

3.7 Pilot Study

The questionnaire was piloted on 10 patients, who were not included in the study. This helped to find out the time taken to administer the questionnaire, comprehension of the questions and its ability to capture data as per the study's aims and objectives. From the piloting study it was found that the questionnaire needed no further modifications.

3.8 Validity

The study was carried out in children aged from 5 - 12 years. The following measures were taken into consideration to ensure validity. Data collection tools were designed in such a way that they:

- Captured all data relevant to the study objectives and the content of the entire study
- Were easy to comprehend by availing English and Swahili versions with a simplified version for the children.
- They were administered to the children by the investigator and/or trained assistant so as to overcome communication barriers. Interviewer and/or trained assistant were able to explain and answer questions regarding the data collection tool on the spot.

Internal validity was ensured by collecting data on vomiting in a timely manner to avoid recall bias. Data on incidences of vomiting was collected daily between 8 am and 9 pm. This timing corresponded to the dosing schedules of most chemotherapeutic agents and CINV prophylaxis medicines. Similar tools were used for all the patients to ensure uniformity in

obtaining information. External validity was ensured by choosing a representative sample size.

3.9 Reliability

Internal reliability of the data collection tools was determined by pretesting them to 10 respondents who were not included in the study. The pretest questionnaires were administered to the respondents at the same time. Chronbach alpha value was calculated using Stata version 13.0. A Chronbach alpha value of 0.7222 was obtained which was a good indicator of internal reliability of the data collection tool that was used.

3.10 Data Collection Techniques

Patients were selected for inclusion into the study at the outpatient clinics and respective inpatient wards. All patients that met the inclusion criteria were approached by the investigator and informed on what the study entailed. Thereafter, their assent and consent to include them into the study was sought. Assent forms and consent forms were required to be signed by the study participants and their parents/guardians before being included into the study. Outpatients that were recruited into the study were followed up in their respective wards after admission. Each of the patients was given a unique patient code so as to ensure their confidentiality during data collection, entry and analysis. Data from the patients was collected by the investigator and one research assistant. Data on incidences of vomiting was collected daily (8am – 9pm) at the patient's convenience for five consecutive days post chemotherapy. This data collection exercise was carried out daily (approximately twenty minutes per participant) for a period of 5 days after chemotherapy session. Patient's biodata was extracted from the patient and from the patient's medical records and entered into the coded questionnaire by either the investigator or the research assistant. For the patients that got discharged before follow up period was over, data was collected through mobile phones call to the caregivers/parent as agreed in the consent and assent documents. All efforts were made to prevent loss to follow up, especially for patients that got discharged before the end of follow up by seeking alternative mobile number(s) in case they were offline during follow up. The investigator engaged the primary care doctors and the nurses in the respective wards so as to brief them on what the study was all about and sought their cooperation. The investigator liaised and shared information on patients with poor control of emesis (>5 episodes/severe emesis) with the primary care physicians, nurses, pharmacists with the sole aim of considering rescue medications. All duly filled forms were kept under lock and key at all times to limit accessibility by any other person other than the investigator.

3.12 Data Analysis

Descriptive analysis was done for all variables and tabulated as frequencies and percentages. Bivariate analysis was done, using Fisher's exact test, to assess associations between various categorical variables and the primary outcome. The primary outcome of interest in this study was complete response rate in acute, delayed and overall phases. Associations were regarded as statistically significant if the p value was equal to or less than 0.05. Strengths of the associations were studied using binary logistic regression model of the independent (risk factors) versus the dependent variables (emesis) and tabulated using crude and adjusted odds ratios, confidence intervals and their corresponding p values.

3.13 Ethical Considerations

Informed assent was sought from the study participant and informed consent from the parent/guardian before joining the study. It was a mandatory requirement for the parent and the child to freely and voluntarily give consent/assent for them to be included into the study. It was sufficiently explained to the participants that joining of the study was voluntary and one could exit the study at any given point in time during the study without repercussions. There were no incentives or compensation for participants joining the study. Ethical approval was sought and granted from the UON/KNH ethics review committee (P52/01/2017). Confidentiality was maintained at all times during data collection by coding of forms, during data analysis and post analysis by keeping all documents under lock and key. Information on patients not responding to prophylaxis (>5 episodes/severe emesis) was noted and in a timely manner relayed to the primary care giver with the sole aim of managing the breakthrough emesis. However the management of breakthrough vomiting was at the discretion of the primary care physician or nurse. The disclosure to the primary care doctor was captured in the consent and assent forms for purposes of informing the patient and the caregiver.

CHAPTER FOUR: RESULTS

4.1 Patients recruitment process

Over the three months data collection period 112 patients were screened for eligibility. Seventeen patients were excluded because they were aged less than 5 years while 7 were excluded because we could not obtain assent or consent. Eighty eight patients met the inclusion criteria and were recruited into the study. **Figure 2**

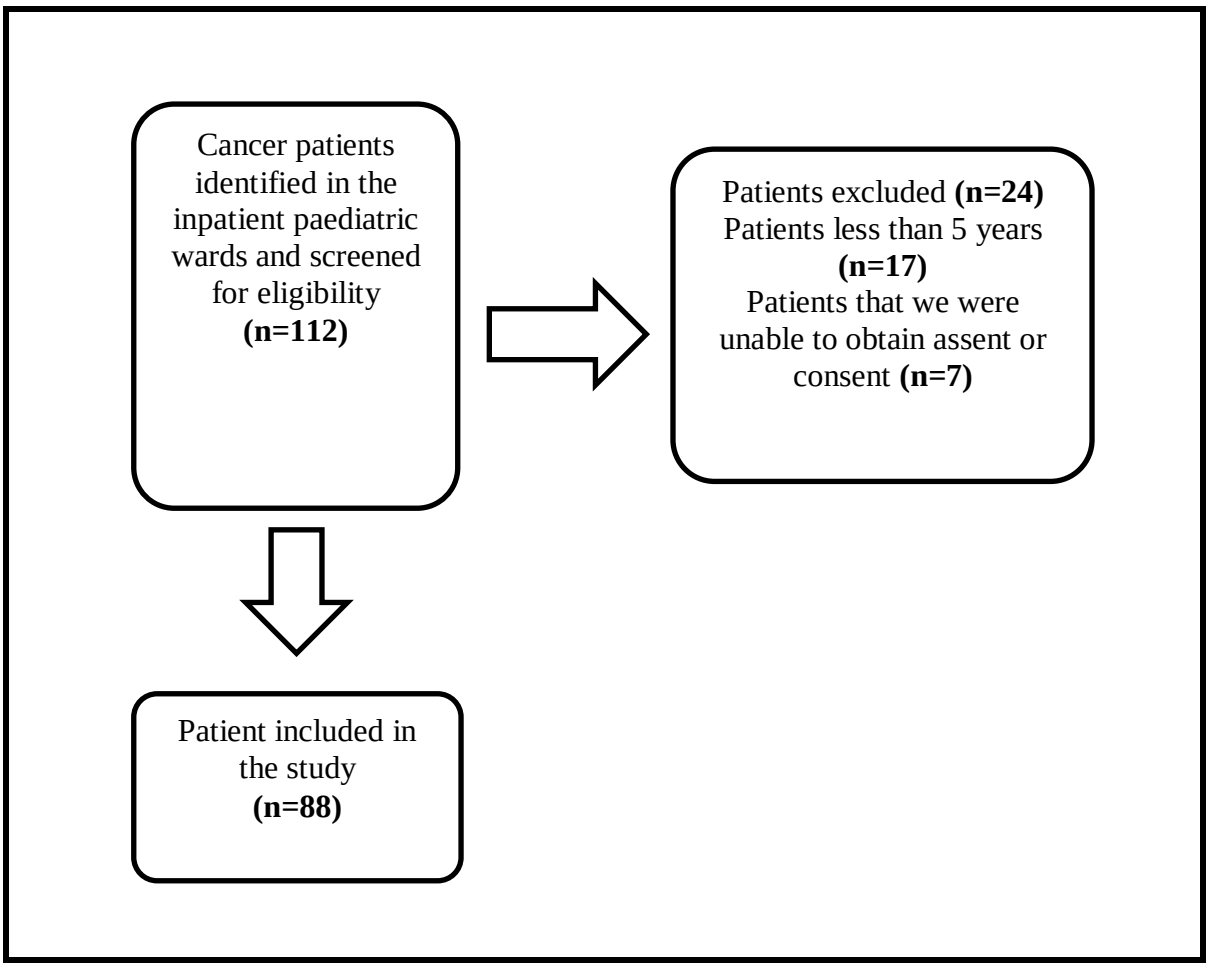


Figure 2: Consort diagram on patients' recruitment process

4.2 Socio-demographic characteristics.

There were more male participants (58, 65.9%) than females (30, 34.1%) as shown in **table 11**. The median weight was 22.25kg (20.0 – 29.0) while the BSA ranged from 0.57 – 1.52M^2 (Mean 0.95±0.21). Acute lymphoblastic leukemia was the most common hematological malignancy (32, 36.36%). Rhabdomyosarcoma was the most common (13, 14.77%) solid tumor. More than half of the patients were on highly emetogenic chemotherapies (46,

52.3%); with the rest of the patients being on either moderate emetogenic chemotherapies (39, 44.3%) or low and minimal emetogenicity chemotherapies (3, 3.4%).

Table 11: Socio-demographic characteristics (N=88)

Variable	Category	Frequency n (%)
Age (years)	5 – 8	50 (56.8)
	9-12	38 (43.2)
Gender	Male	58 (65.9)
	Female	30 (34.1)
Types of cancer	Hematological malignancies	55 (62.5)
	Solid tumors	33 (37.5)

Figure 3: Frequencies of hematological cancers

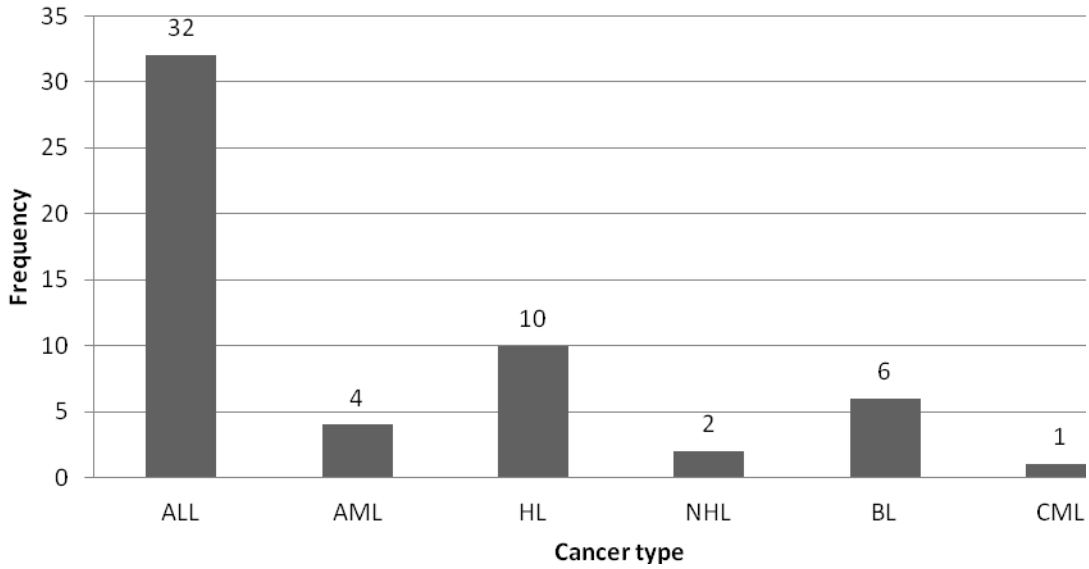
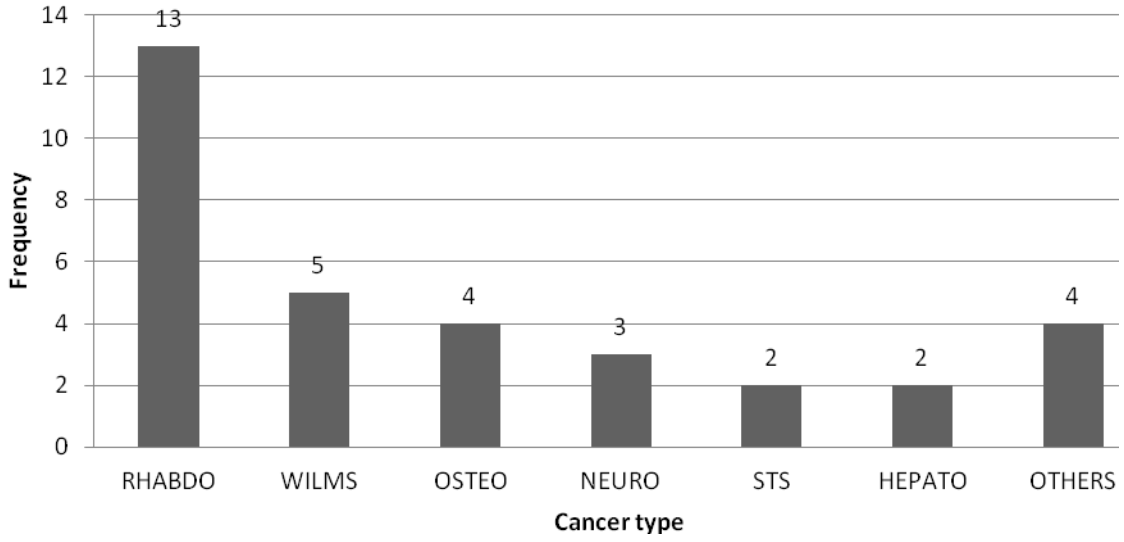


