PROACTIVE RISK ASSESSMENT OF INTRATHECAL CHEMOTHERAPY IN
PAEDIATRIC ONCOLOGY AT KENYATTA NATIONAL HOSPITAL

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U51/81440/2015

A thesis submitted in partial fulfilment of requirements for the award of the Degree of Master of Pharmacy in Pharmacoepidemiology and Pharmacovigilance of the University of Nairobi

Department of Pharmacology and Pharmacognosy

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DEDICATION

I dedicate this work to my son, Christian Amari. “God made you the way He wanted you to be and He does not make mistakes. He has a plan for your life that is much bigger than you can imagine.”
ACKNOWLEDGMENT

I thank God for health, strength and daily provisions.

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My parents; Mr. Justus Muteti and Mrs. Joyce Nyamai. I am forever indebted to you.

My siblings; Samuel Muteti, James Muema and Geroge Mbuvi. I am because you are.
**LIST OF ABBREVIATIONS AND ACRONYMS**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>AIDS</td>
<td>Acquired Immunodeficiency Syndrome</td>
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<tr>
<td>ALL</td>
<td>Acute Lymphoid Leukaemia</td>
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<tr>
<td>AML</td>
<td>Acute Myeloid Leukaemia</td>
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<tr>
<td>BL</td>
<td>Burkitt’s Lymphoma</td>
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<tr>
<td>BOPA</td>
<td>British Oncology Pharmacists Association</td>
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<tr>
<td>CHOP</td>
<td>Cyclophosphamide, Adriamycin, Vincristine, Prednisolone</td>
</tr>
<tr>
<td>CHOP-Bleo</td>
<td>Cyclophosphamide, Adriamycin, Vincristine, Prednisolone, Bleomycin</td>
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<tr>
<td>CI</td>
<td>95% Confidence Interval</td>
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<tr>
<td>CMS</td>
<td>Centres for Medicare and Medicaid Services</td>
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<tr>
<td>CNS</td>
<td>Central Nervous System</td>
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<tr>
<td>CPOE</td>
<td>Computerized Physician Order Entry</td>
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<tr>
<td>DNA</td>
<td>Deoxyribonucleic Acid</td>
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<tr>
<td>EBV</td>
<td>Epstein – Barr Virus</td>
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<td>ERC</td>
<td>Ethics and Research Committee</td>
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<tr>
<td>HFMEA</td>
<td>Healthcare Failure Mode Effect Analysis</td>
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<td>HIV</td>
<td>Human Immunodeficiency Virus</td>
</tr>
<tr>
<td>ISMP</td>
<td>Institute of Safe Medication Practices</td>
</tr>
<tr>
<td>ITC</td>
<td>Intrathecal Chemotherapy</td>
</tr>
<tr>
<td>JCAHO</td>
<td>Joint Commission on Accreditation of Healthcare Organizations</td>
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<tr>
<td>KNH</td>
<td>Kenyatta National Hospital</td>
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<tr>
<td>NCCP</td>
<td>National Cancer Control Programme</td>
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<tr>
<td>Abbreviation</td>
<td>Full Form</td>
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<tr>
<td>NHL</td>
<td>Non-Hodgkin’s Lymphoma</td>
</tr>
<tr>
<td>OR</td>
<td>Odds Ratio</td>
</tr>
<tr>
<td>UK</td>
<td>United Kingdom</td>
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<tr>
<td>USA</td>
<td>United States of America</td>
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<tr>
<td>UoN</td>
<td>University of Nairobi</td>
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<tr>
<td>VHA</td>
<td>Veterans Health Administration</td>
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OPERATIONAL DEFINITION OF TERMS

**Adverse Drug Reaction:** A response to a drug which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease, or for the modifications of physiological function.

**Failure mode:** Manners or ways in which a process or a sub process may fail to achieve the desired result.

**Medication Error:** Unintentional errors in prescribing, dispensing, administration or monitoring of medicines while under the control of a healthcare professional, patient or consumer.

**Medication related problems:** An event or circumstance involving drug treatment that actually or potentially interferes with the patient experiencing an optimum outcome of medical care.

**Prescribing:** Writing of instructions by specialist registrars, a consultant paediatricians or haematologists stating the name, form, dosage, frequency, route and duration of administration of a medicine. It takes into account; the patient and medication history, clinical examination, prescription of complementary tests (if required) and the benefit-risks balance when writing the medicine order.

**Proactive risk assessment:** Identification and prevention of process problems before they occur using a structured approach that involves process experts.

**Probability:** How often a failure mode is likely to occur.

**Severity:** How serious the outcome of the failure mode is likely to be.

**Specialist registrar:** A doctor who is receiving advanced training in a specialist field of medicine in order eventually to become a consultant.
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ABSTRACT

**Background:** Chemotherapeutic agents are listed as high alert medications due to their high toxicity, narrow therapeutic range and high potential for medication related problems arising from the complexities associated with their use. The goal of intrathecal chemotherapy is to maximize central nervous system drug exposure in the cerebrospinal fluid while reducing or eliminating systemic drug toxicity. Intrathecal chemotherapy use is associated with potentially fatal but preventable medication errors.

**Objectives:** This study aimed to determine the extent of use of intrathecal chemotherapy and identify potential risks to patient safety and the appropriate mitigation strategies in paediatric oncology in Kenyatta National Hospital, Nairobi, Kenya.

**Methodology:** The first phase of the study was a cross-sectional study whereby a universal sampling of medical records for paediatric oncology patients admitted in Kenyatta National Hospital between January and December 2015 was done. Patient demographics such as age, sex, admission diagnosis, rationale for intrathecal chemotherapy the medication administered and number of doses received was collected via a structured data collection tool. Descriptive statistics were used to summarize data using mean, median, range, frequency and percentages. Logistic regression was used to present within-variable difference using odds ratio, p-values and confidence intervals.

The second phase applied Healthcare Failure Mode and Effect Analysis, a proactive risk assessment method to identify the potential hazards associated with the prescribing, dispensing, preparation and administration of intrathecal chemotherapy in paediatric oncology. A multi-disciplinary team elaborately described the processes and sub processes of intrathecal chemotherapy. The risk assessment identified the potential failure modes, their cause and the appropriate mitigation strategies through development of recommendations that upon implementation, would improve the quality of care in paediatric oncology.

**Results:** A total of 281 patient records were retrieved, 198 patients were on chemotherapy. There were 33 patients on intrathecal chemotherapy, representing a prevalence of 16.7% (CI 13.0-
21.3). A total of 151 Intrathecal doses were administered to 63.6% of Acute Lymphoid Leukaemia (ALL) and 63.3% of Non Hodgkins Lymphoma (NHL) patients. Methotrexate was used as prophylaxis for central nervous system infiltration or in combination with cytarabine as treatment for confirmed disease. Among ALL patients, males were 11.0 times likely to receive intrathecal chemotherapy when compared to females (p = 0.022).

The study identified 54 failure modes which were subjected to hazard and decision tree analyses. Ten failure modes were deemed to have a sufficient likelihood of occurrence and severity to warrant control measures. A further 7 failure modes were identified as single point weaknesses whose occurrence would lead to process failure. Recommendations for these 17 failure modes were made on the basis of criticality, absence of effective control measures and lack of detectability.

**Conclusion:** In paediatric oncology, intrathecal chemotherapy is used as treatment of confirmed CNS disease or as prophylaxis for infiltration. Out of the 198 paediatric patients who received chemotherapy in 2015, 16.7% received intrathecal chemotherapy that involved the use of intrathecal methotrexate alone or in combination with cytarabine. Intrathecal chemotherapy was used as a component of combined therapy for management of ALL and NHL. All intrathecal doses were administered via lumbar puncture. This prospective risk assessment identified key gaps in the current practice of intrathecal chemotherapy in paediatric oncology in KNH and consultatively developed the appropriate mitigation strategies to improve efficiency and the safety of patients and providers.
1.0. CHAPTER ONE: INTRODUCTION

Cancer is a group of non-communicable diseases characterized by the uncontrolled growth and spread of abnormal cells. It is caused by external factors, such as tobacco, infectious organisms, and radiation, and internal factors, such as genetic mutation, hormones, and immune conditions acting together or in sequence [1,2]. The increased prevalence of these causal factors coupled to population growth and ageing are expected to increase the burden of cancer and other non-communicable diseases [3,4].

Cancer is a leading cause of death in the world, second only to cardiovascular diseases. In 2012, 14.1 million new cancer cases were reported globally and 8.2 million deaths occurred due to cancer in the same period [5]. In 2013, the incidence rose to 14.9 million cases and a mortality of 8.2 million cases globally [3]. In both periods, prostate cancer, trachea, bronchus and lung cancers, colon and rectum cancers had the highest incidence in men and breast cancer, colon and rectum cancers, trachea, bronchus and lung cancers in women [3,5].

In Kenya, cancer ranks third as a cause of death after infectious diseases and cardiovascular disease and causes 7% of the total national mortality each year [6,7]. The global burden of cancer report for 2013 shows that breast, oesophageal, cervical, prostate and colon and rectum cancers had the highest incidence in Kenya while oesophageal, cervical, breast, stomach and liver cancers reported the highest mortality [3,7].

The global incidence of cancers in children is reported at 160,000 new cases per year and an annual mortality of 90,000 cases [8]. In the USA, cancer is the leading disease based cause of death among children below the age of 14 years. Over 10,000 new cases of childhood cancers were expected in 2015 [1,9]. Childhood cancers may be classified into leukaemia (acute and chronic), brain and other central nervous system tumours like neuroblastoma, lymphomas (Hodgkin’s and non-Hodgkin’s), Wilm’s tumour, rhabdomyosarcoma [3]. Within the age groups 0–4 years, 5–9 years, and 10–14 years, childhood cancers exhibits less variability than do the incidence rates of cancer in adults [8]. There are some well documented geographical and ethnic differences for certain childhood cancers; paediatric Burkitt’s lymphoma in sub-Saharan Africa is associated with Epstein–Barr virus infection in conjunction with malaria [8,10]
Lymphoma, kidney cancer, eye tumours (retinoblastoma) and leukaemia constitute about 80% of all childhood cancers in Kenya and majority respond well to treatment [2]. Leukaemia peaks at between 8 and 11 years of age while lymphoma peaks at between 5 and 8 years [11].

Cancer treatment has supportive and specific treatment plans conducted through a multi-disciplinary approach. The specific treatment is divided into surgery, radiation and chemotherapy and one or more of these can be applied based on type and stage of cancer [2,11,12]. Childhood cancers are fast growing and respond well to chemotherapy. Evidence based treatment protocols for chemotherapy have been developed and adopted by oncology groups in Europe, USA and other regions of the world. In Kenyatta National Hospital (KNH), the Kasili’s Synopsis of the Management of Paediatric Cancers in Kenya and the National Guidelines for Cancer Management Kenya, 2013 form the basis of the definitive drug treatment of paediatric oncology patients. These emphasize the use of combination chemotherapy regimens to accomplish three important objectives: Combination chemotherapy provides maximum cell kill within the range of toxicity tolerated by the host for each drug, provides a broader range of coverage of resistant cell lines in a heterogeneous tumour population and also prevents the development of new drug-resistant cell lines [12].