Figure 4: Frequencies of solid cancers



4.2.1 Types of chemotherapies used

There were 6 (6.82%) chemotherapy naïve patients and 82 (93.18%) chemotherapy exposed participants in the study. Out of all the chemotherapies that were given, the most common regimen consisted of vincristine, doxorubicin, cyclophosphamide and cisplatin and accounted for 10 (11.36%) of the rgimens. Chemotherapies were classified according to their respective emetogenicity levels based on Hesketh's classification (**table 1 and 2**). Majority of the chemotherapy combinations were in the high emetogenicity (46, 52.3%) category. Moderate emetogenic chemotherapies (level 3 and 4) were the second most common category at 39 (44.3%). Low and minimal emetogenic chemotherapy had the lowest frequencies (3, 3.4%) as per **Table 12a**. Chemotherapy combinations were further classified into four categories namely: platinum based regimens, cylophosphamide based regimens and combinations of cyclophosphamide and platinum compounds. Agents that did not fall in any of those categories were grouped together as 'others'. Thirteen chemotherapy combinations (14.77%) were platinum and cyclophosphamide based, 6 (6.82%) were platinum based, 42 (47.73%) were Cyclophosphamide based and the rest were 27 (30.68%) as per **Table 12c**. Dosages of platinum and cyclophosphamide based regimens encountered are summarized in **Table 12b.** To assess the effects of steroids in the chemotherapy regimen, additional classification was developed into: steroid containing regimens and those without a steroid (**Table 12c)**. There were 66 (75%) regimens without a steroid and 22 (25%) with a steroid. Steroid containing regimens were used in management of hematological cancers. Fifty three regimens (60.23%) were given as single day treatment and the rest (35, 39.77%) as multiday therapies.

Table 12a: Chemotherapy regimens given to study participants (N=88)

Variable	Category	Frequency n (%)
Emetogenicity level	Level 1	1 (1.1)
	Level 2	2 (2.3)
	Level 3	9 (10.2)
	Level 4	30 (34.1)
	Level 5	46 (52.3)
Duration of chemotherapy	Single day chemotherapy	53 (60.23)
	Multiday chemotherapy	35 (39.77)
Exposure status	Chemo naïve	6 (6.82)
	Prior chemotherapy exposure	82 (93.18)

Table 12b: Dosing ranges of a few selected chemotherapy regimens (N=88)

Chemotherapy type	Agent	Dosing	Frequency
CPP based	CPP	≤750mg/ m^2	48 (87.27%)
		>750 - ≤1500mg/ m^2	7 (12.73%)
	IFOS	1800mg/ m^2	2 (50%)
		2000mg/ m^2	2 (50%)
PLT based	CARB	200mg/m^2	1 (16.67%)
		450 mg/m^2	3 (50%)
		500 mg/m^2	1 (16.67%)
		600 mg/m^2	1 (16.67%)
	CIS	≤50mg/ m^2	10 (76.92%)
		>50mg/ m^2	3 (23.08%)

Table 12c: Combination of various chemotherapy regimens (N=88)

	Category	Frequency
Presence of PLT or CPP	CPP + PLT based regimen	13 (14.77%)
	PLT based regimen	6 (6.82%)
	CPP based regimen	42 (47.73%)
	Other regimens	27 (30.68%)
Regimen steroid status	With steroid	22 (25%)
	without steroid	66 (75%)

Table 13: Type of cancer and the frequency of exposure to various chemotherapy regimens (N=88)

	Cancer type	CPP based	PLT based	CPP and PLT based	Others
Leukemias	ALL	12 (32.43%)	0	0	20 (54.05%)
	AML	0	0	0	4 (10.81%)
	CML	0	0	0	1 (2.70%)
Lymphomas	HL	9 (50%)	0	0	1 (5.56%)
	NHL	7 (38.89%)	0	1 (5.56%)	0
Solid tumors	Rhabdo	10 (30.30%)	2	1 (3.03%)	0
	Osteo	0	0	4 (12.12%)	0
	Wilms	0	0	4 (12.12%)	1 (3.03%)
	Neuro	2 (6.06%)	0	1 (3.03%)	0
	Others	2 (6.06%)	4 (12.12%)	2 (6.06%)	0
Total		**42**	**6**	**13**	**27**

4.3: Interventions given in acute, delayed and breakthrough emesis

4.3.1 Acute emesis

Eighty six (97.7%) participants received prophylaxis for acute emesis. Ondansetron and granisetron monotherapy was used as prophylaxis in 77 (87.5%) and 6 (6.8%) participants respectively. Three (3.4%) participants got two drug combination prophylxis with ondansetron and dexamethasone. All the 86 participants received prophylaxis at leats thirty minutes before chemotherapy. Dosing of prophylaxis interventions was within the guideline

recommended limits of 0.15mg/kg in 39 patients (44.32%). Nine patients (10.23%) got doses below guideline recommended limits while 38 (43.18%) patients got doses above the guideline recommended limits. Ondansetron monotherapy was given as prophylaxis in 77 (87.5%) patients. Eighty three patients (94.32%) got single prophylactic dose of 5-HT_3 antagonsist for acute nausea. Seventy five patients (85.23%) got prophylaxis on the first day while 11 (12.50%) got it for more than one day.

Table 14: Prophylaxis of acute vomiting (N=88)

Characteristic	Response	Frequency n, (%)
Vomiting status	Present	47 (53.41)
	Absent	41 (46.59)
Prophylaxis given	Yes	86 (97.73)
	No	2 (2.27)
Choice of prophylaxis	Ondansetron	77 (87.50)
	Ondansetron/dexamethasone	3 (3.41)
	Granisetron	6 (6.82)
	No prophylaxis	2 (2.27)
Dosing appropriateness	Below guideline recommendation	9 (10.23)
	Per guideline	39 (44.32)
	Above guideline recommendation	38 (43.18)
	No prophylaxis given	2 (2.27)
Timing	Given 30 minutes before chemotherapy	86 (97.73)
	No prophylaxis given	2 (2.17)
Frequency	OD (ondansetron)	83 (94.32)
	BD (dexamethasone)	1 (1.14)
	TID (dexamethasone)	2 (2.27)
Duration	Single day prophylaxis	75 (85.23)
	Multiday prophylaxis	11 (12.50)

4.3.2 Delayed emesis

Delayed emesis was reported in 49 (55.68%) participants; 10 (20.41%) of whom had received prophylaxis. The administration of prophylaxis in delayed emesis was much lower (10, 11.36%) compared to acute phase (86, 97.73%). Ondansetron was given to 7 (7.95%) respondents while 3 (3.41%) got dexamethasone and ondansetron combination as

prophylaxis. Prophylaxis was given for more than one day in 9 out of the 10 participants. Dosing was within guideline limits in 2 (66.67%) out of the 3 patients on dexamethasone. Two out of the ten (20%) patients on ondansetron had lower than recommended dosing. The frequency of delayed vomiting prophylaxis was: once daily in 8 participants (9.09%), twice daily in 1 participant (1.14%) and three times daily in 1 participant (1.14).

Table 15: Prophylaxis of delayed vomiting (N=88)

Characteristic	Response	Frequency n, (%)
Delayed vomiting	Present	49 (55.68)
	Absent	39 (44.32)
Prophylaxis given	Yes	10 (11.36)
	No	78 (88.64)
Choice of prophylaxis	Ondansetron	7 (7.95)
	Ondansetron +Dexamethasone	3 (3.41)
Dosing appropriateness	Below guideline recommendation	3 (3.41)
	As per guideline recommendation	7 (7.95)
Timing	Beginning on day 2 of chemotherapy	10 (11.36)
Frequency	24 hourly	8 (9.09)
	12 hourly	1 (1.14)
	8 hourly	1 (1.14)
Duration	Single day therapy	1 (1.14)
	Multiday therapy	9 (10.23)

4.3.3 Breakthrough vomiting

Breakthrough vomiting was reported in 56 (65.12%) participants. Only 12 (13.64%) out of the 56 participants who experienced breakthrough vomiting got rescue therapy. Ondansetron was the only agent that was given to the patients as rescue treatment. Out of the 12 rescue doses, 8 (66.67%) were given at a dose of 0.15mg/kg while 4 were given at doses more than 0.15mg/kg dosing. Rescue therapy was given as once daily dosing frequency in all the participants with breakthrough vomiting. Ten respondents (11.36%) got rescue therapy for one day only and 2 (2.28%) received for more than one day.

Table 16: Prophylaxis for breakthrough vomiting (N=88)

Breakthrough vomiting	Category	Frequency n, (%)
Incidence	Breakthrough vomiting	56 (65.12)
	No breakthrough vomiting	30 (34.88)
Rescue treatment status	Rescue treatment given	12 (13.95)
	Rescue treatment not given	44 (51.16)
Choice of rescue medication	Ondansetron	12 (13.95)
Dosing appropriateness	As per guideline recommendation	8 (9.3)
	Above guideline recommendation	4 (4.65)
Frequency	Once daily dosing	12 (13.95)
Duration	Single day rescue treatment	10 (11.63)
	Multiday rescue treatment	2 (2.33)

4.4: Antiemetic response rates

4.4.1 Overall response rates

Complete response in acute, delayed and overall phase of emesis was 53.4%, 55.7% and 34.1% respectively. Emesis was at its peak on the first day of chemotherapy (41, 46.59%) and then reduced gradually during the follow up period with lowest incidences on the fifth day post-chemotherapy (6, 6.82%). Participants experienced a mean of 2 vomiting episodes in both acute and delayed phases. Severity of vomiting was classified according to the number of episodes of emesis; mild (1 -2 episodes), moderate (3 – 5 episodes) and severe (more than 5 episodes). During this period, there were 20 (22.73%) cases of mild vomiting, 17 (19.32%) cases of moderate vomiting and 21 (23.86%) cases of severe vomiting (**Table 17)**.

Table 17: Response rates and severity of emesis (N=88)

Category	Frequencies n (%)		
Episodes of vomiting	**Acute vomiting**	**Delayed vomiting**	**Overall (Day 1 – 5)**
0 episodes	47 (53.41)	49 (55.68)	30 (34.09)
1 -2 episodes	17 (19.32)	17 (19.32)	20 (22.73)
3 – 5 episodes	15 (17.05)	13 (14.77)	17 (19.32)
>5 episodes	9 (10.23)	9 (10.23)	21 (23.86)

4.4.2 Effect of chemotherapy regimens on antiemetic response rate

4.4.2.1 Emetogenicity of the regimen

Increase in emetogenicity level was generally associated with lower complete response rates in all the phases of CINV (**Table 18)**. Participants on level 5 (high emetogenicity) regimens had the lowest levels of complete response in all phases while those on level 1 (minimal emetogenicity) had the highest complete response rates.

Table 18: Complete response rates at varying emetogenicity of chemotherapy regimen

	Acute phase	**Delayed phase**	**Overall Phase**
Emetogenicity level	**CR (%)**	**CR (%)**	**CR (%)**
Level 1 (n=1)	1 (100%)	1 (100%)	1 (100%)
Level 2 (n= 2)	0 (0%)	1 (50%)	0 (0%)
Level 3 (n=9)	7 (77.78%)	7 (77.78%)	5 (55.56%)
Level 4 (n=30)	19 (63.33%)	20 (66.67%)	14 (46.67%)
Level 5 (n=46)	20 (43.48%)	20 (43.48%)	10 (21.74%)

4.4.2.2 Composition of chemotherapy

Composition of chemotherapy regimen had an effect on incidences of emesis. In acute emesis, patients on regimens containing both cyclophosphamide and platinum compound had the lowest response rates 2/13 (15.38%). In the delayed phase, patients on platinum based regimens had the lowest response rate (0%). Overall, patients with regimens consisting of platinum based compound had the lowest response rate (0%). One participant (7.69%) on regimen consisting of both cyclophosphamide and platinum compound had complete

response rate. Regimens were further grouped into two categories based on presence of a steroid in the chemotherapy regimen. Prednisolone was incorporated into the treatment regimen mostly in management of leukemias. Patients with steroid containing regimens had better responses in all phases of CINV as tabulated in **Table 19b** compared to patients on regimens without steroid.

Table 19a: Incidence and severity of vomiting (N=88)

		Number of vomiting episodes				
Phase	**Regimen**	**0**	**1 -2**	**3 – 5**	**>5**	**CR rate**
Acute phase	Other regimens	19	3	4	1	70.37%
	CPP only	22	9	7	4	52.38%
	PLT only	4	1	1	0	66.67%
	PLT + CPP	2	4	3	4	15.38%
Delayed phase	Other regimens	17	2	3	5	62.96%
	CPP only	27	9	2	4	64.29%
	PLT only	0	5	1	0	0%
	PLT + CPP	5	1	7	0	38.47%
Overall phase	Other regimens	14	3	4	6	51.85%
	CPP only	15	11	9	7	35.71%
	PLT only	0	4	1	1	0%
	PLT + CPP	1	2	3	7	7.69%

Table 19b: Incidence and severity of vomiting in various chemotherapy types (N=88)

		Number of episodes				
Phase	**Regimen**	**0**	**1 -2**	**3 – 5**	**>5**	**CR rate**
Acute	No steroid	32	15	14	5	48.48%
	Steroid	15	2	1	4	68.18%
Delayed	No steroid	31	17	12	6	46.97%
	Steroid	18	0	1	3	81.82%
Overall	No steroid	18	18	15	15	22.27%
	Steroid	12	2	2	6	54.55%

Table 19c: Distribution of various chemotherapies according to cancer type (N=88)

Type	PLT + CPP based	PLT based	CPP based	Others	Steroid present	Steroid absent
Hematological	1	0	28	26	22	33
Solid tumor	12	6	14	1	0	33

4.5 Bivariate analysis

4.5.1 Association between sociodemographic characteristics and incidence of emesis

Eighteen males (31.03%) and twelve females (40%) had complete response over the 5 day follow up period. Majority of the respondents (58, 68.91%) had emesis even after prophylaxis. Thirty four participants (68%) within the 5 – 8 years age category did not achieve complete response while twenty four (63.16%) of the participants within the 9 – 12 years age category did not achieve complete response (**Table 20).** Effect of age and sex on emesis was not statistically significant.

Table 20: Association between age, sex and overall emesis (N=88)

		Overall complete response		
Variable	**Classification**	**No emesis**	**Emesis**	**P value**
Sex	Male	18	40	
	Female	12	18	0.271
Age	5 – 8 yrs	16	34	
	9 – 12 yrs	14	24	0.401

4.5.2 Association between type of chemotherapy regimens and antiemetic response

4.5.2.1 Categories of Chemotherapy

There was a statistically significant association between overall complete response, and categories of chemotherapy regimens. One participant (7.69%) on platinum and

cyclophosphamide (Combined) based regimens achieved complete response. The low response rate was due to synergistic emetic effect of cyclophosphamide and platinum regimens. All the patients on platinum based regimens did not achieve response. Fifteen participants (35.71%) on cyclophosphamide based regimen achieved complete response. Cyclophosphamide based regimens were found to be less emetogenic than platinum based regimens. Twelve participants (54.55%) who used steroid containing regimens achieved complete response compared to 18 (27.27%) on regimens without a steroid. The higher response rate in the steroid containing regimens is due to the antiemetic effect of steroids in both acute and delayed emesis. Participants on high emetogenic regimens had lower complete response rates compared to lesser emetogenic regimens as tabulated in **table 21**. These associations are expounded further in binary logistic regression section.

Table 21: Association between types of chemotherapy and overall response (N=88)

		Overall response		
Variable	**Classification**	**complete response**	**No response**	**P value**
Chemotherapy type	PLT + CPP	1 (7.69%)	12	0.010
	PLT	0 (0%)	6	
	CPP	15 (35.71%)	27	
	Others	14 (51.85%)	13	
Presence of steroid	Absent	18 (27.27%)	48	0.036
	Present	12 (54.55%)	10	
Emetogenicity level	Level 1	1 (100%)	0	0.023
	Level 2	0 (0%)	2	
	Level 3	5 (55.56%)	4	
	Level 4	14 (46.67%)	16	
	Level 5	10 (21.74%)	36	

4.5.2.2. Effect of duration of chemotherapy administration on emesis

Chemotherapy duration had a statistically significant effect in the acute and delayed phases of CINV as tabulated in **table 22**. Complete response rates in participants on multiple day chemotherapy rates were lower than those of patients on single day therapy. This is attributed

to continued exposure to chemotherapeutic agents for a longer duration leading to higher cumulative doses than single day chemotherapy.

Table 22: Effect of chemotherapy duration on emesis (N=88)

	Complete response rate, p – value					
Duration of therapy	**Acute phase**	**p value**	**Delayed phase**	**p value**	**Overall Phase**	**p value**
Single day	54.72%	0.010	66.04%	0.049	37.73%	0.271
Multi-day	51.42%		40%		28.57%	

4.5.3 Association between type of antiemetic, dosing appropriateness and emesis

4.5.3.1. Acute phase

Eighty six participants (97.73%) got prophylaxis against acute emesis. Despite the high rates of acute emesis prophylaxis, 56 (65.11%) patients did not achieve complete response. There was no statistically significant difference between ondansetron and granisetron in the control of emesis. The frequencies of the observations were too few to make conclusions on superiority/inferiority of either ondansetron or granisetron in management of emesis. Complete response in cases where ondansetron or granisetron was used was 31.82% and 33.2% respectively. Eighty three participants (94.32%) got a single dose of antiemetic thirty minutes before chemotherapy and thirty of them achieved complete response in the acute phase. Prophylaxis was given on a single day (first day) in 75 (87.21%) patients whereas 11(12.79%) participants received for more than one day. Associations that were found between control of emesis and type, timing, dosing, frequency and duration of acute prophylaxis interventions were not statistically significant.

Table 23: Association between prophylaxis dosing and acute emesis (N=88)

		Response		
Variable	**Classification**	**CR**	**No CR**	**P value**
Prophylaxis given	Yes	30 (34.09%)	56 (63.64%)	
	No	0 (0%)	2 (2.27%)	0.545
Dosing accuracy	Low	3 (3.41%)	6 (6.82%)	
	Guideline recommended	13 (14.77%)	26 (25.55%)	
	High	14 (15.91%)	24 (27.27%)	0.947
Choice of prophylaxis	Ondansetron	28 (31.82%)	52 (59.09%)	
	Granisetron	2 (2.27%)	4 (4.55%)	0.999
Frequency	Once daily dosing	30 (34.09%)	53 (60.23%)	
	Twice daily dosing	0 (0%)	1 (1.14%)	
	thrice daily dosing	0 (0%)	2 (2.27%)	0.699
Timing	Given 30min before chemo	30 (34.09%)	56 (63.64%)	
	Not given 30min before chemo	0 (0%)	2 (2.27%)	0.432
Duration	Single day	28 (31.82%)	47 (53.41%)	
	Multiple day	2 (2.27%)	9 (10.23%)	0.315

4.5.3.2 Delayed emesis

A greater proportion of participants who got prophylaxis for delayed emesis 9/10 (90%) achieved better response compared to patients who did not (49/78, 62.8%, *p*-value 0.154). Perhaps due to low frequencies, it was not possible to determine superiority/or inferiority of combination therapy versus monotherapy. All the participants who received per guideline prophylaxis achieved complete response in the delayed phase compared to those who got none or below guideline doses (*p*-value 0.124). However, the frequencies were quite low to draw concrete associations from the findings. There were no statistically significant associations at different frequencies, timings or duration of prophylaxis.

Table 24: Association between dosing appropriateness and delayed emesis

		Delayed Emesis		
Variable	**Classification**	**Yes n, (%)**	**No n, (%)**	**P value**
Prophylaxis given	Yes (n=10)	1 (10%)	9 (90%)	
	No (n=78)	29 (37.2%)	49 (62.8%)	0.154
Dosing accuracy	Low (n=3)	1 (33.3%)	2 (66.7%)	
	Accurate (n=7)	0 (0%)	7 (100%)	
	No prophylaxis (n=78)	29 (37.2%)	49 (62.8%)	0.124
Type	Ondansetron (n=7)	0 (0%)	7 (100%)	
	DEX + ondansetron (n=3)	1 (33.3%)	2 (66.7%)	
	No prophylaxis (n=78)	29 (37.2%)	49 (62.8%)	0.124
Frequency	Once daily dosing (n=8)	0 (0%)	8 (100%)	
	Twice daily dosing (n=1)	1 (100%)	0 (0.0%	
	Thrice daily dosing (n=1)	0 (0%)	1 (100%)	0.200
Timing	Daily after chemotherapy (n=10)	1 (10%)	9 (90%)	
	No prophylaxis (n=78)	29 (37.2%)	49 (62.8%)	0.154
Duration	Single day (n=1)	0 (0%)	1 (100%)	
	Multiple day (n=9)	1 (11.1%)	8 (88.9%)	1.000

4.5.3.3 Breakthrough emesis

Rescue treatment was given to 13 (14.77%) participants out of 58 (65.9%) participants that had at least one episode of breakthrough emesis. Ten out of thirteen (76.92%) participants had no vomiting episodes after receiving rescue therapy. This translates into rescue therapy success rate of 76.92%. There was a statistically significant association between achievement of complete response and the use of rescue medicines in breakthrough vomiting (p = 0.000). This indicates there was a difference in overall emesis contol between those who got rescue therapy and those who did not. However, the strength of this association could not be determined through binary logistic regression due to low frequencies.

Table 25: Association between use of rescue therapy and overall control of emesis

	Severity of emesis (overall)				P value
Rescue given?	No emesis	1 – 2 episodes	3 – 5 episodes	>5 episodes	
Yes	0	0	2	11	**0.000***
No	30	20	15	10	

Table 26: Association between rescue therapy appropriateness and overall control of emesis (N=88)

		Emesis		
Variable	**Classification**	**No (n, %)**	**Yes (n, %)**	**P value**
Rescue therapy given	Yes	0 (0%)	13 (14.77%)	
	No	30 (34.09%)	45 (51.14%)	0.007*
Dosing accuracy (ondansetron)	0.15mg/kg	0 (0%)	9 (10.23%)	
	High	0 (0%)	4 (4.55%)	
	No rescue given	30 (34.09%)	45 (51.14%)	0.031*
Choice of rescue drugs	Ondansetron	0 (0%)	13 (14.77%)	
	No prophylaxis	30 (34.09%)	45 (51.14%)	0.007*
Frequency	OD	0 (0%)	13 (14.77%)	
	No prophylaxis	30 (34.09%)	45 (51.14%)	0.007*
Duration of prophylaxis	Single day	0 (0%)	11 (12.50%)	
	Multiple day	0 (0%)	2 (2.27%)	
	No prophylaxis	30 (34.09%)	45 (51.14%)	0.010*

Bivariate analysis showed that in terms of dosing appropriateness, there was statistically significant difference between the groups that got prophylaxis and the one that did not regardless of the prophylaxis administration schedule. It was not possible to determine the strength of the association in binary logistic regression due to low frequencies.

4.6: Adherence to guideline recommendations

Most guidelines recommend use of a $5HT_3RA$ together with a steroid and a neurokinin receptor antagonist in prophylaxis of acute emesis in HEC regimens. Steroids or neurokinin receptor antagonists are avoided in situations where they are contraindicated. POGO does not recommend use of aprepitant (NK_1RA) in children less than 12 years. Therefore in HEC and MEC it recommends use of 5HT3RA combined with either a steroid or an adjunct drug like metoclopromide, chlorpromazine or nabilone as outlined in **table 8**. However the use of NK_1RA's like aprepitant is limited by its availability in the Kenyan market. In LEC, POGO and MASCC/ESMO recommends use of $5HT_3RA$ alone. Forty three participants (95.56%) on HEC got $5HT_3RA$ only as prophylaxis in the acute phase. Two participants (4.44%) on HEC got $5HT_3RA$ combined with a steroid. Similarly, 38 participants (97.44%) on MEC chemotherapy got a $5HT_3RA$ only as prophylaxis. Only one participant (2.56%) on MEC got

combination of $5HT_3RA$ with a steroid. The $5HT_3RA$ and dexamethasone for acute emesis prophylaxis was given thirty minutes prior to chemotherapy.

For delayed emesis MASCC/ESMO, POGO guidelines and Kasili's synopsis recommend use of dexamethasone in HEC and MEC as tabulated in **Table 3 - 8**. Three patients got dexamethasone combined with ondansetron for delayed vomiting while seven patients got ondansetron only for delayed emesis. These drugs were given as from the second day of chemotherapy for delayed emesis prophylaxis. Use of ondansetron is only recommended in acute vomiting prophylaxis and breakthrough vomiting. Further research is required to evaluate knowledge and adherence levels to guideline recommendations.

Table 27: Antiemetics used in acute vomiting prophylaxis in the study participants

Emetogenicity	Ondansetron n (%)	Granisetron n (%)	ondansetron + dexamethasone n (%)
HEC (Level 5)	42 (47.7)	1 (1.14)	2 (2.27)
MEC (Level 4)	25 (28.4)	4 (4.55)	1 (1.14)
MEC (Level 3)	8 (9.1)	1 (1.14)	0
LEC (Level 2)	1 (1.14)	0	0
MINIMAL (Level 1)	1 (1.14)	0	0

Table 28: Antiemetics used in delayed vomiting prophylaxis in the study participants

Emetogenicity	Ondansetron (n, %)	Ondansetron + Dexamethasone (n, %)
HEC (Level 5)	4 (4.55)	2 (2.27)
MEC (Level 4)	2 (2.27)	1 (1.14)
MEC (Level 3)	1 (1.14)	0
LEC (Level 2)	0	0
MINIMAL (Level 1)	0	0

4.7 Logistic regression analysis

4.7.1 Effect of sex and age

It was found that the females are 39% less likely to experience emesis over the entire follow up period of 5 days (p=0.553). In the acute phase females are16% less likely to experience acute emesis (p=0.660). In the delayed phase (day 2 to 5) female were 14.2% (p = 0.772) more likely to experience delayed vomiting. Participants in the 9 – 12 years age category are 12% less likely to experience emesis over the entire 5 days follow up period. In the acute phase, the 9 – 12 years age category patients are 41.8% (p = 0.445) more likely to have acute emesis. However in the delayed phase patients in the 9 – 12 years age category are 27% less likely to have delayed emesis.