The blood-brain barrier prevents the penetration of many systemically administered drugs into the cerebro-spinal fluid. Intrathecal chemotherapy is a form of drug therapy that circumvents this limitation by maximizing the central nervous system expose to anticancer agents with reduced systemic drug toxicity. Intrathecal preparations are sterile, isotonic, preservative free solutions prepared under aseptic technique. Intrathecal chemotherapy is indicated in the prophylaxis of acute lymphoid leukaemia and non-hodgkin’s lymphoma or treatment of suspected or confirmed Central Nervous System (CNS) disease, as a component of combination chemotherapy [2,11,13].

In 2003, the Institute for Safe Medication Practices (ISMP) reported that cancer chemotherapy tops the list of high-alert medications, outranking intravenous potassium chloride and insulin as potential threats to patient safety [14]. Cancer chemotherapy has a narrow therapeutic range, are associated with numerous adverse reactions and have a high susceptibility to medication errors...
due to the complexities involved in their use [13,15]. Effective drug regimens for leukaemia and lymphomas commonly include a vinca alkaloid to be given intravenously and methotrexate or cytarabine administered intrathecally to eradicate malignant cells sequestered within the blood-brain barrier [2,11,13]. Inadvertent intrathecal injection of the vinca alkaloids (usually vincristine) causes devastating damage to the CNS which in most cases has been fatal or left severe and permanent neurological damage to the few survivors [16]. Studies report that since 1968, this error has been reported in a variety of international setting 55 times [17,18]. Erroneous intrathecal administration of vindesine, L-asparaginase, bortezomib, daunorubicin and dactinomycin has been reported [19]. This continues to occur despite the development and adoption of numerous preventive measures in form of intrathecal chemotherapy guidelines and policies across many settings all over the world. Overdose of intrathecal methotrexate or accidental intrathecal administration of an intravenous dose can result in acute arachnoiditis, seizures, spinal cord lesions, and encephalopathy [19].

Studies into medication errors among paediatric oncology patients reveal that improper dose or quantity, wrong timing, dose omission, wrong administration technique and failure to adhere to the chemotherapy sequence are the commonest errors reported. The cited causes included; performance and knowledge deficits, lack of communication, heavy workload and equipment and medication delivery devices [20]. It is possible that a majority of these errors are unrecognized or unreported.

In Kenya, there is limited literature on medication related problems associated with intrathecal chemotherapy. A retrospective approach into the risks to patient safety arising from the intrathecal chemotherapy processes of prescribing, dispensing, preparation and administration in KNH is likely to yield limited information due to lack of incidence reports. A proactive approach that provides a structured means of identifying and addressing potential medication errors and their resulting consequences on the patient and the processes of intrathecal chemotherapy before such errors occur is paramount.

This study utilized Healthcare Failure Modes and Effects Analysis (HFMEA) of intrathecal chemotherapy processes of prescribing, dispensing, preparation and administration in paediatric
oncology in KNH. It is a prospective method that identified potential gaps, their cause and developed appropriate mitigation strategies to make intrathecal chemotherapy more efficient and safe [22,23].

1.1. Problem statement

Cancer chemotherapy tops the list of high-alert medications, outranking intravenous potassium chloride and insulin as potential threats to patient safety [14]. These anticancer medication have a narrow therapeutic range, are associated with numerous adverse reactions and have a high susceptibility to medication errors due to the complexities involved in their use [13,15]. Intrathecal chemotherapy is an important component of the management of malignancy and symptom control. Effective drug regimens for leukaemia and lymphoma commonly include a vinca alkaloid to be given intravenously and methotrexate, alone or in combination with cytarabine administered intrathecally to eradicate malignant cells sequestered within the blood-brain barrier [2,11,13].

Intrathecal chemotherapy is a prime example of a procedure which should be identified within a clinical service as a high risk process. Errors associated with intrathecal chemotherapy almost invariably have devastating consequences. For example, erroneous intrathecal injection of the vinca alkaloids (usually vincristine) causes devastating damage to the CNS which in most cases has been fatal or left severe and permanent neurological damage to the few survivors [16]. Such errors continues to occur despite the development and adoption of numerous preventive measures in form of intrathecal chemotherapy guidelines and protocols across many settings all over the world [17,18]. Effective clinical governance therefore requires that there is an explicit local strategy to contain that risk [16,30,31]. Children are 3 times more susceptible to medication related problems as compared to adults. Kaushal et al reported a medication error rate of 5.7% of 10,778 medication orders in a prospective cohort study [56]. A review of 310 paediatric chemotherapy error reports by Rinke et al revealed that 85% reached the patient, 15.6% required additional patient monitoring or therapeutic intervention, 48% of errors occurred during administration and 30% during dispensing [20].
In Kenya, there is limited literature on medication related problems associated with intrathecal chemotherapy.

1.2. Study justification

There have been cases of intravenous antineoplastic agents being inadvertently administered intrathecally. Vincristine, vindesine, L-asparaginase, bortezomib, daunorubicin and dactinomycin have all been implicated [19]. This rare hazard has fatal consequences, and the available recovery methods are of little or no benefit [16]. It is possible that a majority of these errors are unrecognized or unreported.

This study set out to address some of these concerns at KNH. Due to lack of incidence reports, retrospective review of medication errors in intrathecal chemotherapy processes among paediatric oncology patients would yield limited information as compared to a prospective approach. Further to this, a proactive Healthcare Failure Modes and Effects Analysis (HFMEA) of intrathecal chemotherapy processes of prescribing, dispensing, preparation and administration among paediatric oncology patients in KNH can identify potential gaps, their cause and develop action plans to make intrathecal chemotherapy more efficient and safe. In the end, this can improve the quality of care for paediatric oncology patients in KNH.

1.3. Overall objective

To conduct a proactive risk analysis of the use of intrathecal chemotherapy in paediatric oncology in Kenyatta National Hospital.

1.3.1. Specific objectives

1. To determine the prevalence and intrathecal-treatment related characteristics of paediatric oncology patients receiving intrathecal chemotherapy at KNH.

2. To evaluate the prescribing, dispensing, preparation and administration processes of intrathecal chemotherapy in paediatric oncology in KNH.

3. To determine the potential risks to patient safety through the conduct of a Healthcare Failure Mode and Effect Analysis of intrathecal chemotherapy in paediatric oncology in KNH and formulate appropriate hazard mitigation strategies.
1.4. Research questions

1. What is the overall prevalence of intrathecal chemotherapy and the intrathecal treatment-related characteristics of paediatric oncology patients in KNH?
2. How are the intrathecal chemotherapy processes of prescription, dispensing, preparation and administration conducted in paediatric oncology in KNH?
3. What are the appropriate mitigation strategies for the potential risks identified though a Healthcare Failure Mode and Effect Analysis of intrathecal chemotherapy in paediatric oncology in KNH?
2.0. CHAPTER TWO: LITERATURE REVIEW

2.1 Introduction
This chapter reviews the available literature on the following; the burden of cancer, childhood cancers, chemotherapy of childhood cancers in KNH, intrathecal chemotherapy in paediatric oncology in KNH, medication related problems in intrathecal chemotherapy and intrathecal chemotherapy guidelines and protocols. This chapter also provided an overview of Healthcare Failure Mode and Effects Analysis (HFMEA).

2.2 Burden of cancer
Cancer refers to a group of diseases in which abnormal cells divide without control and are able to invade other tissues [1,2]. There are over 100 known types of cancers, named according to the organ or cell type of origin [24]. In 2012, 14.1 million new cancer cases and 8.2 million cancer related deaths occurred globally [5]. In 2013, the global incidence rose to 14.9 million cases and a mortality of 8.2 million cases [3]. In both reporting periods, prostate cancer, trachea, bronchus and lung cancers, colon and rectum cancers had the highest incidence in men and breast cancer, colon and rectum cancers, trachea, bronchus and lung cancers in women [3,5]. If this trend continues, the World Health Organization has predicted a 68% increase in the incidence of cancers to 23.6 million new cases by 2030 [5].

In developing countries, the incidence rates of cancer have increased since 1990 and pose a threat due to ill-equipped health systems to deal with complex resource intense cancer treatment regimens [3].

In Kenya, cancer ranks third as a cause of death after infectious and cardiovascular diseases [6]. The true burden is not clear due to scanty, mainly hospital-based data [25]. In 2014, the WHO cancer profile for Kenya reported 25,400 deaths attributable to cancer [6,7]. Breast, oesophageal, cervical, prostate, colonic and rectal cancers had the highest incidence. Oesophageal, cervical, breast, stomach and liver cancers reported the highest mortality over the same period [3,7].
2.3 Childhood cancers

The global incidence of cancers in children is reported at 160,000 new cases per year and an annual mortality of 90,000 cases [8]. Leukaemia (acute and chronic), brain and other central nervous system tumours, neuroblastoma, lymphoma (Hodgkin’s and non-Hodgkin’s), Wilm’s tumour and rhabdomyosarcoma are the most common global childhood cancers [3]. Within the age groups below 1–4 years, 5–9 years, and 10–14 years, childhood cancers exhibits less variability than do the incidence rates of cancer in adults [8]. Paediatric Burkitt’s lymphoma in sub-Saharan Africa is associated with Epstein–Barr virus infection in conjunction with malaria [8,10]. Children, including the embryo, foetus, infant and subsequent life stages up to end of adolescence have a different and increased risk of cancer compared to adults because; they have different and unique exposures, dynamic developmental physiology, longer life expectancy and are politically powerless [26].

In Kenya, lymphoma, Wilm’s tumour, eye tumours (retinoblastoma) and leukaemia constitute about 80% of all childhood cancers [2]. In 1999, a 6 month study on cancers in children under 16 years in Kenyatta National Hospital indicated that of the 157 cases evaluated, 45% had Burkitt’s lymphoma, 14% had neuroblastoma, 9.5% Hodgkin’s lymphoma and 7% acute lymphoid leukaemia [27]. 80% of childhood cancers are curable if diagnosed early and treated as per protocol. However, only an estimated 20-30% of children treated for cancer in KNH experience long term disease-free survival due to delayed initiation of treatment as a result of late diagnosis [2]. In the USA, early diagnosis and appropriate evidence based treatment has led to an increase in 5 year survival rates from 58% to 83% and reduced mortality rates from 6.3 per 100,000 to 2.1 per 100,000 by 2011 [1]. The type and stage of cancer and quality of care are the main determinants of outcome [2].

2.3.1 Childhood Leukaemia

Leukaemia represents a malignant proliferation of the leucopoietic tissues usually producing an abnormal increase in leucocytes in blood. They are clinically classified as acute or chronic depending on the degree of differentiation or as myelocytic, granulocytic or lymphocytic depending on the predominant proliferating cells [24].
Leukaemia is the most common childhood malignancy in USA and Europe [4,8]. Acute lymphoid leukaemia account for about 85% of the cases and the rest are acute myeloid leukaemia. In Kenya, leukaemia peaks at between 8 and 11 years of age [11].

2.3.2 Childhood Lymphoma

Lymphoma is a term that represents tumours of the lymphatic tissue. They are classified into two major groups, Hodgkin’s lymphoma and non-Hodgkin’s lymphoma (NHL) and represent almost 50% of the childhood tumours in Kenya [2,11,27]. The majority of the lymphomas in childhood are NHL most of which are Burkitt’s lymphoma (BL), a B-cell malignancy [2]. In countries where HIV/AIDS occurs in high numbers, the prevalence of NHL is higher in people living with HIV/AIDS [2,11,27]. There exists a pathogenetic link between lymphoma and viruses such as HHV8, EBV and HIV [2]. Childhood lymphoma peaks between the age of 5 and 8 years in Kenya [11].

2.4 Chemotherapy of childhood cancers in Kenyatta National Hospital

The National Guidelines for Cancer Management in Kenya, 2013 and the Kasilis Synopsis of the Management of Paediatric Cancers in Kenya form the basis of management of paediatric cancers in KNH. These were developed via evidence based approach with the aim to improve quality of care, promote cost effective and efficient chemotherapy practices, minimize harm and avoid inappropriate variations in cancer care [2,11]. They provide the treatment protocols developed through empirical trials or modifications and alterations of already existing ones from oncology groups in USA and Europe to suit the resource deficiencies in Kenya. The use of combination chemotherapy is constant across all treatment protocols.

Chemotherapeutic protocols are recorded as: induction, consolidation or intensification and maintenance, (Central Nervous System) CNS prophylaxis or treatment. Within these are divisions and subdivisions: cycle, course and pulse [11]. Induction refers to initial chemotherapy given to rapidly kill neoplastic cells, set stage for normal tissue function and restoration of near normal state. Induction aims at achieving or inducing remission. Consolidation/Intensification stage is the second phase of consolidating what has been achieved.
during induction using stronger drugs. Maintenance phase aims at maintaining remission by keeping mass of cancer cells to near zero or achieve total elimination using low doses of longer intervals. Non-Hodgkin’s lymphoma (NHL) and acute lymphoid leukaemia (ALL) frequently involve the CNS while retinoblastoma and neuroblastoma rarely involve the CNS. For prophylaxis of CNS involvement, intrathecal methotrexate or cytarabine is given after cerebral spinal fluid (CSF) examination shows no malignant cells but there is potential infiltration. Treatment of CNS disease is done when the CSF examination demonstrates malignant cells [2,11]. Remission is obtained in over 85% of acute lymphoid leukaemia with an overall six year survival of 50% in children [11]. Complete remission is defined as less than 5% of leukaemic blasts in the bone marrow after restoration of bone marrow cellularity following induction phase of chemotherapy [2].

2.4.1 Definitive chemotherapy of acute lymphoid leukaemia

There are 2 treatment protocols for the management of ALL in KNH namely; Option A and Option B.

2.4.1.1 Option A (Appendix 3)

This involves a 4 week induction period using weekly doses of vincristine and doxorubicin/daunorubicin, daily oral prednisolone for 4 weeks, tapered thereafter for 1 weeks and weekly age related doses of Intrathecal methotrexate to a maximum of 5 doses. The consolidation phase starts 10-14 days after induction is completed. It involves intravenous cyclophosphamide and vincristine and subcutaneous cytarabine. Maintenance phase begins 4 weeks after consolidation and is done over 24 months for patients showing continued remission. It involves the use of daily oral doses of 6-mercaptopurine and methotrexate, adriamycin and cyclophosphamide every three months and intrathecal methotrexate every 8 weeks for 1st year for those without CNS disease. Re-induction is done for 4 weeks where there is no remission using a weekly dose of vincristine and daunorubicin, a daily oral dose of dexamethasone tapered in the fourth week and weekly dose for age intrathecal methotrexate. This is immediately followed by re-consolidation using cyclophosphamide, intrathecal methotrexate, 6-mercaptopurine and cytarabine then maintenance phase as in Option A after a 2 week rest [11].
2.4.1.2 Option B (Appendix 4)
It starts with an induction phase comprised of daily oral Prednisolone for 4 weeks, weekly daunorubicin and vincristine for 4 weeks, l-asparaginase for 2 weeks. Consolidation phase begins following a 7 day break irrespective of remission. During consolidation, intravenous cyclophosphamide, intrathecal methotrexate, 6-mercaptopurine and sub-cutaneous cytarabine are utilized. If there is no remission or there is relapse, re-induction is done using oral dexamethasone, weekly intravenous vincristine and doxorubicin. Re-consolidation phase is immediately started using intravenous cyclophosphamide, intrathecal methotrexate, oral 6-mercaptopurine and sub-cutaneous cytarabine. Maintenance phase uses 6-mercaptopurine and intravenous methotrexate.

2.4.2 Definitive chemotherapy of paediatric non-Hodgkin’s lymphoma in KNH
In KNH, Burkitt’s lymphoma constitutes over 95% of NHL in childhood [11]. There are 2 treatment protocols available for the management of NHL among paediatric oncology patients in KNH.

2.4.2.1 CHOP Regimen (Appendix 5)
This is a 4 drug regimen composed of cyclophosphamide, adriamycin/doxorubicin, vincristine, and prednisone. CHOP is currently the protocol of choice for induction of remission in Burkitt’s lymphoma in KNH. The induction phase consists of intravenous cyclophosphamide and vincristine given on the first day and weekly for 6 weeks, adriamycin on day 1, day 22 and day 43, daily oral prednisolone for 4 weeks, tapered thereafter for 2 weeks, intrathecal methotrexate twice weekly during induction and consolidation. The consolidation phase starts 10-14 days after induction using intravenous cyclophosphamide and vincristine together with sub-cutaneous cytarabine. Maintenance phase is started 4 weeks after consolidation in the presence of remission and is done over a period of 24 months. It involves the use of daily oral methotrexate and 6-mercaptopurine, monthly intravenous vincristine, adriamycin and cyclophosphamide every three months for 24 months, CNS prophylaxis using Intrathecal methotrexate given every 8 weeks for first year for those without CNS disease.
2.4.2.2 CHOP-Bleo Regimen (Appendix 6)

This regimen is composed of cyclophosphamide, adriamycin/doxorubicin, vincristine, prednisone and bleomycin. Intrathecal methotrexate should be given twice weekly as in CHOP induction and consolidation for Burkitt’s lymphoma. This regimen is indicated for re-induction of recurrent NHL before reaching maintenance phase or in older children aged 8-15 years with non-Burkitt’s non-Hodgkin’s lymphoma. If remission is achieved, consolidation and maintenance should be like in ALL treatment.

2.5 Intrathecal chemotherapy

2.5.1 Introduction

Intrathecal chemotherapy is a form of parenteral therapy where small doses of drugs are administered into the CSF producing very high drug concentration with minimal systemic toxicity [13,31] because the CSF has a smaller volume of distribution as compared to plasma (140 ml vs. 3500 ml) [13]. This administration can be done by intralumbar or intraventricular routes. Intraventricular drug administration is done via an indwelling intraventricular device such as an Ommaya reservoir thus facilitating repeated access to the intrathecal space. Intrathecal drug delivery can also be done using an intralumbar catheter that is connected to subcutaneously implanted reservoir/access device or performing a lumbar puncture using a lumbar puncture needle attached to a drug containing syringe [11,13]. Systemic administration of chemotherapy for CNS tumours is associated with a high failure rate due to poor CNS penetration.

Formulations for intrathecal administration should be sterile, isotonic and preservative-free, prepared under aseptic conditions because the CSF is sterile and lacks immune defence mechanisms. The volume for intrathecal injections ranges from 0.5ml to 5ml [32].

There is a rapid increase in CSF volume with growth in infants and young children. For this reason, intrathecal doses are based on age and not body surface area [11,13,31]. Intrathecal Chemotherapy is an important component of the management of malignancy and symptom
control. It is a complex high risk process that should be conducted by qualified personnel in the presence of explicit local strategy to contain the risk [16,24,25].

2.5.2 Applications of intrathecal chemotherapy

Intrathecal chemotherapy is routinely prescribed in oncology as prophylaxis or treatment of CNS disease due to a primary haematological disease or a metastatic disease due to any other malignancy. Parenchymal or meningeal disease at diagnosis or relapse are very poor prognostic factors [31,33,34]. The aim of intrathecal chemotherapy is to produce high CSF concentrations with minimum systemic toxicity [31].

Methotrexate and cytarabine are the drugs frequently prescribed for intrathecal administration. Methotrexate is a dihydrofolate reductase inhibitor which prevents tetrahydrofolate formation required for thymidylate synthesis which is essential for DNA synthesis. Intrathecal methotrexate is usually prescribed for prophylaxis in patients with ALL or NHL where there is a high risk of CNS involvement or for treatment of confirmed or suspected CNS disease. It is preferred over cranial irradiation because radiation is associated with secondary malignancies, growth retardation, and developmental delay in paediatric patients [13,33]. Intrathecal methotrexate is associated with headache, seizures, coma, neurological deficit, aphasia, and cardiovascular compromise [34].

Cytarabine is a pyrimidine nucleoside analogue which inhibits the synthesis of DNA at the S phase of the cell cycle. Liposomal cytarabine is prepared in the form of biodegradable, lipid base particles thus prolonging the exposure in the CSF (1 week in paediatrics, 2 weeks in adults). Conventional cytarabine has a duration of action of 24 hours. Intrathecal liposomal cytarabine is associated with chemical arachnoiditis characterised by headache, back pain, fever, nausea, and vomiting [13,33].

2.5.3 Intrathecal chemotherapy guidelines

Many countries have developed guidelines that govern the safe handling of chemotherapeutic agents throughout their life cycle[35–37]. Additionally, specific hospital policies for intrathecal chemotherapy have been developed from the guidelines[ 24,25,38,39,40, 41] Their development
is an acknowledgment that in chemotherapy, medication errors do occur but the application of specific policies and procedures reduces their incidence, along with a multidisciplinary approach[16,35]. Hospitals in Europe, America, Asia and the Pacific regions have customized national guidelines into policies and procedures that ensure the safe prescribing, dispensing, preparation and administration of intrathecal chemotherapy for both adults and paediatric oncology patients [40–42].

The key aspects addressed by the guidelines, policies and procedures are; the establishment of an intrathecal chemotherapy register; the provision of formal induction/education programme and periodic competence reviews for all staff involved in the prescribing, dispensing, checking, issuing or administering intrathecal chemotherapy [43]; roles, responsibilities and checks in intrathecal chemotherapy processes; handling of intrathecal chemotherapy; purpose designed chemotherapy prescription chart and periodic multi-disciplinary audits of intrathecal chemotherapy processes[40–42]. There are no guidelines for intrathecal chemotherapy in KNH.

### 2.5.4 Medication related problems in intrathecal chemotherapy

Medication errors can occur at any stage of the chemotherapy treatment process, from the prescribing a medication through to the administration [43].

The management of leukaemia and lymphoma commonly include a vinca alkaloid to be given intravenously and methotrexate or cytarabine administered intravenously and/or intrathecally to eradicate or prevent malignant cells sequestered within the blood-brain barrier [2,11,13]. Inadvertent intrathecal administration of the vincristine causes devastating neurotoxicity which can be fatal within days or lead to severe and permanent neurological damage to the few survivors [16,19]. In the UK in 2013, an analysis of reports relating to intrathecal chemotherapy in patients also prescribed intravenous vinca alkaloids revealed 38 patient safety incidents reported over a 10 year period. The dispensing, storage, transportation, administration and documentation were the medication processes reported despite the existence of defence measures [43].