Table 29: Association between age, sex and overall control of vomiting

	Variable	COR	P value	AOR	P value
Entire period					
Sex	Male	1		1	
	Female	0.68 (0.27 – 1.69)	0.401	0.61 (0.28 – 1.96)	0.553
Age category	5 – 8 yrs	1			
	9 – 12 yrs	0.81 (0.33 – 1.96)	0.635	0.88 (0.34 – 2.26)	0.790
Acute phase					
Sex	Male	1		1	
	Female	0.82 (0.34 – 1.99)	0.660	0.84 (0.33 – 2.13)	0.715
Age category	5 – 8 yrs	1		1	
	9 – 12 yrs	1.53 (0.66 – 3.59)	0.323	1.42 (0.58 – 3.48)	0.445
Delayed phase					
Sex	Male	1		1	
	Female	1.16 (0.48 – 2.80)	0.750	1.14 (0.47 – 2.81)	0.772
Age category	5 – 8 yrs	1		1	
	9 – 12 yrs	0.85 (0.36 – 2.00)	0.716	0.73 (0.30 – 1.78)	0.488

4.7.2 Effect of type of chemotherapy on emesis

4.7.2.1 Platinum based chemotherapies

Patients on platinum based or platinum and cyclophosphamide based regimens had 20.36 odds of having emesis over the entire follow up period (p = 0.023). Patients on platinum

based regimens were about five times more likely to get emesis in both the acute (AOR = 5.06, P = 0.095) and delayed vomiting phases (AOR = 4.76, P = 0.017) compared to patients on regimens without platinum compound and/or cyclophosphamide in the regimen.

4.7.2.2 Cyclophosphamide based regimens

Patients on cyclophosphamide based regimens had 1.9 times the odds of developing emesis (overall period) compared to patients on regimens without platinum compound or cyclophosphamide (p=0.242). Patients on cyclophosphamide based regimens were twice as likely (AOR = 2.29, P = 0.165) to experience emesis during the acute phase compared to regimens without cyclophosphamide and/or platinum compound. However, in the delayed phase those on cyclophosphamide were 11% less likely (AOR = 0.89, P = 0.843) to experience vomiting as compared to those on regimens without cyclophosphamide and/platinum compounds. Participants on high doses of cyclophosphamide (>750mg/m^2 - <1500mg/m^2) had higher risk of emesis compared to those on lower doses (<750mg/m^2) (OR 2.43 95%CI (0.27 – 21.96) P=0.428)).

4.7.2.3 Presence of steroid in the regimen

Patients on steroid containing regimens were 73.9% less likely to experience emesis over the 5 day follow up period (AOR = 0.261, p = 0.012) compared to those on regimens without a steroid as part of chemotherapy regimen. This protective effect against emesis was more pronounced during the delayed vomiting phase (AOR = 0.15, P = 0.008) compared to the acute phase (AOR = 0.69, P = 0.550).

Table 30a: Effect of chemotherapy type on emesis (overall period)

Variable		COR	P value	AOR	P value
Type of chemotherapy	Other	1		1	
	CPP	1.94 (0.72 – 5.18)	0.187	1.90 (0.65 – 5.58)	0.242
	PLT	19.38 (2.26 – 166.5)	**0.007***	20.36 (1.52 – 272.98)	**0.023***
Presence of steroid	Absent	1		1	
	Present	0.31 (0.12 – 0.85)	**0.022***	0.26 (0.09 – 0.75)	**0.012***

Table 30b: Effect of chemotherapy type on acute emesis

Variable		COR	P value	AOR	P value
Type of chemotherapy	Others	1		1	
	CPP	2.16 (0.78 – 6.01)	0.141	2.29 (0.71 – 7.39)	0.165
	PLT	5.15 (1.44 – 18.36)	**0.012***	5.06 (0.75 – 34.00)	0.095
Presence of steroid	Absent	1		1	
	Present	0.44 (0.16 – 1.22)	0.113	0.69 (0.21 – 2.30)	0.550

Table 30c: Effect of chemotherapy type on delayed emesis

Variable		COR	P value	AOR	P value
Type of chemotherapy	Others	1		1	
	CPP	0.94 (0.35 – 2.58)	0.911	0.89 (0.28 – 2.86)	0.843
	PLT	4.76 (1.32 – 17.22)	**0.017***	6.48 (0.83 – 50.63)	0.075
Presence of steroid	Absent	1		1	
	Present	0.20 (0.06 – 0.64)	**0.007***	0.15 (0.04 – 0.61)	**0.008***

4.7.3 Effect of emetogenicity and duration of chemotherapy on emesis

4.7.3.1 Emetogenicity

For purposes of analysis level 1 – 4 categories were merged due to low frequencies in each cell. Patients on high emetogenicity regimens had 3.3 times the odds of having emesis over the entire follow up period compared to patients who were on moderate, low or minimal emetogenicity regimens (p = 0.018). Patients on high emetogenic regimens were two times and three times more likely to develop emesis in the acute phase (AOR = 2.14, P = 0.128) and delayed phases respectively (AOR = 3.04, P = 0.025).

4.7.3.2 Duration

Patients on multiple day chemotherapy were twice as likely (AOR = 2.39, P = 0.341) to have emesis over the overall follow up period compared to those on single day chemotherapy. Patients on multiple day chemotherapy were five times more likely (AOR = 4.91, p = 0.004), to experience emesis in the delayed phase (day 2 – 5) and 14% more likely to experience vomiting in the acute phase.

Table 31a: Association between duration and emetogenicity on emesis (overall)

Variable		COR	P value	AOR	p value
Duration of therapy	Single	1		1	
(days)	Multiple	1.52 (0.60 – 3.80)	0.376	1.51 (0.57 – 3.98)	0.402
Emetogenicity	level 1 – 4	1		1	
	level 5	3.27 (1.30 – 8.26)	**0.012***	3.30 (1.22 – 8.88)	**0.018***

Table 31b: Association between duration and emetogenicity on acute emesis

Variable		COR	P value	AOR	p value
Duration of therapy	Single	1		1	
(days)	Multiple	1.14 (0.49 – 2.68)	0.762	1.45 (0.53 – 3.97)	0.468
Emetogenicity	level 1–4	1		1	
	level 5	2.34 (0.99 – 5.53)	0.052	2.14 (0.80 – 5.70)	0.128

Table 31c: Association between duration and emetogenicity on delayed emesis

Variable		COR	P value	AOR	p value
Duration of therapy	Single	1		1	
(days)	Multiple	2.92 (1.21 – 7.06)	**0.018***	4.91 (1.66 – 14.57)	**0.004***
Emetogenicity	level 1 – 4	1		1	
	level 5	2.9 (1.21 – 7.06)	**0.017***	3.04 (1.15 – 8.02)	**0.025***

4.7.4 Effects of appropriateness of acute and delayed emesis interventions

4.7.4.1 Dosing

Patients that got guideline recommended dosing of antiemetics were 23% less likely (AOR = 0.77, p = 0.742) to experience emesis (overall period) compared to those that got doses lower than the guideline recommended dosing. Patients who got doses that were higher than the guideline recommended were 35% less likely (P = 0.603) to experience emesis over the entire follow up period.

4.7.4.2 Type of prophylaxis

There was no significant difference in overall emesis control in patients on either ondansetron or granisetron (AOR 1 versus 0.94). Combination of ondansetron and dexamethasone reduced the risk of vomiting in acute phase (p=0.451) and entire period (p=0.457) by 64% and 71% respectively. In the delayed phase patients on who had gotten granisetron for acute emesis were 50% less likely to develop delayed emesis (p=0.453). Patients who got ondansetron and dexamethasone for delayed emesis prophylaxis had 2.87 odds of having emesis (p=0.428)

Table 32a: Association between dosing appropriateness and emesis (overall)

Variable	characteristic	COR	P value	AOR	P value
Dosing	Low	1		1	
	Accurate	1 (0.21 – 4.65)	1	0.77 (0.16 – 3.71)	0.742
	High	0.86 (0.18 – 3.98)	0.844	0.65 (0.13 – 3.28)	0.603
Type	Ondansetron	1		1	
	Granisetron	1.08 (0.19 – 6.28)	0.932	0.94 (0.15 – 5.86)	0.951
	ondansetron + DEX	1.08 (0.09 – 12.46)	0.951	0.29 (0.01 – 7.39)	0.457
Duration	Single day	1		1	
	Multiple day	2.68 (0.54 – 13.30)	0.228	2.3 (0.40 – 14.43)	0.341

Table 32b: Association between dosing appropriateness and acute emesis

Variable	Characteristic	COR	P value	AOR	P value
Dosing	Low	1		1	
	Accurate	1.46 (0.34 – 6.27)	0.612	1.62 (0.34 – 7.77)	0.544
	High	0.73 (0.17 – 3.17)	0.674	0.64 (0.13 – 3.19)	0.586
Type	Ondansetron	1		1	
	Granisetron	1.20 (0.23 – 6.32)	0.830	1.12 (0.20 – 6.29)	0.901
	Ondansetron + DEX	0.6 (0.05 – 6.90)	0.682	0.36 (0.03 – 5.15)	0.451

Table 32c: Association between dosing appropriateness and delayed emesis

Variable	Characteristic	COR	P value	AOR	P value
Dosing	Low	1		1	
	Accurate	0.76 (0.18 – 3.26)	0.712	0.65 (0.06 – 7.44)	0.727
	High	0.52 (0.12 – 2.26)	0.385	1.73 (0.36 – 8.23)	0.494
Type	Ondansetron	1		1	
	Granisetron	0.6 (0.10 – 3.47)	0.568	0.50 (0.08 – 3.02)	0.453
	ondansetron + DEX	2.4 (0.21 – 27.59)	0.482	2.78(0.22 – 34.62)	0.428

5.0 DISCUSSION

There were more males than females in the study. The most common malignancy was acute lyphoblastic leukemia followed by rhabdomyosarcoma. Similar findings, from a paediatrics study, were reported by Mark Holdsworth et al(1). However, a retrospective study done by Macharia at a referral hospital in Kenya and another one carried out in Nigeria reported lymphomas as the most common malignancies in children (76,77).

Complete responses achieved in the acute phase, delayed phase and overall period were 53.41%, 55.68% and 34.1% respectively. Complete response rates in participants on MEC in acute, delayed and overall follow up period were 66.67%, 69.23% and 48.72% respectively. Complete response rates in participants on HEC in acute, delayed and overall phase were 43.48%, 43.48 and 21.74% respectively. In a similar study, where patients (4 -11years) were on MEC and on ondansetron 0.3mg/kg prophylaxis, complete control rates of 73.1% and 61.3% were reported in acute and delayed emesis phases respectively(1). There is limited data on complete response rates in HEC patients receiving single drug therapy. Complete control rates of 39.1% and 43.5% in patients on HEC regimens and on ondansetron (0.45mg/kg) and dexamethasone (10mg/m^2) have been reported. However higher doses of ondansetron (0.3mg/kg versus 0.15mg/kg) and higher rates of double therapy (100% versus 3.49%) were used in the study compared to what was used in this study.

The key statistically significant predictors of emesis in the study were: the emetogenicity level of the regimen (p=0.018), the duration of chemotherapy (p=0.004) and the composition of chemotherapy. Intrinsic emetogenicity of chemotherapy cited as the main predictor of emesis among other factors (8). Determination of the emetogenicity level of chemotherapy before initiation of treatment is important because it guides the choice of antiemetic treatment. According to Dupuis *et al*, this practice is not done routinely and may be the reason for poor control of CINV (6). In this study, it was not possible to find out the criterion that was adopted by the clinicians to decide on what antiemetic to use for a particular patient. Future studies are needed to assess this aspect.

Presence of a platinum compound or cyclophosphamide in the regimen increased the overall risk of emesis (p=0.023, p=0.242 respectively). In the acute phase, the risk of emesis in patients on platinum based regimens was five times higher (p=0.095) than in those without

platinum or cylophosphamide. Those on cyclophosphamide based regimens had twice the risk of developing acute emesis (p=0.165) compared to patients on regimens without either platinum with or without combination with cyclophosphamide. In delayed CINV phase, the risk of emesis was still about five times compared to non-platinum based regimens. Cyclophosphamide delayed emesis risk was similar to other non platinum based regimens. This implies that patients on platinum based regimens are more likely to experience emesis in both acute and delayed phases compared to to other regimens whose effect is more pronounced in the acute phase. Similar findings have been reported by Dupuis *et al*(78).

Presence of a corticosteroid, as part of chemotherapy, reduced the risk of emesis in the overall follow up period (p=0.012). The steroid effect as more significant in the delayed phase than acute phase (p= 0.008 versus p=0.550). Multiday chemotherapies increased the risk of delayed emesis; similar findings have been reported in previous studies(78).More aggressive prophylaxis and management of emesis in patients receiving multiday chemotherapy is recommended. Participants with regimens with platinum compounds (cisplatin) and/cyclophosphamide were found to have higher risk of emesis compared with those without. Patients on doses of cyclophosphamide more than 750mg/m^2 but less than 1500mg/m^2 had a higher risk of emesis compared to those on lower doses of <750 mg/m^2 (p=0.428).

Female participants had a lower risk of developing emesis during the acute phase and in the overall study period. However they had increased risk of emesis in the delayed phase. The findings in the acute and overall phase are inconsistent with previous studies which indicate that female gender is a positive predictor of emesis.

Older participants (9-12 years) had lower risk of emesis in the overall period. This is consistent with emerging evidence that younger patients are more prone to emesis than older ones. However in the acute phase, older participants had higher risk of emesis (AOR 1.42) but a lower risk in delayed emesis (AOR 0.73). This is despite the fact that patients in the 9-12 years age category had a higher percentage (27%) of platinum containing regimens compared to the 5–8 years age category (18%) which are known high risk emetogenic agents.

Single agent prophylaxis, a second generation 5HT3RA, was used in 83/88 participants for acute vomiting and in 7/10 for delayed vomiting. Double therapy, a 5HT3RA and a corticosteroid, was given to 3/86 participants for acute emesis and to 3/10 for delayed emesis. Most guidelines recommend use of a triple therapy or double therapy as prophylaxis for HEC and double therapy for MEC regimens (**table 3 – 9**). Monotherapy with 5HT3RA was given to 43/45 participants on HEC and to 38/39 participants on MEC regimens. This was inconsistent with both local and international guideline recommendations. Two participants, one on LEC and the other on HEC, did not get prophylaxis at all. This is inconsistent with guideline recommendations which exempt routine use of prophylaxis in minimal emetogenic regimens. Use of 5HT3RA in prophylaxis of delayed emesis is inconsistent with guideline recommendations which advocate for use of corticosteroids and use of alternative agents where thery are contraindicated. A Chinese retrospective study found that 89.9% and 71.5% of the study participants got prophylaxis in acute and delayed phases. Mixed regimen prophylasis was given to 93.3% of the participants while 6.3% got single agent prophylaxis(79)

Guideline recommended dosing was given to 39/86 participants in acute vomiting and to 7/10 participants in delayed emesis. In breathrough emesis, 9/13 participants got dosing similar to those recommended in management of acute/delayed emesis while 4/13 got higher doses. Therapy was given as a single dose in 11/13 particpants and as multiday dosing in 2/13 participants. Most guidelines, except APPHON, lack recommendations on how to manage breakthrough emesis. Guideline recommended timing of prophylaxis was adhered to in 86/86 participants in acute emesis. There were variations in guideline recommendations on the dosing schedules of prophylaxis as reported by other studies(36). In the acute phase single daily dosing was given to 83/86 of the participants, twice daily dosing to 1/86 participants and three times daily to 2/86 participants. In the delayed phase prophylaxis was given as a single daily dose in 8/10 participants, twice daily dosing in 1/10 participants and three times daily dosing in 1/10 participants. Based on the local recommendations, Kasilis synopsis, a total of three doses of ondansetron is given in acute prophylaxis (**table 9**).

Most patients (75/86) got prophylaxis only on the first day of chemotherapy in the acute phase. Prophylaxis was given for more than one day to 11/35 patients on multiday chemotherapy (both intravenous and oral). Use of appropriate and most effective antiemetics in the acute phase has been shown to have a positive correlation with level of contol of

delayed emesis (80). All the guidelines do not have recommendations on what to give as prophylaxis in multiday chemotherapy. In delayed emesis, 9/10 patients got prophylaxis for more than one day while one had it for only one day (second day after chemotherapy).

The reasons for non adherence to guideline recommendations need to be studied. Some of the postulated reasons for non adherence according to Marjolein(37) are: lack of guideline recommended interventions like NK1RAs (in the Kenyan market), poor guideline on the choice of alternatives where some drugs are contraindicated, organizational constraints and lack of awareness on guideline recommendations(37).

5.1 Conclusion

Management of acute and delayed emesis in children at still remains a big challenge. Future research needs to find out why there is poor adherence to existing CINV management recommendations. There is need to revise the current local recommendations to fill in the gaps in practice and align with the current best practices. Some of the recommendations to improve on the local guideline:

- Inclusion of a table and algorithm to determine the level of emetogenicity of chemotherapy
- A comprehensive information/algorithm on choice of antiemetic prophylaxis based on emetogenicity level and other risk facors
- Provision of information on management of breakthrough and refractory vomiting.
- Performance of an implementation study to promote implementation of the research findings.

6.0 References

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7.0 Appendices

7.1 Appendix I: Questionnaire

Study title: Evaluation of adequacy of control of chemotherapy induced vomiting in paediatric patients with cancer at KNH

Date …. /…../….

Patient study Number ……..

Socio-demographic characteristics

1. Gender Male …….. Female ……
2. Age (yrs) ……
3. Age category

Age category in years	Code
5-8	1
9–12	2

4. Weight ……. Kg
5. Height ……. M

6. BMI

BMI Kg/M^2	Code
< 18	1
18 – 25	2
25 – 30	3
31 – 35	4
Above 35	5

7. BSA …….. M^2

8. Diagnosis

Type of cancer	stage

9. Chemotherapy regimen the patient is on

Regimen	Dosing schedule and time of administration

10. Emetogenicity classification of regimen based on Hesketh's table.

Level of emetogeniciy	Tick appropriate box	code
High		1
Moderate		2
Low		3
Minimal		4

CINV prophylaxis regimens and dosing appropriateness

11. Prophylaxis regimen

Prophylaxis regimen	Dose/Route/Frequency/Duration/time of administration
1	
2	
3	
4	
5	

12. Dosing appropriateness indicate Yes or No on column 2 to 4.

    For this question, Yes response scores 1 and No response scores 2

Agent number as per Q12	Is the dose appropriate?	Is the route appropriate?	Is the frequency appropriate?	Is the duration appropriate?	Conformance to international guidelines?	Total score
1						
2						
3						
4						
5						
6						
7						

    Dosing appropriateness % score……..

13. Rescue medications given? If yes answer Q14 and Q15. If none was given skip to Q16.

Rescue medicines	Dose/Route/Frequency/Duration
1	
2	
3	
4	
5	

14. Assessment of dosing appropriateness of rescue medications.

For this question, Yes response scores 1 and No response scores 2

Agent number as per Q14	Is the dose appropriate?	Is the route appropriate?	Is the frequency appropriate?	Is the duration appropriate?	Conformance to international guidelines?	Total score
1						
2						
3						
4						
5						
6						
7						

Dosing appropriateness % score……..

<u>Assessment of incidences of vomiting 0 – 120 hours post chemotherapy</u>

15. Acute vomiting episodes within 24 hours

Did you vomit today 1 hour before chemo? Yes …….. No …….

Did you vomit today (0 – 12 hours after chemo)? Yes …….. No …….

Did you vomit today (13 - 24 hours after chemo)? Yes …….. No …….

16. If yes to Q12 how many episodes?

	At least 1 hr before chemo	0 – 12 hours	13 – 24 hours	Totals
Vomiting episodes				

17. Delayed vomiting assessment from day 2 o day 5 every morning and evening

	Indicate number of vomiting episodes daily		
Day	Morning assessment	Evening assessment	Totals
2			
3			
4			
5			

18. Cumulative number of vomiting episodes

	Cumulative number of vomiting episodes in 5 days	Code
Day 1		
Day 2		
Day 3		
Day 4		
Day 5		

19. Categories of vomiting episodes

Number of vomiting episodes in 5 days	code
0	1
1 -2	2
3 – 4	3
>5	4

7.2 Appendix II: Consent and assent documents

7.2.1 Consent information sheet (English version)

Informed Consent Form for parents/guardians of children participating in the research titled. "Evaluation of adequacy of control of chemotherapy induced vomiting in paediatric in patients with cancer at Kenyatta National Hospital"

Principle Investigator	Manghe Zephaniah Kiambi
Name of institution:	University of Nairobi, School of Pharmacy, Dept. of Pharmaceutics and pharmacy practice
Supervisors:	Dr. P.N Karimi Dr. D. E. Wata
Title of the study:	Evaluation of adequacy of control of chemotherapy induced vomiting in paediatric in patients with cancer at Kenyatta National Hospital

This Informed Consent Form has two parts:

- Information Sheet (to share information about the study with you)
- Certificate of Consent (for signatures if you agree that your child may participate)

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

Part I: Information Sheet

Introduction

I am Manghe Zephaniah Kiambi, a postgraduate student at the University of Nairobi school of Pharmacy. I am doing a research to assess how well vomiting due to cancer medications is controlled in children. In this research we will ask a number of questions to the children on cancer medications. In studies involving children, we talk to the parent/guardian and ask for permission for the child to participate. After permission is granted, we will talk to the child and ask for permission to participate in the study. The parent and the child have to independently agree to participate in the study before inclusion into the study.

You are free to ask for clarifications on matters that are not clear to you on the study at any stage to the study. You are free to consult or talk to someone else before you give your agreement to participate in the study.

Purpose

Most cancer medicines are known to cause vomiting in both children and adults. In this study we will talk to the children and ask them about vomiting episodes during treatment. This information will help to understand how well vomiting is controlled during treatment and therefore help in ensuring that vomiting is adequately controlled during treatment.

Type of Research Intervention

A questionnaire with structured questions will be administered to the study participants. In this case the participant will be your child whom we will talk to, so as to get his/her agreement.

Selection of Participants

Kenyatta National hospital is one of the few public hospitals that manage children with cancer in Kenya. Patients at Kenyatta National Hospital have been considered due to the large number of children on treatment for cancer as inpatients. We would like to ask your son/daughter to participate in this study because his/her participation will give us information to improve treatment outcomes at the hospital and among children on cancer medications.

Voluntary Participation

Participation in this study is voluntary. Both the parent/guardian and the child will be involved in the decision making. No patient will be discriminated against on the basis of study participation. You can ask questions and seek clarification on matters that are not clear to you before you make the decision.

Procedure

Information will be collected using a structured questionnaire which will be read out aloud to the child. He/she will then give a response which will be entered directly into the form. The child is free to skip questions that he/she does not wish to answer. All information collected is confidential and access will be restricted to the principal investigator and the research assistant.

Duration

The study will involve use of a questionnaire which I will read out loud to the child and make entries based on his/her response. This will take about twenty minutes. There will be a daily follow up for five days after medication. Therefore we are asking for twenty minutes daily for the five days that your child will be followed up. All the questionnaires will be administered at your convenience. If the child is discharged before the five days are over, I request that you allow us to follow up on phone through the parent/guardian. The information can be collected outside work/school hours to avoid any inconveniency.

Risks and Discomforts

This study is likely to consume the child/parent's personal time during the administration of the questionnaire. However due diligence will be observed to ensure that this study is done without inconveniencing you as the study participant. This is an observational study and therefore there will be no additional medication or interventions other than what has been prescribed by your primary care doctor. The child may feel uncomfortable answering some of the questions due to illness or the medication they are on. The child does not have to answer any questions if he/she does not feel comfortable to do so. No explanations/reasons are required for not participating in the questionnaire process. There is risk of disclosing confidential information during the questionnaire filling. It is not our wish for this to happen. All information will be confidential and we will not share the questions or the responses obtained during the study.

Benefits

Some children who do not respond to drugs that prevent vomiting caused by cancer medicines might be noticed earlier during follow up. This information will be shared with the primary care giver so as to initiate alternative therapies. The study findings, in the long term, will help us to improve health outcomes especially in management of vomiting caused by cancer medicines in children by helping in developing guidelines and protocols.

Reimbursements

There will be no payments, incentives or gifts as a result of participation in the study to the children or parents.

Confidentiality:

The information that will be obtained will be handled confidentially. To protect your privacy, no names shall be used in data collection tools. Data collection tools will be given a number that is only known to the investigator for privacy purposes. All duly filled data collection forms shall be kept under lock and key accessible only to the investigator and the research assistant.

Sharing of Research Findings

During the research findings will not be shared except with the primary care physician in cases of patients who are not responding to medications to prevent vomiting episodes. This will be done in a timely manner while still maintaining confidentiality so as to benefit the patient in such cases. When the research is over, findings will be shared through publication in a journal and in conferences so that the study findings can benefit people interested in such information.

Right to refuse or withdraw

Participation in this study is voluntary for you as a parent and the child. The decision, as a parent/child, to participate or not to participate in the study will not affect how you will be treated. You have a right to refuse to join the study and also to withdraw from the study at any stage without any consequences or reasons expected.

Who to Contact

All questions and clarifications can be directed to the principal investigator, supervisors or Kenyatta National Hospital/University of Nairobi ethics review board through the contacts availed in the certificate of consent. This can be done during the study period and after the study period.

7.2.2 Consent information form (Swahili version)

Fomu ya habari kwa ajili ya kushiriki kwa utafiti

Hii fomu ni ya wazazi wa watoto tunaokaribisha kushiriki kwa utafiti wetu. Utafiti wetu unachunguza kama kutapika kunaosababishwa na madawa ya kansa kumeweza kuzuiwa kwa kiasi gani katika watoto walio na kansa katika hospitali ya kitaifa ya Kenyatta.