A WHO report shows that since 1968, inadvertent intrathecal administration of vincristine has been reported 55 times in both adults and children and still continues to occur despite repeated
warnings over time and extensive labelling requirements and standards [17]. Among children, 31 reported cases have resulted in 25 fatalities [18]. In most cases, the cause is not reported and further exploration has revealed multiple causes including; mislabelling of syringes, mistaking vincristine for intrathecal administration, intrathecal and intravenous chemotherapy brought into treatment area at the same time, incomplete warning label, inexperienced staff, treatment given outside working hours and failure to check patient records.[19]

Overdose of intrathecal methotrexate resulting from the use of doses prepared from concentrated solutions rather than standard solutions of methotrexate or intrathecal administration of an intended intravenous dose of methotrexate has been reported. Methotrexate overdose presents with severe headache, seizures, apnoea, coma, back pain, sacral numbness and respiratory failure.[45,46]

Intrathecal treatment is associated with chemical arachnoiditis, progressive myelopathy, and leukoencephalopathy[34]. Severe, permanently incapacitating, ascending myelitis has been reported in children who received preserved formulations of cytarabine and methotrexate intrathecally. Benzyl alcohol, is the most common preservative used for medications and diluents. [34]

Drug handling misadventures such as inappropriate hand washing before and after preparation, wrong technical method for body decontamination and failure to use gloves during administration of injections [47] are potential sources of risks to patient safety during intrathecal chemotherapy.

Prescription errors in chemotherapy can result in patient harm or diminished response to treatment, further worsening quality of life. In 2015, Mathaiyan et al reported a chemotherapy prescription error rate of 2.8 per prescription (n = 1500 prescriptions). In the study, 47.1% were due to omissions like patient name, age, diagnosis, pre-medication, dosage form, drug name, units of dose, diluents name and timing of administration. A further 23.3% of the errors were due to abbreviations such as Ara C (cytarabine), MTX (methotrexate), 5-FU (5-fluorouracil), cyclo (cyclophosphamide), carbo (carboplatin)[48]. Understanding the factor and causes of
medication related problems in intrathecal chemotherapy is important in formulating the appropriate mitigation strategies.

In Kenya, there is no sufficient data relating to incidence, causes and strategies to mitigate medication related problems associated with intrathecal chemotherapy in adults and paediatric patients.

2.6 Healthcare Failure Mode and Effects Analysis

2.6.1 Overview of Healthcare Failure Mode and Effects Analysis

In 1998, Veterans Health Administration (VHA) established the National Centre for Patient Safety (NCPS) which customized Failure Mode and Effects Analysis (FMEA), originally used in military and aerospace industries, into Healthcare Failure Mode and Effects Analysis (HFMEA) with the aim of creating a culture of safety in its hospitals. HFMEA is a structured way of identifying and addressing potential problems or failures and their resulting effects before an adverse event occurs. It breaks an identified high risk procedure or process down to individual events or activities and shows the logical relationship between them [49]. This analysis involves a detailed mapping of steps and sub-steps in a high risk process, identifying the potential high risk failure modes for each step, their cause and effect on the overall success of the process.

A failure mode is defined as the different ways in which a process or a sub process can fail to accomplish its intended purpose. In intrathecal chemotherapy, the failure of a process or a sub process has the potential to compromise patient safety and quality of care. The analysis is performed by a multi-disciplinary team composed of subject matter experts who finally develop risk mitigation strategies in form of recommendations and action plans for the high risk failure modes.

In 2000, Goldspiel et al established a multi-disciplinary task force to prospectively evaluate the ordering, checking, processing, and administering cancer chemotherapy agents in an American hospital where 8500 doses of chemotherapy agents are dispensed annually. Protocol development, error follow up and healthcare practitioner education were among the 7 areas that
needed improvement. Twenty three modification were made to the existing system leading to a 23% reduction in chemotherapy prescription errors [50]. HFMEA has been successfully used to analyze the ordering and administration other high risk medications such as Potassium Chloride and Potassium Phosphate in intensive care unit. Selecting the wrong drug, inaccurate and incomplete labels and distractions during preparation were identified as the high risk failure modes leading to 11 recommendations [51]. The HFMEA multi-disciplinary team for this study described the method as “easy to use and makes the approach to a complicated process relatively easy”.

In paediatric medicine and chemotherapy, HFMEA has been applied to great effect [23,52,53]. In a hospital in Taiwan, HFMEA approach identified 11 high risk failure modes in chemotherapy in both in-patients and out-patients and 26 associated causes. A decision tree analysis revealed 14 causes that required further action, leading to 3 recommendations. The hospital implemented one recommendation, a Computerized Physician Order Entry (CPOE) system that reduced paediatric chemotherapy prescription errors rate from 7.5% to 5.3% and the overall chemotherapy error rate from 3.34% to 0.40% [22]. In 2012, an Italian paediatric hospital carried concurrent multiple HFMEA analyses across 5 units, including onco-haematology unit. 37 high risk failure modes in prescribing, preparation and administration were identified and attributed to 71 causes and effects. Dosage calculation for infusion drugs had the highest hazard score. Implementation of recommendations led to a 66% reduction in high risk failure modes in the onco-haematology unit and 60% reduction across all units [23]. A HFMEA of the prescription, preparation and administration of vincristine among paediatric patients in teaching hospital in Netherlands identified 61 potential failure modes, 14 being high risk. A decision tree analysis revealed 4 high risk failures that were not covered by hospital protocols resulting in 5 recommendations. In addition a further 4 recommendations regarding non high risk failure modes were made. The hospital implemented 6, including creation of check-points and communication of changes in prescriptions, administered via a peripheral intravenous access only by a paediatric oncologist to avoid extravasation [53].

Given the lack of data on medication related problems associated with intrathecal chemotherapy in KNH, a proactive risk analysis of the prescribing, dispensing, preparation and administration
of intrathecal chemotherapy is more suitable as opposed to retroapective approach. HFMEA has been shown to be an effective way of identifying and reducing errors associated with a high risk [22,51,53]. In 2003, the Institute for Safe Medication Practices reported that cancer chemotherapy tops the list of high-alert medications, outranking intravenous potassium chloride and insulin as potential threats to patient safety [14] and has advocated for proactive risk analysis to prevent medication errors [53].

2.6.2 The steps for conducting a healthcare failure mode and effect analysis

This is a 5-step process that uses a team approach to evaluate a health care process (Figure 1)

<table>
<thead>
<tr>
<th>STEP 1. DEFINE THE TOPIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>A high risk process that has high vulnerabilities and potential for impacting patient safety is chosen for evaluation.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>STEP 2. FORMATION OF A MULTI-DISCIPLINARY TEAM</th>
</tr>
</thead>
<tbody>
<tr>
<td>HFMEA multi-disciplinary team composed of subject matter experts to provide technical merit to the analysis and a team leader.</td>
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</tbody>
</table>

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<tr>
<th>STEP 3. GRAPHICALLY DESCRIBE THE PROCESS</th>
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<tbody>
<tr>
<td>The team constructs a detailed flow diagram mapping and numbering all the steps and sub-steps for each process evaluated.</td>
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<tr>
<th>STEP 4. CONDUCT A HAZARD ANALYSIS</th>
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<tbody>
<tr>
<td>Within each sub-step, list all the potential failure modes and determine their severity and probability. Identify the potential causes of failure for each sub-step. Calculate their Hazard Score and subject them to a Decision Tree Analysis to determine the need for further analysis.</td>
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<tr>
<th>STEP 5. OUTCOME AND ACTION MEASURES</th>
</tr>
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<tr>
<td>Team decision on hazard mitigation strategies in form of action plans and recommendations aimed at controlling the identified failure modes that warrant further analysis.</td>
</tr>
</tbody>
</table>

Figure 1: Steps for conducting healthcare failure mode and effect analysis
2.6.3 Key aspects of the healthcare failure mode and effect analysis process

The interdisciplinary team uses process flow diagramming, a Hazard Scoring Matrix and the HFMEA decision tree analysis to identify and assess potential vulnerabilities. The HFMEA Worksheet is used to record the team’s assessment, proposed actions, and outcome measures. HFMEA includes testing to ensure that the system functions effectively and new vulnerabilities have not been introduced elsewhere in the system [49].

The Joint Commission on Accreditation of Healthcare Organizations (JCAHO) promoted HFMEA in their prospective analysis of healthcare processes in order to prevent possible medication errors and has been requesting its subordinate medical institutions to analyze at least one high-risk medical process per year [56]. The JCAHO standard (LD.5.2) requires eight actions by hospitals: Select at least one high-risk process, identify steps where failure modes may occur, identify possible effects on patients, conduct a Root Cause Analysis to determine why failures may occur, redesign the process to minimize the risk to patients, test and implement the redesigned process, monitor the effectiveness of the new process, implement a strategy to maintain the process [49].

2.7 Conceptual framework

The Donabedian model for quality improvement [57] was used to evaluate the practice of intrathecal chemotherapy among paediatric oncology patients in KNH, in order to identify the potential sources of risks to patient safety.
<table>
<thead>
<tr>
<th>STRUCTURES</th>
<th>ITC PROCESSES</th>
<th>PROCESS OUTCOMES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Availability of protocols, policies and guidelines for (intrathecal) chemotherapy.</td>
<td>Rational prescribing of intrathecal chemotherapy</td>
<td>Success of intrathecal chemotherapy.</td>
</tr>
<tr>
<td>Availability of equipment for intrathecal chemotherapy.</td>
<td>Appropriate dispensing of intrathecal chemotherapy.</td>
<td>Improved health status of patients on intrathecal chemotherapy.</td>
</tr>
<tr>
<td>Enabling working environment for personnel involved in ITC.</td>
<td>Appropriate preparation of medication for intrathecal chemotherapy.</td>
<td>Improved quality of life.</td>
</tr>
<tr>
<td>Competent ITC staff.</td>
<td>Appropriate administration of intrathecal chemotherapy medication.</td>
<td>Patient and staff safety throughout the processes of ITC.</td>
</tr>
<tr>
<td>Reporting systems for Medication related problems.</td>
<td>Appropriate documentation and record keeping through the processes of ITC.</td>
<td>Reduced incidence of ITC medication related problems.</td>
</tr>
<tr>
<td>Organizational safety culture.</td>
<td></td>
<td>Reporting of ITC medication related problems and feedback.</td>
</tr>
<tr>
<td>Risk management committee.</td>
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<tr>
<td>Management support.</td>
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**QUALITY OF CARE.**

Safe use of intrathecal chemotherapy among paediatric oncology patients in KNH

*Figure 2: Conceptual framework*
3.0. CHAPTER THREE: METHODOLOGY

Preamble

This chapter describes the research design, the study location, study population, sampling technique, the research instruments, quality assurance, data collection techniques, data management and analysis, logistics and ethical considerations.

The study had a quantitative and a qualitative component, and the methodologies for these two components were presented separately.

3.1. QUANTITATIVE PHASE

This was the first phase of the study. The aim was to determine the proportion and treatment related characteristics of paediatric oncology patients who received intrathecal chemotherapy in KNH from January 2015 to December 2015.

3.1.1. Research design

This phase was a descriptive cross-sectional study of medical records for paediatric oncology patients to determine the prevalence and characteristics of intrathecal chemotherapy. A review of medical records at the Health Records and Information Department was conducted for all patients admitted at the paediatric oncology wards from the beginning of January 2015 to end of December 2015.

3.1.2. Study site

The study was conducted at the Health Records and Information Department and the general paediatric and paediatric oncology wards in KNH. KNH is the biggest teaching and referral hospital in East and Central Africa. It has a bed capacity of 1800. Patients below the age of 13 years are admitted into the paediatric wards. According to the KNH Health Management Information Systems (HMIS) 2016, the hospital has four general paediatric wards (3A, 3B, 3C and 3D), and one paediatric oncology ward (1E). The bed capacity of the general paediatric wards is 237 with an average bed occupancy rate of 133% and an average admission rate of 174
patients monthly. The paediatric oncology ward has a capacity of 28 beds with an average occupancy rate of 87.6% and an average monthly admission of 10 patients.

### 3.1.3. Study population

The study utilized patient medical records for paediatric oncology patients below the age of 13 admitted into the paediatric wards in KNH between January 2015 and December 2015.

### 3.1.4. Eligibility criteria

Medical records for all paediatric patients aged 13 years and below admitted with a diagnosis of cancer into wards 3A, 3B, 3C, 3D and1E in KNH between January 2015 and December 2015 were eligible for inclusion. Medical records which had missing information on the diagnosis or the prescribed chemotherapy were excluded from the study. A Screening and Eligibility form (Appendix 1A) was used to determine eligibility.

### 3.1.5. Sample size

A universal sampling of medical records for all paediatric oncology patients admitted to KNH between January 2015 and December 2015 was conducted. A list of inpatient numbers of patients admitted during this period was obtained from the Health Management Information Systems at the Health Records and Information Department. Guided by this list, all available patient records were retrieved and reviewed for eligibility. 281 patient medical records met the inclusion criteria.

### 3.1.6. Data collection procedure and Variables of Interest

Two research assistants were trained on the data collection process, data collection tools and data handling. Data from patient records were abstracted into a Data Collection Form (Appendix 1B). A separate list of serial numbers and inpatient numbers was maintained by the principal investigator to avoid duplication when selecting a patient record.

The following demographic and clinical variables were extracted from each patient record: age, gender, weight and height, body surface area, date of admission, the diagnosis, the chemotherapy prescribed, dose and route of administration. In addition, for patients on
intrathecal chemotherapy, the purpose for intrathecal chemotherapy, whether they were on first time chemotherapy or retreatment after relapse, and the number of doses received in induction, consolidation and maintenance phases of treatment was also obtained.

3.1.7. Data management and Quality Assurance

The Screening and Eligibility Form (Appendix 1A) and Data Collection Form (Appendix 1B) were pretested on 5 randomly picked patient medical records in the paediatric oncology ward.

Patient information was extracted from the patient records within the Health Records and Information unit and during office hours. The information was accessible to the principal investigator only. The collected patient information was entered into a password protected Microsoft Excel (2010) sheet on the same day. All entries were double checked by the principal investigator to ensure accuracy and completeness. Upon completion of the study, the screening forms were shredded.

3.1.8. Statistical analysis and data presentation

Data were analyzed using Stata® version 13 (Stata Corp, USA). Descriptive statistics were used to summarize data using median, range, frequency percentages and presented as tables. The prevalence of intrathecal chemotherapy was calculated and reported as a percentage.

For patients on intrathecal chemotherapy, the interrelationship of the study variables such as the diagnosis, type of patient, purpose for intrathecal chemotherapy, the number of intrathecal doses received during induction, consolidation and maintenance stages of treatment was presented in form of frequency tables. Bivariate logistic regression was used to analyse the relationship between gender and intrathecal treatment. This was presented as odds ratio and 95% confidence interval the same frequency table.

3.2. QUALITATIVE PHASE

This component of the study applied the HFMEA method to characterize the current processes of prescribing, dispensing, preparation and administration of intrathecal chemotherapy in KNH among paediatric patients.
3.2.1. Study site

The HFMEA study was conducted in the general paediatric wards 3A, 3B, 3C, 3D, 3E, the paediatric oncology ward 1E and the oncology pharmacy in KNH.

3.2.2. Research design

A prospective descriptive approach via the Healthcare Failure Mode & Effect Analysis (HFMEA) methodology was used to assess the characteristics and processes of intrathecal chemotherapy in paediatric patients. HFMEA is a stepwise and structured way of identifying and addressing potential failure modes within a process and the resultant effects on the process before an adverse event occurs. The idea generation technique of brainstorming sessions was utilized to trigger ideas and solutions through intensive, non-restrained group discussions. Every participant was encouraged to think and suggest as many ideas as possible. Participants observed and recorded the various process/es in their respective work sites and also consulted process users for additional input. Evaluation and analysis of the ideas was done collectively during each brainstorming session. Seven sessions were conducted, each on an agreed upon date every 2 weeks. Each session lasted not more than 2 hours. The principal investigator was responsible for scheduling of team sessions, data management and provision of tools.

3.2.3. Healthcare failure mode and effect analysis process

HFMEA is a five step process which starts with: defining the HFMEA topic, followed by assembling a multi-disciplinary team, then graphically describing the process through detailed process flow diagrams), conducting hazard and decision tree analyses and finally developing recommendations and actions measures.

Step1. Selection of the process to be analyzed

Intrathecal chemotherapy in paediatric oncology in KNH was selected as the topic to be studied. The following processes of intrathecal chemotherapy were selected for analysis: Intrathecal chemotherapy prescribing in the wards 3A, 3B, 3C, 3D and 1E, Intrathecal chemotherapy dispensing at the oncology pharmacy and Intrathecal chemotherapy preparation and administration in wards 3A, 3B, 3C, 3D and 1E. These are the core processes of intrathecal
chemotherapy, and were selected due to the high risks involved. Transportation and storage were viewed as low risk processes.

**Step 2. Selection of a multi-disciplinary team and induction training**

In paediatric wards in KNH, intrathecal chemotherapy is prescribed, prepared and administered to the patient by specialist registrars under the supervision of consultant paediatricians. All intrathecal chemotherapy doses are calculated manually and handwritten on the prescription sheets from which medication orders are generated. The dispensing of medication prescribed for intrathecal chemotherapy is carried out in the oncology pharmacy by pharmacists and pharmaceutical technologists, under the supervision of an oncology pharmacist. Nursing staff play an important role in the patient preparation, observation and documentation before, during and after intrathecal chemotherapy processes on a daily basis.

HFMEA guidelines propose a multidisciplinary approach, based on a team of 6 to 10 consisting key users of the process or experienced personnel related to the methods and techniques used in the chosen process, advisor/s and a team leader [49]. For this study, the HFMEA multi-disciplinary team comprised of 3 paediatrics specialist registrars, 1 pharmacist, 1 pharmaceutical technologist and 2 nurses from the paediatric oncology wards, 1 consultant paediatrician, 1 consultant oncology pharmacist and the principal investigator as the team leader. The participants were purposively selected to enable the study capture diverse viewpoints and insights into the actual application of intrathecal chemotherapy in paediatric oncology in KNH, provide cover for potential absenteeism from team sessions and/or any unforeseen opt-out by a participant.

Specialist registrars, nursing staff with basic training in oncology, pharmacists or pharmaceutical technologists who have participated in the prescribing, dispensing, preparation and administration of intrathecal chemotherapy for paediatric patients in KNH in 2016 were eligible for inclusion upon providing voluntary informed consent (Appendix 2). The team was taken through an introductory session using the HFMEA Training Manual (Appendix 11) to explain in detail, the features of HFMEA procedure and their responsibilities such as: to identify and describe the steps involved in the process of prescribing, dispensing, preparing and
administering intrathecal chemotherapy at their respective units (producing flow diagrams), to identify the potential sources of failure at each step, to clarify the reason why a failure might occur in completing each step, to quantify the severity of the effects of such potential failures, to independently score the likelihood of a specific failure occurring, its severity and the chances of the failure being detected and intercepted before it could occur, calculating the specific hazard score. All HFMEA tools addressed in the training manual were provided to the participants. All queries and concerns raised by the participants regarding the method or any aspect of the study were adequately addressed.

After the training session, team members independently visited their respective work sites to observe the processes and sub-processes of ITC, consultatively develop a logical flow diagram detailing all the steps involved in ITC in readiness for the second session. As a member of the team, the principal investigator independently tracked the processes of intrathecal chemotherapy to enable familiarization and facilitate informed contribution during subsequent brainstorm sessions.

**Step 3. Detailed description of the processes of intrathecal chemotherapy**

The second session was used by the HFMEA multi-disciplinary team to consolidate and refine the individual flow diagrams into a final comprehensive process flow diagram of intrathecal chemotherapy and consecutively number each process step (for example, 1, 2, 3, . . .) as well as the sub-process steps (1A, 1B . . . 3A, 3B . . .).

**Step 4. Hazard analysis**

The team convened a third session to brainstorm through potential failure modes for each step i.e. the different ways that a process or sub-process can fail to provide the anticipated result. Team members were assigned to consult with process users in their respective work stations for input on additional failure modes, failure mode accuracy and completeness. A HFMEA work sheet (Appendix 7) was used by the principal investigator to record failure modes.

During a fourth session, the team refined the failure modes on the basis of input from process users. This session was also used to consultatively identify all the potential failure mode causes.
and their respective effects on the patient or the process of intrathecal chemotherapy. When determining effects, emphasis was on the most likely effect and not the worst case scenario. Individual team members were assigned to consult with process users for additional input. A HFMEA work sheet (Appendix 7) was provided to record failure mode causes and their respective effects.

In the fifth session, the HFMEA multi-disciplinary team refined the failure mode causes and effects on the basis of input from process users. The principal investigator consolidated the agreed failure modes and failure mode causes and effects to a final HFMEA work sheet (Appendix 7) after the session. Based on the experience and knowledge of the HFMEA multi-disciplinary team, the severity (how serious the effect of the failure is likely affect the patient or the process) and probability (how often the failure is likely to occur) of each potential failure mode and the respective causes were rated collectively. This was done through the use of four point Likert-type scales. A Severity Rating Scale (Appendix 8) and a Probability Rating Scale (Appendix 9) were used to respectively rate the effect and the likelihood of occurrence of failure modes and their cause.

The HFMEA Hazard Scoring Matrix (Appendix 10) was then used to calculate the hazard score for each potential failure mode and cause based on its severity and probability rating. A hazard score is a product of the severity and probability scores. A failure mode or failure mode cause with a hazard score of 16 was deemed as having the highest risk to patient safety necessitating immediate corrective measures.

Failure modes with a hazard score of 8 or more were subjected to HFMEA Decision Tree Analysis during the sixth session to determine whether the failure mode warrants further action on the basis of criticality, absence of effective control measures and lack of detectability. These were classified as high risk failure modes, defined as involving a sufficient likelihood of occurrence and severity to warrant control measures.