Mtafiti mkuu:	Manghe Zephaniah Kiambi
Chuo:	Chuo kikuu cha Nairobi
	Shule ya Famacia
	Idara ya Pharmaceutics na Mazoezi ya famacia
Wasimamizi wangu:	Dr. P.N Karimi
	Dr. D. E. Wata
Utafiti:	Uchunguzi wa kubaini kama kutapika kunaosababishwa na madawa ya kutibu kansa katika watoto waliolazwa hospitali ya Kenyatta kunathibitiwa inavyofaa.

Hii fomu iko na sehemu mbili

- fomu ya maelezo
- cheti cha makubaliano/idhini

Utapatiwa fomu moja ya idhini baada ya kuijaza.

Sehemu ya kwanza: Maelezo

Ninaitwa Zephaniah Kiambi. Kazi yangu inahusu utumizi mwema wa madawa yanayotibu magonjwa. Madawa mengine huwa na manufaa na mengine huwa na madhara kwa miili yetu. Kwa mfano, madawa mtoto wako anayotumia yanaweza kumfanya atapike. Kuna madawa mengine anayopewa ili kuzuia kutapika. Tungependa kujua kama hayo madawa yanazuia kutapika kwa kiasi gani katika watoto wanotibiwa na kulazwa katika hospitali ya Kenyatta. Tunakuomba uturuhusu tuongee na mtoto wako ili ajiunge nasi kwa utafiti huu ili tuweze kupata habari kuhusu jambo hili.

Uko na haki ya kuamua mwenyewe kama ungetaka tuongee na mtoto wako ili ajiunge na utafiti huu. Matibabu yake yataendelea kama kawaida ikiwa utakubali tuongee na mtoto wako ama kama utakataa. Unaweza kuniuliza swali lolote ikiwa hauelewi jambo lolote kuhusu huu utafiti. Sio lazima uamue saa hii. Ikiwa unahitaji muda zaidi ili uamue ni sawa. Ikiwa utakubali unaweza kubadili mawazo yako ambayo tutatii.

Maana ya utafiti huu: Kwa nini tunafanya utafiti huu?

Madawa huwa na madhara na manufaa kwa miili yetu. Madawa mtoto wako anayotumia yanaweza kusababisha kutapika. Kuna madawa mengine anayopatiwa ili kuzuia kutapika. Tungependa kujua kama hayo madawa ya kuzuia kutapika yanasaidia kupunguza kutapika kwa kiasi gani. Hiyo habari itasaidia kuboresha matibabu ya watoto walio na kansa.

Watakaojiunga na utafiti: kwa nini umechagua mtoto wangu?

Tumechagua kuongea na mtoto wako kwa sababu yale madawa anatumia yanaweza kusababisha kutapika. Tungependa kuongea na wale watoto waliolazwa sababu tungependa kuongea nao kila siku kwa siku tano. Itakuwa rahisi kufuatilia utafiti kwa walw waliolazwa ukilinganisha na wanaoenda nyumbani. Matibabu yao hayatakuwa tofauti na ya wale wengine ambao hawatajiunga na huu utafiti.

Kujiunga kwa hiari: lazima ujiunge ama mtoto wako ajiunge na huu utafiti?

La. Sio lazima ukubali kushiriki kwa huu utafiti. Pia sio lazima mtoto wako kukubali kujiunga na utafiti hata baada ya wewe kukubali tuongee naye. Uamuzi wa kujiunga ni wa hiari na tutauheshimu. Unaweza kubadili mawazo yako? Ndio. Ikiwa utasema hautaki mtoto wako aendelee na utafiti baada ya kujiunga, tutaheshimu uamuzi wako. Je, matibabu ya mtoto wangu yatabadilika nikikataa kushiriki? Hapana. Mtoto wako atatibiwa sawa na wengine ikiwa utakubali ama utakataa kushiriki. Una uhuru wa kuuliza maswali uliyo nayo kwangu ama kwa mtu mwingine ambaye utachagua.

Utafiti utafanywaje: mtamfanyia nini mtoto wangu katika utafiti?

Ukikubali tuongee na mtoto wako, tutamueleza na kumuuliza mtoto wako akubali kujiunga na utafiti huu. Akikubali kujiunga na utafiti huu, tutamuuliza maswali machache. Nitakuwa na fomu yenye maswali ambayo nitamusomea. Mtot anaweza kuniuliza swali lolote ikiwa kuna jambo lolote ambalo haeelewi wakati wowote. Tutamuuliza ikiwa umekuwa ukitapika au la baada ya matibabu yake. Kama utakuwa akitapika, tutamuuliza mara ngapi umepatika

kwa siku. Tutamuuliza haya maswali kila siku kwa siku tano. Ningeomba dakika ishirini kila siku ili niweze kumuuliza maswali hayo. Ikiwa ataenda nyumbani kabla ya siku tano kuisha, tungependa uturuhusu tuwasiliane na yeye kupitia kwa simu yako (mzazi/mlezi). Tutawasiliana na wewe na mtoto wako wakati hayuko shule ambao utatufahamisha.

Madhara: ni mambo gani mabaya yatanitendekea mtoto wangu?

Hatutarajii huu utafiti uwe na madhara yoyote. Je, kuna dawa ama sindano ama huduma tofauti atapata? Hapana. Hatutabadilisha matibabu yoyote ambayo anapata kwa sasa. Tutamuuliza maswali tu kuhusu vile atakuwa unahisi wakati wa matibabu. Lazima mtoto ajibu maswali hayo? Hapana. Sio lazima ajibu maswali ambayo hataki kujibu. Je, matibabu yake yatakuwa sawa na ya watoto wengine? Ndio. Hakutakuwa na mabadiliko yoyote kwa matibabu yake.

Je, mtoto atapata maumivu yoyote?

Hapana. Tutamuuliza tu maswali kuhusu vile atakavyokuwa unaendelea wakati wa matibabu. Ikiwa atapata maumivu yoyote sababu ya madawa anayopewa ama sababu ya ugonjwa alio nao, ataweza kutibiwa na daktari na wauguzi wengine katika hospitali.

Manufaa: Nitapata manufaa gani kutoka kwa utafiti?

Wakati huu wa utafiti hakutakuwa na manufaa mengi. Basi, ni nani atanufaika. Utafiti huu utanufaisha watoto wengine kupitia habari ambazo tutapata. Habari za utafiti zitaweza kusaidia madaktari wengine na wanasayansi kuboresha matibabu ya tototo wenye kansa.

Malipo: nitalipwa ama kupewa msaada wowote kutoka kwa huu utafiti?

Je, nitalipwa ili kujiunga na utafiti? Hapana. Je, nitalipwa baada ya utafiti? Hapana. Hata hivyo tunakushukuru kwa kukubali wewe na mtoto wako kujiunga na utafiti.

Utaambia nani kuhusu yale nitakwambia?

Yale yote utatuambia yatakuwa siri yetu. Naweza mkama mzazi kuongea na mtu mwingine? Ndio. Unaweza kuongea na rafiki ama mtu yeyote utakayechagua kuhusu huu utafiti ili kukusaidia kufanya uamuzi. Ikiwa tutaona kwamba mtoto wako anatapika sana, tutamjulisha daktari wake ili amsaidie. Zile fomu mtajaza mtapeleka wapi? Tutafungia hizo fomu kwa kabati ili mimi na msaidizi wangu pekee tuweze kuzitumia. Baada ya utafiti, tutazichoma ili hizo fomu siziweze kutumiwa na watu wengine.

Je, nitalipwa ikiwa mtoto wangu ataumia?

Hatutarajii kuwe na maumivu yoyote ama mambo mengine mabaya wakati wa utafiti. Ikiwa mtoto atapata maumivu sababu ya madawa ama ugonjwa, atapata matibabu kutoka kwa madaktari na wauguzi hapa hospitalini ya Kenyatta.

Je, nitajulishwa juu ya matokeo ya utafiti?

Hatutaweza kukujulisha binafsi kuhusu matokeo ya utafiti. Mtajulisha nani? Tutaandika ripoti ambayo yeyote ambaye anataka kuisoma ataipata. Itasidia madaktari na wanasayansi kuweza kuboresha matibabu ya kansa katika watoto.

Ninaweza kukataa kujiunga na utafiti?

Ndio. Ni haki yako kufanya uamuzi wa kujiunga na utafiti. Pia unaweza kutoka kwa utafiti wakati wowote ikiwa utabadili uamuzi wako. Je, matibabu ya mtoto wangu yatabadilika sababu ya uamuzi wangu? Hapana. Mtoto wako atatibiwa tu kama watoto wengine ambao hawako kwenye utafiti.

Ninaweza kuongea na nani ama kuuliza maswali?

Unaweza kuniuliza maswali yoyote ambayo ungetaka kuuliza ama uulize mtu mwingine yeyote utakayemchagua. Anaweza kuwa daktari mwenzangu, muuguzi au rafiki yako.

Tutakupatia fomu moja baada ya kujiunga na utafiti.

Je, uko na swali ungependa kuniuliza?

7.2.3 Consent certificate (English version)

PART II: Certificate of Consent

Study title: Evaluation of adequacy of control of chemotherapy induced vomiting in paediatric inpatients with cancer at Kenyatta National Hospital

Institution: Department of Pharmaceutics and Pharmacy Practice,
School of Pharmacy,
University of Nairobi,
P.O BOX 30197-00400,
Nairobi.

Investigator: MANGHE, Zephaniah Kiambi
Mobile Tel: 0723315843

Supervisors:

1st Supervisor - Dr. KARIMI P. N. – Clinical Pharmacist, Department of Pharmaceutics and Pharmacy Practice, UON
Tel: 0722436019

2nd Supervisor - Dr. WATA D. E. – Clinical Pharmacist, Pharmacy department, KNH
Tel: 0722473589

Ethical Approval Board:

Kenyatta National Hospital/ University of Nairobi Ethical and Research Committee,
P.O Box 20723 - 00100,
Nairobi
Tel: 2726300/2716450 Ext 44102

Certificate of Consent

I have been asked to give consent for my daughter/son to participate in this research study which will involve her completing a daily twenty minute long questionnaire for five consecutive days. I have read the foregoing information, or it has been read to me. I have had

the opportunity to ask questions about it and any questions that I have asked have been answered to my satisfaction. I consent voluntarily for my child to participate in this study. I also give the researcher/research assistant consent to contact me for follow up if my child is discharged before the five days period is over. He/she can contact me on mobile phone number _____or_____at _____ am/pm for five days after the child joins the study.

Print Name of Parent or Guardian _____

Signature of Parent of Guardian_____

Date _____

Day/month/year

If illiterate

I have witnessed the accurate reading of the consent form to the parent of the potential participant, and the individual has had the opportunity to ask questions. I confirm that the individual has given consent freely.

Print name of witness_____ AND Thumb print of participant

Signature of witness _____

Date _____

Day/month/year

A copy of this Informed Consent Form has been provided to the parent or guardian of the participant ____

Print Name of Researcher/person taking the consent_____

An Informed Assent Form will ____ OR will not ____ be completed.

7.2.4 Consent certificate (Swahili version)

Sehemu ya pili: Cheti cha makubaliano ya kuomba idhini

Jina la utafiti: Uchunguzi wa kubaini kama kutapika kunaosababishwa na madawa ya kutibu kansa katika watoto waliolazwa hospitali ya Kenyatta kunathibitiwa inavyofaa.

Mtafiti mkuu: Manghe Zephaniah Kiambi
Nambari ya simu: 0723315843

Chuo: Chuo kikuu cha Nairobi
Shule ya Famacia
Idara ya Pharmaceutics na Mazoezi ya famacia
S.L.P 30197- 00400
Nairobi.

Bodi ya maadili na utafiti: Kamati ya maadili na utafiti ya Kenyatta National Hospital /Chuo Kikuu cha Nairobi
S.L.P 20723-00100,
Nairobi
Simu: 2726300/2716450 Ext 44102

Watafiti wenzangu/wasimamizi:

1. Dkt. karimi P. N. - Idara ya Pharmaceutics and mazoezi ya famacia, Chuo kikuu cha Nairobi
   Simu: 0722436019
2. Dkt. Wata D. E. – Idara ya famacia, hospitali kuu ya Kenyatta
   Simu: 0722473589

Cheti cha idhini

Nimeulizwa niweze kupeana idhini kwa niaba ya mtoto wangu ili ajiunge na utafiti huu. Huu utafiti utahusu kujazwa ka fomu ya mahojiano ambayo mtoto atasomewa maswali na kujibu kila siku kwa muda wa siku tano mfululizo. Nimesomewa/nimejisomea habari kuhusu huu

utafiti. Nimepewa nafasi ya kuuliza maswali na yamejibiwa yote. Ninakubali kwa hiari mtoto wangu ajiunge na utafiti iwapo atakubali pia. Nimekubali mtafiti/msaidizi wake aweze kuwasiliana na mimi kwa simu namba _____ama_____ saa _____ asubuhi/jioni katika wakati wa siku tano za utafiti iwapo mtoto wangu ataruhusiwa kwenda nyumbani kabla ya muda wa utafiti kumalizika.

Jina la mzazi/mlezi _____

Sahihi ya mzazi/mlezi _____

Tarehe _____

Siku/mwezi/mwaka

Ikiwa mzazi/mlezi hajui kusoma: hii sehemu ijazwe na anayeshuhudia na mzazi/mlezi.