Single point weakness (criticality) measured if the process would fail if that particular step of the process failed. An effective control measure was defined as any design that can eliminate or significantly reduce the likelihood of the failure occurring in the form of checks,
documentation, policies, guidelines and standard operating procedures. Detectability of a hazard was defined as the likelihood of detecting a failure or the effect of a failure before its occurrence (is the hazard obvious and readily apparent that a control measure is not warranted?). The summary of the decision tree analysis was presented in the form of a complete HFMEA Work Sheet (Appendix 7). Failure mode causes that were deemed as critical, non-detectable and lacking an effective control measure required further analysis in step 5.

**Step 5. Recommending mitigation measures**

The seventh session was used to determine the fate of all the causes of failure. Three categories were used for this purpose: eliminate, control or accept. The HFMEA multi-disciplinary team made recommendations for each failure mode cause that was to be eliminated or controlled. The recommendations were made on the basis of identifying other events that may occur prior to the failure mode and can serve as “alerts” that the failure mode might happen or adding a step to the process that intervenes at the earlier event to prevent the failure.

3.2.4. **Data analysis and presentation**

The multi-disciplinary team in consultation with other process users developed a comprehensive flow diagram outlining the practice of intrathecal chemotherapy in paediatric oncology in KNH (Figures 3, 4, 5 and 6). A consultatively analysed HFMEA work sheet of failure modes, causes, hazard scores and recommendations was presented (Tables 8, 9, 10). The work sheet was also summarized according to the number of steps per processes and presented as tables.

3.3. **Ethical Considerations**

3.3.1. **Ethical approval**

Approval to carry out the study was granted by the Kenyatta National Hospital-University of Nairobi Ethics and Research Committee (KNH-UoN-ERC) (Appendix 12). The study was also registered at the KNH Research and Program department after permission to conduct the study was obtained (Appendix 13). Patient names or their inpatient numbers were not used for the
study. Every patient record was allocated a serial number to assure confidentiality of information.

**3.3.2. Informed consent**

Voluntary informed consent was obtained from eligible members prior to inclusion into the HFMEA multi-disciplinary committee (Appendix 2). A full description of their obligations was provided by the principal investigator. A signed copy declaration of consent was maintained as evidence of consent.

**3.3.3. Confidentiality**

Each Data Collection Form was assigned a unique identifier code to ensure confidentiality.
4.0. CHAPTER FOUR: RESULTS

Data obtained from the Health Records and Information Department in KNH revealed that there were 514 paediatric oncology patients admitted between January 2015 and December 2015. A total of 281 medical records that met the eligibility criteria were retrieved and included for analysis.

Of these 281 patients, 155 (55.2%) were male and 126 (44.8%) were female patients. The median age was 5 years with an interquartile range of 3 and 9 years. The minimum and maximum age was 4 months and 13 years respectively. In most patient records, the weight and height parameters were recorded for patients on chemotherapy only. Table 1 provides a summary of demographic characteristics.

Table 1: Summary of patient’s demographic characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Number of patients (%) of total patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>155 (55.2)</td>
</tr>
<tr>
<td>Female</td>
<td>126 (44.8)</td>
</tr>
<tr>
<td>Age in years</td>
<td></td>
</tr>
<tr>
<td>Median (IQR): 5 (3, 9) years</td>
<td>279 (99.3)</td>
</tr>
<tr>
<td>Min - max: 4 months - 13</td>
<td></td>
</tr>
<tr>
<td>Weight in kilograms</td>
<td></td>
</tr>
<tr>
<td>Median (IQR): 18.0 (12.6, 25.0)</td>
<td>194 (69.0)</td>
</tr>
<tr>
<td>Min-max: 2.5 – 55.0</td>
<td></td>
</tr>
<tr>
<td>Height in centimetres</td>
<td></td>
</tr>
<tr>
<td>Median (IQR): 111.0 (92.5,130.0)</td>
<td>192 (68.3)</td>
</tr>
<tr>
<td>Min-max: 43.0-190.0</td>
<td></td>
</tr>
</tbody>
</table>

4.1. Types and frequency of cancer diagnosis

A total of 36 types of cancers were recorded. Retinoblastoma (27.4%), Wilm’s tumour (14.9%), non-Hodgkin’s lymphoma (13.1%) acute lymphoid leukaemia (8.9%) and Hodgkin’s lymphoma (7.1%) were the top 5 cancers, accounting for 71.4% of the paediatric cancer patients. Table 2
provides a detailed distribution of the frequency of each type of cancer among these patients. A total of 198 [70.5%, 95% CI: 64.8 - 75.5%] of the patients were on chemotherapy.

Table 2. Table of frequency distribution of patients and diagnosis

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Frequency (%)</th>
<th>Gender distribution of diagnosis</th>
<th>Number (%) on chemotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Male (%)</td>
<td>Female (%)</td>
</tr>
<tr>
<td>Retinoblastoma</td>
<td>77 (27.4)</td>
<td>37 (48.1)</td>
<td>40 (51.9)</td>
</tr>
<tr>
<td>Wilm’s tumour</td>
<td>42 (14.9)</td>
<td>24 (57.1)</td>
<td>18 (42.86)</td>
</tr>
<tr>
<td>Non-Hodgkin’s lymphoma</td>
<td>34 (13.1)</td>
<td>20 (58.8)</td>
<td>14 (41.2)</td>
</tr>
<tr>
<td>Acute lymphoid leukaemia</td>
<td>25 (8.9)</td>
<td>13 (52.0)</td>
<td>12 (48.0)</td>
</tr>
<tr>
<td>Hodgkin’s lymphoma</td>
<td>20 (7.1)</td>
<td>19 (95.0)</td>
<td>1 (5.0)</td>
</tr>
<tr>
<td>Rhabdomyosarcoma</td>
<td>19 (6.8)</td>
<td>11 (57.9)</td>
<td>8 (42.1)</td>
</tr>
<tr>
<td>Osteosarcoma</td>
<td>10 (3.6)</td>
<td>7 (70.0)</td>
<td>3 (30.0)</td>
</tr>
<tr>
<td>Neuroblastoma</td>
<td>9 (3.1)</td>
<td>6 (66.7)</td>
<td>3 (33.3)</td>
</tr>
<tr>
<td>Acute myeloid leukaemia</td>
<td>7 (2.5)</td>
<td>3 (42.9)</td>
<td>4 (57.1)</td>
</tr>
<tr>
<td>Ovarian tumours</td>
<td>3 (1.1)</td>
<td>0 (0.0)</td>
<td>3 (100.0)</td>
</tr>
<tr>
<td>Brain stem tumours</td>
<td>3 (1.1)</td>
<td>2 (66.7)</td>
<td>1 (33.3)</td>
</tr>
<tr>
<td>Supratentorial PNET</td>
<td>3 (1.1)</td>
<td>1 (33.3)</td>
<td>2 (66.7)</td>
</tr>
<tr>
<td>Medulloblastoma</td>
<td>2 (0.7)</td>
<td>0 (0.0)</td>
<td>2 (100.0)</td>
</tr>
<tr>
<td>Yolk sac tumour</td>
<td>2 (0.7)</td>
<td>0 (0.0)</td>
<td>2 (100.0)</td>
</tr>
<tr>
<td>Nasopharyngeal carcinoma</td>
<td>2 (0.7)</td>
<td>1 (50.0)</td>
<td>1 (50.0)</td>
</tr>
<tr>
<td>Pineoblastoma</td>
<td>2 (0.7)</td>
<td>2 (100.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
<td>2 (0.7)</td>
<td>0 (0)</td>
<td>2 (100.0)</td>
</tr>
<tr>
<td>Others*</td>
<td>19 (6.8)</td>
<td>9 (47.4)</td>
<td>10 (52.6)</td>
</tr>
<tr>
<td>Total</td>
<td>281 (100.0)</td>
<td>155 (55.2)</td>
<td>126 (44.8)</td>
</tr>
</tbody>
</table>

* represents those cancers that had a diagnosis frequency of 1 patient. These include: chronic myeloid leukemia, hepatoblastoma, odontogenic sarcoma, palatal tumour, myxoid spindle cell neoplasm, Kaposi sarcoma, parotial tumour, peripheral nerve sheath tumour, and posterior fossa tumour in males. pilocytic astrocytoma, cord tumour, Ewing’s sarcoma, familial giant cell fibrousseous tumour, germ cell tumour, haemoendothelioma, craniopharyngioma, fibrosarcoma, sacrococcygeal tumour and ventricular tumour in females.

4.2. Prevalence of intrathecal chemotherapy

A total of 33 patients received intrathecal chemotherapy in 2015. This represents a prevalence of 16.7% [95%, CI: 13.0% - 21.3%] of paediatric patients on chemotherapy. These patients had a
diagnosis of either acute lymphoid leukaemia (14, 42.4%) or non-hodgkin’s lymphoma (19, 57.6%). This represents 63.6% of ALL and 63.3% of NHL patients on chemotherapy.

In addition to this, 69.9% of patients who received intrathecal chemotherapy were male whereas 57.9% of patients whose treatment did not involve intrathecal doses were female. Among the patients on chemotherapy, the median age did not differ between patients who received intrathecal chemotherapy and those who did not.

Male patients who had a diagnosis of ALL had 11 times the odds of receiving intrathecal chemotherapy compared to females, p= 0.022, [95%, CI 1.4-85.2]. For NHL patients, gender was not a predictor for likelihood of receiving intrathecal chemotherapy Odds Ratio 1.4, p=0.643, [95%, CI 0.3-6.5].

Table 3 is a summary comparison of the characteristics of ALL and NHL patients on chemotherapy.
Table 3: Table of characteristics for acute lymphoid leukaemia and non-Hodgkin’s lymphoma patients on chemotherapy

<table>
<thead>
<tr>
<th>Variable</th>
<th>Acute lymphoid leukaemia</th>
<th>Non-Hodgkin’s lymphoma</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>With intrathecal chemotherapy</td>
<td>Without intrathecal chemotherapy</td>
</tr>
<tr>
<td>Gender</td>
<td>Male</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>3</td>
</tr>
<tr>
<td>Odds ratio</td>
<td></td>
<td>11.0</td>
</tr>
<tr>
<td>P value</td>
<td></td>
<td>0.022</td>
</tr>
<tr>
<td>95%, CI</td>
<td></td>
<td>1.4-85.2</td>
</tr>
<tr>
<td>Age in years</td>
<td>Median age</td>
<td>9.0</td>
</tr>
<tr>
<td></td>
<td>IQR</td>
<td>(5.0, 10.0)</td>
</tr>
<tr>
<td></td>
<td>Min-max</td>
<td>3.0-11.0</td>
</tr>
<tr>
<td>Height in Cms</td>
<td>Median</td>
<td>122.5</td>
</tr>
<tr>
<td></td>
<td>IQR</td>
<td>(104.0, 136.0)</td>
</tr>
<tr>
<td></td>
<td>Min-max</td>
<td>88.0-143.0</td>
</tr>
<tr>
<td>Weight in Kgs</td>
<td>Median</td>
<td>24.0</td>
</tr>
<tr>
<td></td>
<td>(IQR)</td>
<td>(18.0, 32.0)</td>
</tr>
<tr>
<td></td>
<td>Min-max</td>
<td>13.1-40.0</td>
</tr>
</tbody>
</table>

4.3. Treatment protocols and roles of intrathecal chemotherapy

Across the 2 diagnoses, intrathecal chemotherapy is administered to first-time chemotherapy patients and retreatment patients upon relapse of disease. The role of intrathecal chemotherapy is to offer prophylaxis against infiltration of cancerous cells into the CNS or treatment of confirmed CNS infiltration.

Among the 33 patients on intrathecal chemotherapy, 27 (81.8%) received intrathecal chemotherapy as first-time chemotherapy patients while 6 (18.2%) were retreatment patients due to relapse of disease. Majority of the first-time chemotherapy patients (26, 96.3%) received intrathecal chemotherapy as prophylaxis while one patient who had a diagnosis of NHL received intrathecal chemotherapy as treatment for CNS infiltration. Of the 6 retreatment
patients, 5 (83.3%) received intrathecal chemotherapy for treatment of CNS infiltration and one retreatment patient with a diagnosis of NHL received intrathecal chemotherapy for prophylaxis (Table 4).

Of the 19 patients diagnosed with NHL and who received Intrathecal chemotherapy, 18 (94.7%) were on the CHOP treatment protocol while 1 patient was on the CHOP-Bleo protocol. Methotrexate was the only intrathecal medication administered to all of the 19 NHL patients who received intrathecal chemotherapy. On the other hand, methotrexate alone (Option A) or in combination with cytarabine (Option A*) were the 2 intrathecal medications administered to the ALL patients who received intrathecal chemotherapy. All 4 retreatment patients with ALL were on Option A* (intrathecal methotrexate and cytarabine) for treatment of CNS infiltration, while all 10 first–time chemotherapy ALL patients were treated using intrathecal methotrexate only (Option A) for prophylactic purposes. None of the 33 patients on intrathecal chemotherapy received hydrocortisone intrathecally.

Table 4 presents a patient summary of the relationship of the type of patient, regimen and the role of intrathecal chemotherapy across the 2 diagnoses.
Table 4: Summary of the relationship between patient type, purpose for intrathecal chemotherapy and the treatment protocol

<table>
<thead>
<tr>
<th>Description of relationship between variables</th>
<th>Acute lymphoid leukaemia (n=14)</th>
<th>Non-Hodgkin’s lymphoma (n=19)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient type</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First time chemotherapy patients</td>
<td>10</td>
<td>17</td>
</tr>
<tr>
<td>Patients on retreatment upon relapse</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td><strong>Purpose for ITC and patient type</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First time patient on prophylaxis</td>
<td>10</td>
<td>16</td>
</tr>
<tr>
<td>First time patient on treatment</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Retreatment patient on prophylaxis</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Retreatment patient on treatment</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td><strong>Treatment protocol and patient type</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHOP and first time patient</td>
<td></td>
<td>16</td>
</tr>
<tr>
<td>CHOP and retreatment patient</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>CHOP-Bleo and first time</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Option A and first time patient</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Option A* and retreatment patient</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td><strong>Purpose for ITC and treatment protocol</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prophylaxis and on Option A</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Treatment and on Option A*</td>
<td></td>
<td>16</td>
</tr>
<tr>
<td>Prophylaxis and on CHOP</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Treatment and on CHOP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prophylaxis and on CHOP-Bleo</td>
<td></td>
<td>1</td>
</tr>
</tbody>
</table>

Option A* refers to intrathecal methotrexate as in Option A plus intrathecal cytarabine.

4.4 Distribution of intrathecal chemotherapy administration across the phases of treatment

A total of 151 intrathecal chemotherapy doses were administered and documented on the chemotherapy prescription sheet in the patient records. These were recorded as having been done at the induction, consolidation or maintenance phases of treatment. In total, 78 (51.7%) of the intrathecal doses were documented as having been administered to ALL patients and 73 (48.3%) to NHL patients. Each combined intrathecal administration involving methotrexate and cytarabine (Option A*) was counted as a single dose since this administration involved a single lumbar puncture procedure.
The induction phase accounted for 82 (54.3%) of all intrathecal doses and 64.6% of these doses were given to ALL patients. Non-Hodgkin’s lymphoma patients received more intrathecal doses during consolidation and maintenance phases when compared to acute lymphoid leukaemia patients. On average, there were 5, 3 and 2 procedures per patient, conducted during induction, maintenance and consolidation phases respectively.

Table 5 below provides a summary of the distribution of intrathecal chemotherapy doses administered during the various phases of treatment across the 2 diagnoses.

Table 5: Table of number of intrathecal doses administered in the phases of treatment

<table>
<thead>
<tr>
<th>Treatment phase</th>
<th>Acute Lymphoid Leukaemia</th>
<th>Non-Hodgkin’s Lymphoma</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Induction</td>
<td>53</td>
<td>29</td>
<td>82</td>
</tr>
<tr>
<td>Consolidation</td>
<td>7</td>
<td>11</td>
<td>18</td>
</tr>
<tr>
<td>Maintenance</td>
<td>18</td>
<td>33</td>
<td>51</td>
</tr>
<tr>
<td>Total</td>
<td>78</td>
<td>73</td>
<td>151</td>
</tr>
</tbody>
</table>

4.5  Proactive risk assessment of intrathecal chemotherapy in paediatric oncology

4.5.1  Constitution of HFMEA multidisciplinary team

HFMEA guidelines propose a multidisciplinary approach that involves a team of 6 to 10 key users of the process or experienced personnel related to the methods and techniques used in the chosen process, advisor/s and a team leader [49]. For this study, the HFMEA multi-disciplinary team comprised of 3 Specialist registrars, 1 pharmacist, 1 pharmaceutical technologist, 2 nurses drawn from the paediatric oncology wards, 1 consultant paediatrician, 1 oncology pharmacist and the principal investigator as the team leader.
4.5.2 Prescribing, dispensing, preparation and administration processes of paediatric intrathecal chemotherapy

The HFMEA multidisciplinary team developed a detailed flow diagram of the steps and sub-steps involved in prescribing, dispensing, preparation and administration of paediatric intrathecal chemotherapy through observation and consultation with key process users. In KNH paediatric wards, intrathecal chemotherapy was prescribed, prepared and administered to the patient by specialist registrars under the supervision of consultant paediatricians.

4.5.2.1 Prescribing process

Before prescribing any chemotherapy, the patients were reviewed to ascertain their fitness for treatment. The review incorporated the results of diagnostic screening tests like complete blood counts, radiological test results, the patient’s general condition, need for supportive treatment for pain, toxicity and infections, tolerability of chemotherapy medications and co-morbidities, nature and extent of disease.

All chemotherapy prescriptions were handwritten on the prescription sheet in the patient’s records. The doses for intrathecal methotrexate were based on the patient’s age: 5.5mg for children aged 1-2 years, 7.5mg for 3-5 year old children and 12.5 mg for children aged 7 years or more. The doses for intrathecal cytarabine were calculated based on the body surface area.

Medication orders were manually generated by nursing staff through the transfer of the handwritten information on the prescription sheet to a requisitioning form (S11) and a non-schedule form. Figure 3 provides a detailed process flow diagram for prescribing intrathecal chemotherapy in paediatric oncology in KNH.
1. Prescribing process.

A. Routine review the patient’s medical notes for treatment planning.
   1. Nature of the malignancy: Availability specific test results for site, type, pathology and staging of disease.
   2. Patient’s medication allergies, previous treatment related reactions, hydration status, co-morbidities, contraindications, toxicities and pain assessment.

B. Patient assessment to ascertain the state of essential body functions.
   1. Vital signs, weight, height age and Body surface area.
   2. Routine oncologic samples for haematologic evaluation, bone marrow studies.

C. Intrathecal chemotherapy dose determination.

D. Prescription detailing on the chemotherapy prescription sheet.
   1. Medication name in full.
   2. Dosage as calculated.
   3. Route of administration in full.
   4. Date of prescription.
   5. Cycle and course numbers.
   6. Prescriber name, designation and signature.

E. Medication order generation.
   1. The requisitioning nurse to copy the details of the prescription onto a medication order/ non schedule form.

**Figure 3: Process flow diagram for prescribing intrathecal chemotherapy in KNH**

**4.5.2.2 Dispensing process**

At the oncology pharmacy, medication orders were verified for completeness and appropriateness to the diagnosis and treatment protocol as stipulated in the standard operating procedures for dispensing cytotoxic medications before retrieval and subsequent dispensing.

At the oncology pharmacy, medications intended for intrathecal route were dispensed together with chemotherapy for other routes, according to the treatment plan. Dispensing was done by
pharmacists and pharmaceutical technologists to the requisitioning nurse upon the completion of the pharmacy verification. The verification exercise entailed checks of patient’s name, inpatient number, ward, correctness and appropriateness of dosage in relation to the treatment protocol, treatment schedule, laboratory parameters and possible drug interactions and toxicities.

The requisitioning nurse was responsible for transportation and storage of dispensed medication in a lockable cabinet in their wards. Intrathecal chemotherapy was prepared by specialist registrars in the procedure rooms for immediate administration. Each ward had a procedure room. There were no biologic safety chambers in all the procedure rooms. Figure 4 below provides a detailed process flow diagram for dispensing intrathecal chemotherapy in KNH.
2. Dispensing process.

A. Receive the appropriately signed medication requisition form (S11), patient’s medical notes, oncology treatment sheet and non-schedule form.

1. For each patient, check for the completeness of the medication order: patient name, inpatient number, diagnosis and staging of disease, intrathecal medication ordered, dose, route, frequency, ordering ward and date of requisitioning.
2. Check for the appropriateness of the medication order in relation to the current treatment protocol and treatment plan.
3. Check the routine oncologic haematology evaluations to ascertain fitness for intrathecal chemotherapy.
4. Calculate the required dose for each intrathecal chemotherapy order according to the current treatment protocol.
5. Document and communicate any changes or adjustments to the requisitioning personnel.
6. Control on the S11 the required quantity of intrathecal medication.
7. Charge, enter and issue the quantity of medication to be dispensed in the electronic dispensing tool.

B. Retrieve the intrathecal medication for dispensing.

C. For each patient, pack the medication in a separate and medicine bag labelled with the patient’s name and ward number.

D. Collection of intrathecal chemotherapy.

1. Requisitioning staff to confirm that right medication is dispensed to the right patient.
2. Issue the intrathecal medication against a duplicate requisition order (S11) signed by dispensing officer and the requisitioning nurse.

Figure 4: Process flow diagram for prescribing intrathecal chemotherapy in KNH

4.5.2.3 Preparation and administration

The principal investigator independently and prospectively tracked 26 preparation and administration procedures across all the paediatric patients’ wards, including the paediatric oncology ward 1E. All doses were administered in the procedure rooms by specialist registrars and none of these involved the use of a lumbar puncture needle as stipulated in the hospital protocol for management of paediatric malignancies. Instead, 18-gauge needles were used to access the intrathecal space. Only 2 (7.7%) of the observed lumbar puncture procedures were
successful on first attempt, 16 (61.5%) were successful on third attempt and 6 (23.1%) were completely unsuccessful. For this exercise, a successful lumbar puncture procedure was defined as one which generated at least 5 drops of non-blood stained CSF into the sample collection bottle.