Nimeshuhudia na kuhakikisha kwamba mzazi/mlezi amesomewa yaliyo katika fomu ma cheti cha idhini na kwamba maswali yake yamejibiwa. Ninashuhudia kwamba huyu mzazi/mlezi amekubali mtoto wake kujiunga na utafiti huu kwa hiari yake.

Jina la anayeshuhudia _____ NA kidole cha gumba cha mzazi/mlezi

Sahihi ya anayeshuhudia _____

Tarehe _____

Siku/mwezi/mwaka

Taarifa ya mtafiti/anayechukua idhini

Nimemsomea mzazi/mlezi hii fomu kulingana na vile imeandikwa ama nimeshuhudia akisomewa kulingana na vile imeandikwa. Mzazi/mtoto amepatiwa nafasi ya kuuliza maswali. Nathibitisha kwamba mzazi/mlezi amekubali kujiunga kwa utafiti kwa hiari yake mwenyewe.

Jina la mtafiti _____

Sahihi ya mtafiti _____

Tarehe _____

Siku/mwezi/mwaka

Kwa matumizi ya mtafiti:

Fomu moja itapatiwa kwa mshiriki wa utafiti _____ (jina la mtafiti/msaidizi)

Mzazi/mlezi ametia sahihi kwa fomu ya idhini ___Ndio ____ La_____(jina la mtafiti/msaidizi)

7.2.5 Assent information form (English version)

Informed assent form for children whom we are inviting to participate in the research titled. "Evaluation of adequacy of control of chemotherapy induced vomiting in paediatric inpatients with cancer at Kenyatta National Hospital"

Principle Investigator	Manghe, Zephaniah Kiambi
Name of Organization	University of Nairobi, School of Pharmacy, Dept. of Pharmaceutics and pharmacy practice
Name of Supervisor	Dr. P.N Karimi Dr. D. E. Wata
Name of Project	Evaluation of adequacy of control of chemotherapy induced vomiting in paediatric inpatients with cancer at Kenyatta National Hospital

This Informed Assent Form has two parts:

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

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

Part I: Information Sheet

Introduction

My name is Zephaniah Kiambi. My job deals with safe use of medicines used to treat various diseases. Medicines usually have some good and bad effects on our bodies. Some of the medicines you are taking can cause some bad things like vomiting and nausea. To prevent the vomiting some other medicines are given to stop the bad effects like vomiting. We would like to find out if these medicines are able to stop the vomiting. I will give you information on what we want to do and then invite you to participate in the study. I have discussed with your parent/guardian about this study and they are aware that we are here to request your participation. You can choose to participate or not participate in the study. You can decide not to agree even if the parent agrees. Your treatment will not be affected whether you agree

or not. In case there is something that you do not understand, please ask me to explain to you. Take your time to decide. You can talk to your parent/guardian or your friends before you decide.

Purpose: Why are you doing this research?

Medicines usually have some good and bad effects on our bodies. Some of the medicines you are taking can cause some bad things like vomiting and nausea. To prevent the vomiting some other medicines are given to stop the bad effects like vomiting. We would like to find out if these medicines are able to stop the vomiting. This will help us to prevent the bad effects from happening to other children that will be taking medicines similar to the ones you are taking.

Choice of participants: Why are you asking me?

We have chosen you because the medicines that you are taking are known to cause vomiting when used for treatment. We are considering children who are admitted because we need to talk to them for at least five days. You will not be treated differently from others who have not been chosen.

Participation is voluntary: Do I have to do this?

You do not have to agree to join this study. If you say no, it is still okay. If you agree and say yes, it is okay. If you change your mind later, just let us know and we will listen to you. Your decision will not affect how you will be treated in any way.

I have checked with the child and they understand that participation is voluntary __ (initial)

Procedures: What is going to happen to me?

We are going to ask you some questions after you take your medicines. We will ask you questions about vomiting after taking your medicines. I will read out the questions and translate to you so that you are able to understand. After you answer, I will record on my form. You do not have to answer the questions if you do not want to. We can skip the questions that you do not want to answer. It is okay if you do that. You can also ask any question if there is something you do not understand. We will ask you about the number of vomiting episodes every day for five days. This might take about twenty minutes every day. You can let us know what times you would like us to talk to you. If you will be go home before the five days are over, we would like to talk to you through your parent/guardians mobile phone for the remaining days. We will not call you when you are in your studies at school.

I have checked with the child and they understand the procedures _____(initial))

Risks: Is this bad or dangerous for me?

We will only ask you questions on how you are doing while you are on medication. We will only ask about the vomiting events during your treatment. You do not have to answer to questions that you do not want to. You can ask questions too. We will take time to answer all of them. All the children will be treated in the same way at the hospital.

Discomforts: Will it hurt?

Only questions will be asked on how you are feeling during the five days of follow up. In case you feel uncomfortable please let us know. We will ensure that you feel comfortable during the process. We will not ask you questions during your school hours. This means you will not miss classes when at home.

I have checked with the child and they understand the risks and discomforts ____ (initial)

Benefits: Is there anything good that happens to me?

There may be nothing good that might happen during the study. The information that we will get will help us prevent bad effects like vomiting. This will benefit children taking similar medicines in the future.

I have checked with the child and they understand the benefits_____ (initial)

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

No money or any kind of gifts will be given to you for participating in this research.

Confidentiality: Is everybody going to know about this?

We will not share the information that you give us with others. No one else, other than the researchers, will see the answers that you will give us. We will put all the documents locked up. If we find out that your vomiting is getting worse, we will need to notify the doctor.

Compensation: What happens if I get hurt?

There is no hurt likely to happen to you due to the research. If you do not feel well because of the treatment or due to sickness, the doctors at the hospital will take care of you.

Sharing the Findings: Will you tell me the results?

We will not tell you about the results directly at the end of the research. We will tell other people about what we have found out. We do this by making one report which we share and discuss in meetings and seminars. This will help other people to take better care of children with similar sickness to yours.

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

You do not have to participate in this research. Even after you have agreed to join the study, you can still change your mind and say no. No one will blame you for that. You will still be treated in the same way even with your change of mind.

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

You can ask me questions at any given time of the research. You can talk to any other person that you feel comfortable with other than me. This can be a parent/guardian, friends or other doctors.

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

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

7.2.6 Assent information (Swahili version)

Fomu ya habari kwa ajili ya kushiriki kwa utafiti.

Hii fomu ni ya watoto tunaokaribisha kushiriki kwa utafiti wetu. Utafiti wetu unachunguza kama kutapika kunaosababishwa na madawa ya kansa kumeweza kuzuiwa kwa kiasi gani katika watoto walio na kansa katika hospitali ya kitaifa ya Kenyatta.

Mtafiti mkuu:	Manghe Zephaniah Kiambi
Chuo:	Chuo kikuu cha Nairobi
	Shule ya Famacia
	Idara ya Pharmaceutics na Mazoezi ya famacia
Watafiti wenzangu/wasimamizi:	Dr. P.N Karimi
	Dr. D. E. Wata
Utafiti:	Uchunguzi wa kubaini kama kutapika kunaosababishwa na madawa ya kutibu kansa katika watoto waliolazwa hospitali ya Kenyatta kunathibitiwa inavyofaa.

Hii fomu iko na sehemu mbili

- Fomu ya maelezo
- Cheti cha makubaliano/idhini

Utapatiwa fomu moja ya idhini baada ya kuijaza.

Sehemu ya kwanza: Maelezo

Ninaitwa Zephaniah Kiambi. Kazi yangu inahusu utumizi mwema wa madawa yanayotibu magonjwa. Madawa mengine huwa na manufaa na mengine huwa na madhara kwa miili yetu. Kwa mfano, madawa unayotumia yanaweza kukufanya utapike. Kuna madawa unayopewa kuzuia kutapika. Tungependa kujua kama hayo madawa yanazuia kutapika kwa kiasi gani katika watoto wanotibiwa na kulazwa katika hospitali ya Kenyatta. Tunakuomba ujiunge nasi kwa utafiti huu ili tuweze kupata habari kuhusu jambo hili.

Nimeongea na mzazi wako ili aturuhusu tuongee na wewe ujiunge na utafiti. Hata hivyo uko na haki ya kuamua mwenyewe kama ungetaka kujiunga na utafiti huu. Matibabu yako yataendelea kama kawaida ikiwa utakubali kujiunga na utafiti au la. Unaweza kuniuliza swali lolote ikiwa hauelewi. Sio lazima uamue saa hii. Ikiwa unataka kuongea na mzazi wako ama mtu mwingine yetote kabla ya kukubali, ni sawa.

Maana ya utafiti huu: Kwa nini tunafanya utafiti huu?

Madawa huwa na madhara na manufaa kwa miili yetu. Madawa unayotumia yanaweza kusababisha kutapika. Kuna madawa mengine unayopatiwa ili kuzuia kutapika. Tungependa kujua kama hayo madawa ya kuzuia kutapika yanasaidia kupunguza kutapika kwa kiasi gani.

Watakaojiunga na utafiti: kwa nini umenichagua?

Tumechagua kuongea na wewe kwa sababu yale madawa unatumia yanaweza kusababisha kutapika. Tungependa kuongea na wale waliolazwa sababu tungependa kuongea na wewe kila siku kwa siku tano. Matibabu yako hayatakuwa tofauti na yale ya wengine ambao hawatajiunga na huu utafiti.

Kujiunga kwa hiari: lazima nijiunge na huu utafiti?

La. Sio lazima ukubali kushiriki hata baada ya mzazi kukubali. Uamuzi wa kujiunga ni wako na tutauheshimu. Unaweza kubadili mawazo yako? Ndio. Ikiwa utasema hautaki kuendelea na utafiti baada ya kujiunga, tutaheshimu uamuzi wako. Je, matibabu yangu yatabadilika nikikataa kushiriki? Hapana. Utatibiwa sawa ikiwa utakubali ama utakataa kushiriki.

Nimehakikisha mtoto anaelewa kwamba kujiunga ni kwa hiari …….. (mara ya kwanza)

Utafiti utafanywaje: mtanifanyia nini katika utafiti?

Ukikubali kujiunga na utafiti huu, tutakuuliza maswali machache. Nitakuwa na fomu yenye maswali ambayo nitakusomea. Unaweza kuniuliza swali lolote ikiwa kuna jambo lolote ambalo hauelewi wakati wowote. Tutakuuliza ikiwa umekuwa ukitapika au la baada ya matibabu yako. Kama umekuwa ukitapika, tutakuuliza mara ngapi umepatika kwa siku. Tutakuuliza haya maswali kila siku kwa siku tano. Ningeomba dakika ishirini kila siku ili niweze kukuuliza maswali. Ikiwa utaenda nyumbani kabla ya siku tano kuisha, tutakuwa tukiwasiliana na wewe kupitia kwa simu ya mzazi wako. Tutawasiliana na wewe wakati hauko shule ambao utatueleza.

Nimehakikisha kwamba mtoto anaelewa vile utafiti utafanyika ..... (mara ya kwanza)

Madhara: ni mambo gani mabaya yatanitendekea?

Hatutarajii huu utafiti uwe na madhara yoyote. Je, kuna dawa au sindano nitadungwa? Hapana. Hatutabadilisha matibabu yoyote ambayo unapata kwa sasa. Tutakuuliza maswali tu kuhusu vile utakuwa unahisi wakati wa matibabu. Lazima nijibu maswali hayo? Hapana. Sio lazima ujibu maswali ambayo hautaki kujibu. Matibabu yangu yatakuwa sawa na ya watoto wengine? Ndio. Hakutakuwa na mabadiliko yoyote kwa matibabu yako.

Je, nitapata maumivu yoyote?

Nitapata kudungwa sindano ama kupewa madawa yoyote? Hapana. Tutakuuliza tu maswali kuhusu vile utakavyokuwa unaendelea wakati wa matibabu. Ikiwa utapata maumivu yoyote sababu ya madawa unayopewa ama sababu ya ugonjwa ulio nao, utaweza kutibiwa hapa hospitalini na daktari wako na wauguzi wengine.

Mimehakikisha kwamba mtoto anaelewa kama kutakuwa na madhara au maumivu yoyote ..... (kwa mara ya kwanza)

Manufaa: Nitapata manufaa gani kutoka kwa utafiti?

Wakati huu wa utafiti hakutakuwa na manufaa mengi. Basi, ni nani atanufaika. Utafiti huu utanufaisha watoto wengine kupitia habari ambazo tutapata. Pia utaweza kusaidia madaktari wengine na wanasayansi kuboresha matibabu ya tototo wenye kansa.

Nimehakikisha kwamba mtoto anaelewa manufaa ya utafitit huu. ..... (kwa mara ya kwanza)

Malipo: nitalipwa ama kupewa msaada wowote kutoka kwa huu utafiti?

Je, nitalipwa ili kujiunga na utafiti? Hapana. Je, nitalipwa baada ya utafiti? Hapana. Hata hivyo tunakushukuru kwa kukubali kujiunga na utafiti.

Utaambia nani kuhusu yale nitakwambia?

Yale yote utatuambia yatakuwa siri yetu. Mimi kama mtoto naweza kuambia watu wengine? Ndio. Unaweza kuambia wazazi wako ama rafiki wako kuhusu huu utafiti ili uweze kufanya uamuzi. Ikiwa tutaona kwamba unatapika sana, tutamjulisha daktari wako ili akusaidie. Zile fomu mtajaza mtapeleka wapi? Tutafungia hizo fomu kwa kabati ili mimi na msaidizi wangu pekee tuweze kuzitumia. Baada ya utafiti, tutazichoma ili hizo fomu siziweze kutumiwa na watu wengine.

Je, nitalipwa ikiwa nitaumia?

Hatutarajii kuwe na maumivu yoyote ama mambo mengine mabaya wakati wa utafiti. Ikiwa utapata maumivu sababu ya madawa ama ugonjwa, utapata matibabu kutoka kwa madaktari na wauguzi hapa hospitalini ya Kenyatta.

Je, nitajulishwa juu ya matokeo ya utafiti?

Hatutaweza kukujulisha binafsi kuhusu matokeo ya utafiti. Mtajulisha nani? Tutaandika ripoti ambayo itasidia madaktari na wanasayansi kuweza kuboresha matibabu ya kansa katika watoto.

Ninaweza kukataa kujiunga na utafiti?

Ndio. Ni haki yako kufanya uamuzi wa kujiunga na utafiti. Pia unaweza kutoka kwa utafiti wakati wowote ikiwa utabadili uamuzi wako. Je, matibabu yangu yatabadilika sababu ya uamuzi wangu? Hapana. Utatibiwa tu kama watoto wengine ambao hawako kwa utafiti.

Ninaweza kuongea na nani ama kuuliza maswali?

Unaweza kuongea na mtu yeyote ambaye utachagua. Pia unaweza kuniuliza maswali yoyote ambayo ungetaka kuuliza ama uulize mtu mwingine yeyote unayetaka. Anaweza kuwa daktari mwenzangu, mzazi au rafiki yako.

Tutakupatia fomu moja baada ya kujiunga na utafiti. Unaweza kuambia mzazi akuwekee hiyo fomu.

Je, uko na swali ungependa kuniuliza?

7.2.7 Assent certificate (English version)

PART 2: Certificate of Assent

Study title: Evaluation of adequacy of control of chemotherapy induced vomiting in paediatric inpatients with cancer at Kenyatta National Hospital

Institution: Department of Pharmaceutics and Pharmacy Practice,
School of Pharmacy,
University of Nairobi,
P.O BOX 30197-00400,
Nairobi.

Investigator: Manghe Zephaniah Kiambi
Mobile Tel: 0723315843

Supervisors:

1st Supervisor - Dr. Karimi P. N. – Clinical Pharmacist, Department of Pharmaceutics and Pharmacy Practice, UON
Tel: 0722436019

2nd Supervisor - Dr. Wata D. E. – Clinical Pharmacist, Pharmacy department, KNH
Tel: 0722473589

Ethical Approval Board:

Kenyatta National Hospital/ University of Nairobi Ethical and Research Committee,
P.O Box 20723 - 00100,
Nairobi
Tel: 2726300/2716450 Ext 44102

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

I agree to take part in the research.

OR

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

Only if child assents:

Print name of child _____

Signature of child: _____

Date: _____

Day/month/year

If illiterate/cannot read:

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

Print name of witness (not a parent)_____ AND Thumb print of participant

Signature of witness _____

Date _____

Day/month/year

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

Print name of researcher_____

Signature of researcher_____

Date_____

Day/month/year

Statement by the researcher/person taking consent

I have accurately read out the information sheet to the potential participant, and to the best of my ability made sure that the child understands what will be done during the study. I confirm that the child was given an opportunity to ask questions about the study, and all the questions asked by him/her have been answered correctly and to the best of my ability. I confirm that the individual has not been coerced into giving consent, and the consent has been given freely and voluntarily.

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

Print Name of Researcher/person taking the assent_____

Signature of Researcher /person taking the assent _____
Date _____
Day/month/year

Copy provided to the participant _____(initialed by researcher/assistant)

Parent/Guardian has signed an informed consent ___Yes ___No_____(initialed by researcher/assistant)

7.2.8 Assent certificate (Swahili version)

Sehemu ya pili: Cheti cha makubaliano ya kuomba idhini

Utafiti:	Uchunguzi wa kubaini kama kutapika kunaosababishwa na madawa ya kutibu kansa katika watoto waliolazwa hospitali ya Kenyatta kunathibitiwa inavyofaa.
Mtafiti mkuu:	Manghe Zephaniah Kiambi Nambari ya simu: 0723315843
Chuo:	Chuo kikuu cha Nairobi Shule ya Famacia Idara ya Pharmaceutics na Mazoezi ya famacia S.L.P 30197- 00400 Nairobi.
Bodi ya maadili na utafiti:	Kamati ya maadili na utafiti ya Kenyatta National Hospital Chuo Kikuu cha Nairobi S.L.P 20723-00100, Nairobi Simu: 2726300/2716450 Ext 44102

Watafiti wenzangu/wasimamizi:

1. Dkt. Karimi P. N. - Idara ya Pharmaceutics and mazoezi ya famacia, Chuo kikuu cha Nairobi
   Simu: 0722436019
2. Dkt. Wata D. E. – Idara ya famacia, hospitali kuu ya Kenyatta
   Simu: 0722473589

Jina la utafiti:	Uchunguzi wa kubaini kama kutapika kunaosababishwa na madawa ya kutibu kansa katika watoto waliolazwa hospitali ya Kenyatta kunathibitiwa inavyofaa.

Nimesoma ujumbe (nimesomewa ujumbe huu) na maswali yangu yote yamejibiwa. Nimeelezewa kwamba naweza kuuliza maswali yoyote wakati wowote kama nitakuwa nayo. Ninakubali kujiunga na huu utafiti.

Ama

Sitaki kujiunga na utafiti huu na sijaweka sahihi yangu kwa fomu hii. ..... (sahihi/jina ya mtoto)

Ikiwa mtoto atakubali kujiunga na utafiti:

Jina la mtoto _____

Sahihi ya mtoto _____

Tarehe _____

Siku/mwezi/mwaka

Ikiwa mtoto hajui kusoma:

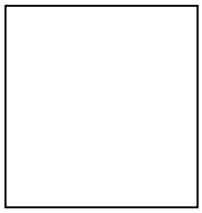
Nimeshuhudia na kuhakikisha kwamba mtoto amesomewa yaliyo katika fomu na kwamba maswali yake yamejibiwa. Ninashuhudia kwamba huyu mtoto amekubali kujiunga na utafiti huu kwa hiari yake.

Jina la anayeshuhudia (ambaye si mzazi) _____ na kidole cha gumba cha mtoto

Sahihi ya anayeshuhudia _____

Tarehe _____

Siku/mwezi/mwaka



Nimemsomea mtoto hii fomu kulingana na vile imeandikwa ama nimeshuhudia akisomewa kulingana na vile imeandikwa. Mtoto amepatiwa nafasi ya kuuliza maswali. Nathibitisha kwamba mtoto amekubali kujiunga kwa utafiti kwa hiari yake mwenyewe.

Jina la mtafiti _____

Sahihi ya mtafiti _____

Tarehe _____

Siku/mwezi/mwaka

Taarifa ya mtafiti/mwenye kuchukua idhini:

Nimemsomea mtoto hii fomu kulingana na vile emeandikwa na kuhakikisha kadiri ya uwezo wangu kwamba mtoto anaelewa yale yote ambayo yatafanyika kwa huu utafiti. Nathibitisha kwamba mtoto alipewa nafasi ya kuuliza maswali kuhusu utafiti huu na kwamba maswali hayo yamejibiwa ipasavyo. Nathibitisha kwamba huyu mtoto hajalazimishwa kukubali kujiunga na utafiti huu. Mtoto amekubali kujiung kwa hiari yake mwenyewe.

Fomu hii itapatiwa anayeshiriki kwa utafiti

Jina la mtafiti/anayechukua idhini _____

Sahihi ya mtafiti/anayechukua idhini _____

Tarehe _____

Siku/mwezi/mwaka

Fomu moja imepatiwa kwa mshiriki wa utafiti _____(jina la mtafiti/msaidizi)

Mzazi/mlezi ametia sahihi kwa fomu ya idhini ___Ndio __ La _____(jina la mtafiti/msaidizi

7.3 Appendix III: Ethical approval and clearances

KENYATTA NATIONAL HOSPITAL APPROVED 23 MAR 2017 KNH/UoN-ERC P.O. Box 20723-00202 NAIROBI

UNIVERSITY OF NAIROBI
COLLEGE OF HEALTH SCIENCES
P O BOX 19676 Code 00202
Telegrams: varsity
Tel:(254-020) 2726300 Ext 44355

KNH-UON ERC
Email: uonknh_erc@uonbi.ac.ke
Website: http://www.erc.uonbi.ac.ke
Facebook: https://www.facebook.com/uonknh.erc
Twitter: @UONKNH_ERC https://twitter.com/UONKNH_ERC

KENYATTA NATIONAL HOSPITAL
P O BOX 20723 Code 00202
Tel: 726300-9
Fax: 725272
Telegrams: MEDSUP, Nairobi

Ref: KNH-ERC/A/103

23rd March 2017

Zephaniah Kiambi Manghe
Reg. No.U56/82680/2015
School of Pharmacy
College of Health Sciences
University of Nairobi

Dear Zephaniah

REVISED RESEARCH PROPOSAL- EVALUATION OF ADEQUACY OF CONTROL OF CHEMOTHERAPY INDUCED VOMITING IN PAEDIATRIC INPATIENTS WITH CANCER AT KENYATTA NATIONAL HOSPITAL (P52/01/2017)

This is to inform you that the KNH- UoN Ethics & Research Committee (KNH- UoN ERC) has reviewed and **approved** your above revised proposal. The approval period is from 23rd March 2017 – 22nd March 2018.

This approval is subject to compliance with the following requirements:

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

For more details consult the KNH- UoN ERC website **http://www.erc.uonbi.ac.ke**

"Protect to Discover"

Yours sincerely,

PROF M. L. CHINDIA
SECRETARY, KNH-UoN ERC

c.c. The Principal, College of Health Sciences, UoN
The Director, CS, KNH
The Assistant Director, Health Information, KNH
The Chair, KNH-UoN ERC
The Dean, School of Pharmacy ,UoN
Supervisors: Dr. Peter Ndirangu Karimi, Dr.David EtaleWata

"Protect to Discover"

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

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

Ref: KNH/PAEDS-AD/48 Vol.I

Date: 5th April 2017

Zephania Kiambi Manghe
School of Pharmacy
College of Health Sciences
University of Nairobi

Dear Zephania

RE: APPROVAL TO COLLECT DATA IN PAEDIATRICS DEPARTMENT

Following approval by the KNH/UON-Ethics & Research Committee for your Research Proposal, this is to inform you that authority has been granted to collect data in **Paediatrics Department**, on your study titled ***"Evaluation of adequacy of control of chemotherapy induced vomiting in paediatric inpatients with cancer at Kenyatta National Hospital"***.

Kindly liaise with the Senior Assistant Chief Nurse, Paediatrics Department for facilitation.

You will also be required to submit a report of your findings to this office after completion of your study.

DR. IRENE INWANI
HEAD OF DEPARTMENT, PAEDIATRICS

Cc. Senior Assistant Chief Nurse, Paediatrics

KNH/R&P/FORM/01

KENYATTA NATIONAL HOSPITAL
P.O. Box 20723-00202 Nairobi

Tel.: 2726300/2726450/2726565
Research & Programs: Ext. 44705
Fax: 2725272
Email: knhresearch@gmail.com

Study Registration Certificate

1. Name of the Principal Investigator/Researcher
   ZEPHANIAH KIAMBI MANGHE
2. Email address: Kiambimanghe@gmail.com Tel No. 0723315843
3. Contact person (if different from PI) N/A
4. Email address: N/A Tel No. N/A
5. Study Title
   EVALUATION of ADEQUACY of CONTROL OF CHEMOTHERAPY INDUCED VOMITING IN PAEDIATRIC INPATIENTS WITH CANCER AT KENYATTA NATIONAL HOSPITAL.
6. Department where the study will be conducted PAEDIATRICS DEPT.
   (Please attach copy of Abstract)
7. Endorsed by Research Coordinator of the Department where the study will be conducted.
   Name: ..... Signature ..... Date .....
8. Endorsed by Head of Department where study will be conducted.
   Name: Dr. J.... Signature ..... Date 4/4/17
9. KNH UoN Ethics Research Committee approved study number P52/01/2017
   (Please attach copy of ERC approval)
10. I ZEPHANIAH KIAMBI MANGHE commit to submit a report of my study findings to the Department where the study will be conducted and to the Department of Research and Programs.
    Signature ..... Date 03/04/2017
11. Study Registration number (Dept/Number/Year) PAED/198/2017
    (To be completed by Research and Programs Department)
12. Research and Program Stamp

KENYATTA NATIONAL HOSPITAL RESEARCH & PROGRAMS 06 APR 2017 P.O. Box 20723-00202 NAIROBI

All studies conducted at Kenyatta National Hospital **must** be registered with the Department of Research and Programs and investigators **must commit** to share results with the hospital.