The administration procedure involved an initial lumbar puncture to collect 3-5mls of cerebrospinal fluid (CSF) using uncalibrated sample collection bottles. This was quickly followed by a replacement with an approximated equivalent volume of the prepared medication and the diluent; usually 0.9% normal saline, in 2 separate 2ml syringes. There was no documentation on the patient’s records to show how the final volumes of the intrathecal medication and the diluent was arrived at or evidence of checks to ensure that the final volume in millilitres provided the desired prescribed dose in milligrams. Upon completion, 18 (69.2%) of the procedures were documented. 11 (61.1%) of the documented intrathecal chemotherapy doses did not indicate the date of administration as required on the chemotherapy prescription sheet. Figures 5 and 6 below provide a detailed process flow diagram for preparation and administration of intrathecal chemotherapy in KNH.
### 3. Preparation and administration

**A. Review prior to preparation of medication.**

1. For each patient, confirm that: the right patient is available and fit for intrathecal chemotherapy, the correct tests have been conducted, and the right medication was prescribed, ordered and delivered.

**B. Wash up and put on gloves, cap, face mask and gown.**

**C. Assemble materials and equipment for intrathecal chemotherapy production in the procedure room.**

1. Check that equipment and ingredients are suitable for intrathecal injection (sterility and expiry dates of equipment and materials).
   - a. Preservative free medication and dilution fluid.
   - b. Sterile dressing pack.
   - c. Alcohol based antiseptic.
   - d. Needle for lumber puncture.
   - e. Sterile gauze.
   - g. Patient’s medical record.

2. Draw the required volume of medication using a 2ml syringe.

3. In a separate syringe, draw sufficient normal saline (to make up 3ml of the medication and normal saline) and confirm the final volume.

4. Affix a label on the medication-containing syringe with the patient’s and medication names clearly displayed.

**D. Patient preparation for lumbar puncture.**

1. Calm the patient, fully explain the nature of the procedure to the patient/guardian, address their concerns adequately and obtain a verbal or written informed consent.
2. For children who fail to calm down, administer sedation via intravenous access.
3. Have the patient lie on a firm couch in the procedure room.
4. Position the patient with head flexed onto chest and knees drawn up for lumber puncture.

---

**Figure 5: Process flow diagram for preparation and administration of intrathecal chemotherapy**
E. Lumbar puncture procedure.

1. Clean the site of injection using alcohol based antiseptic (L4 and L5 or L5 and S1) and allow to dry.
2. Insert the lumbar puncture needle, draw 3 to 5ml of CSF into a specimen bottle for cytology and/or biochemistry.
3. Slowly and carefully attach the medication containing syringe onto the lumbar puncture needle.
4. Aspirate CSF into the syringe to ascertain that the needle is still in position in the subarachnoid space. Slowly push the medication and diluent into the intrathecal space. Quickly withdraw the needle upon completion to avoid tracking back the intrathecal medication.
5. Clean the site of injection using alcohol based antiseptic and allow to dry.
6. Apply dressing with gauze and tape on the site of injection.
7. Assist the patient in re-positioning to promote comfort.
8. Advice patient to remain in bed for at least 30 minutes to avoid development of headache.

F. Cytotoxic waste handling post procedure.

1. Clear the work area and dispose the vials, syringe and needles according to the hospital cytotoxic waste management policy.
2. Remove personal protective equipment and wash hands.

G. Post-procedure documentation.

1. Document the date of administration on the prescription sheet.

**Figure 6: process flow diagram for preparation and administration of intrathecal chemotherapy (continuation)**

**Table 6** provides a summary of the number of steps involved in intrathecal chemotherapy process in KNH and details the major steps and sub-steps.
Table 6: Table of the number of major steps and sub-steps of intrathecal chemotherapy in Kenyatta national hospital

<table>
<thead>
<tr>
<th>Stage of medicine use process</th>
<th>Major steps</th>
<th>Sub-steps</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
</tr>
<tr>
<td>Prescribing</td>
<td>5</td>
<td>31.3</td>
</tr>
<tr>
<td>Dispensing</td>
<td>4</td>
<td>25.0</td>
</tr>
<tr>
<td>Preparation and administration</td>
<td>7</td>
<td>43.7</td>
</tr>
<tr>
<td>Total</td>
<td>16</td>
<td>100</td>
</tr>
</tbody>
</table>

4.5.3 Failure mode determination and analysis

The process flow diagram was used to investigate and determine the potential failure modes in intrathecal chemotherapy in paediatric oncology. A potential failure mode was defined as any manner or way in which a process step or sub-step may fail to achieve the desired result.

4.5.3.1. Hazard Analysis

These failure modes were subjected to a hazard analysis. Each failure mode and cause was assigned a final hazard score based on how seriously the occurrence of a failure mode would affect the process or the patient (severity) (Appendix 8), how often the failure was likely to occur (probability) (Appendix 9) and what could happen should a failure mode occur (effect) and all their potential causes.

A total of 54 potential failure modes were identified. 16 potential failure modes were identified in the prescribing process, 16 in dispensing and 22 in preparation and administration processes. 44 (81.5%) failure modes had a hazard score less than 8 while 10 failure modes had a score of 8 or more. In the prescribing process, the highest and lowest hazard scores awarded were 12 and 2 respectively. In dispensing, preparation and administration processes, the highest and lowest hazard scores were 12 and 1 respectively. None of the 54 failure modes was awarded the maximum hazard score of 16.
4.5.3.2. Decision Tree Analysis

The failure modes and their causes were then subjected to decision tree analysis. In accordance with the HFMEA guidelines [49], a failure mode with a hazard score of 8 and above was considered as having a sufficient likelihood of occurrence and severity to warrant a control measure (high risk). Ten failure modes were identified and classified as high risk. Failure modes that had a hazard score less than 8 were investigated as to whether they were single point weaknesses. A single point weakness was defined as one whose occurrence would result in failure of that specific process of intrathecal chemotherapy. Seven failure modes were single point weaknesses were identified and classified as single point weaknesses. 60% of the high risk failure modes and 42.8% of single point weaknesses were likely to occur during preparation/administration and dispensing process respectively. Thirty seven (68.5%) potential failure modes were neither high risk nor single point weaknesses and for this study, these were collectively termed as non-single point weaknesses.

Decision tree analysis also involved an investigation whether the causes of these high risk failure modes and single point weaknesses had an effective control measure and whether they were obvious and readily apparent such that a control measure was not warranted (detectability). The causes of the 10 high risk failure modes and 7 single point weaknesses were deemed as lacking effective control measures and undetectable and therefore deserved additional measures for control, elimination or acceptance. The summary of these failure modes is presented in table 7 below.

Table 7: Table of type and number of failure modes for intrathecal chemotherapy processes

<table>
<thead>
<tr>
<th>Stage of medicine use process</th>
<th>Total failure Modes</th>
<th>High Risk Failure Modes</th>
<th>Single point Weaknesses</th>
<th>Non-single point weaknesses</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No</td>
<td>%</td>
<td>No.</td>
<td>%</td>
</tr>
<tr>
<td>Prescribing</td>
<td>16</td>
<td>29.6</td>
<td>3</td>
<td>30.0</td>
</tr>
<tr>
<td>Dispensing</td>
<td>16</td>
<td>29.6</td>
<td>1</td>
<td>10.0</td>
</tr>
<tr>
<td>Preparation and administration</td>
<td>22</td>
<td>40.8</td>
<td>6</td>
<td>60.0</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>54</strong></td>
<td><strong>100</strong></td>
<td><strong>10</strong></td>
<td><strong>100</strong></td>
</tr>
</tbody>
</table>
4.5.4 Failure modes description, causes and effect

Table 8 below provides a summary of all the failure modes. The 17 potential failure modes were further discussed and presented based on the stage of intrathecal chemotherapy where they are likely to occur.

Table 8: Table of summary of the potential failure modes in intrathecal chemotherapy

<table>
<thead>
<tr>
<th>Failure modes for prescribing intrathecal chemotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Inability to determine the date the preceding intrathecal dose was administered</td>
</tr>
<tr>
<td>2. Failure to relate a medication event to previously administered intrathecal chemotherapy</td>
</tr>
<tr>
<td>3. Error in Intrathecal dose determination</td>
</tr>
<tr>
<td>4. Inappropriate prescription</td>
</tr>
<tr>
<td>5. Incorrect medication order generated from a prescription</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Failure modes for dispensing intrathecal chemotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>6. Failure to thoroughly verify a medication order for completeness and appropriateness</td>
</tr>
<tr>
<td>7. Failure to document and/or communicate changes or adjustments to intrathecal treatment</td>
</tr>
<tr>
<td>8. Intrathecal medication stock out</td>
</tr>
<tr>
<td>9. Dispensing unlabelled medication for intrathecal administration</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Failure modes for preparation and administration of intrathecal chemotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>10. Contamination of the preparation by operator, material or working environment in the procedure room</td>
</tr>
<tr>
<td>11. Incomplete labelling of the intrathecal preparation</td>
</tr>
<tr>
<td>12. Unsuccessful attempted administration of intrathecal chemotherapy</td>
</tr>
<tr>
<td>13. Inability to ascertain the volume of cerebro-spinal fluid withdrawn</td>
</tr>
<tr>
<td>14. Administration of undiluted intrathecal medication</td>
</tr>
<tr>
<td>15. Inadvertent erroneous intrathecal administration of a medication in relation to the medication, formulation,</td>
</tr>
</tbody>
</table>
dose, volume and timing


17. Failure to document the date of intrathecal administration on the prescription sheet

4.5.4.1 Failure modes for prescribing intrathecal chemotherapy

Failure mode 1. Inability to determine the date the preceding intrathecal dose was administered

This is likely to occur when formulating a treatment plan for a patient on chemotherapy. The date of administration of intrathecal chemotherapy should be entered on the prescription sheet upon completion of the procedure. The team noted that the area provided for documenting the date of administration is inadequate. The prescription sheet has no provision for documenting the scheduled day of treatment (Day 1, Day 7 etc) as stated in the hospital protocol and that the terms ”cycle” and “course” of treatment were used interchangeably. The effect of this failure mode is loss of tracking whether and/or when the previous intrathecal treatment was administered, leading to additional doses or missed doses.

Failure mode 2. Failure to relate a medication event to previously administered intrathecal chemotherapy

Intrathecal methotrexate or cytarabine are associated with adverse drug reactions, toxicities and other medication related problems. The team noted that failure to pick these reactions and proceeding to prescribe the medication has the potential of worsening the reactions if administered.

Failure mode 3. Error in Intrathecal dose determination

The dose for intrathecal cytarabine is calculated based on body surface area. However, there is no documentation that shows how the final dose was arrived at. When this calculation is based
on outdated parameters of weight and height, the teams view was that there is likelihood to overdose or under-dose the patient.

**Failure mode 4. Inappropriate prescription**

This failure mode was informed by the observed tendency to use non-standard and handwritten abbreviations with regard to intrathecal medication names and route of administration when prescribing chemotherapy or when a prescription does not adhere to treatment protocol in regard to the schedule day for intrathecal treatment without a documented explanation of non-adherence.

**Failure mode 5. Incorrect medication order generated from a prescription**

In KNH, medication orders are generated manually from handwritten prescriptions by the requisitioning nursing staff. The team observed that during this process, transfer of abbreviations, a numeric or decimal points from illegible prescriptions has a likelihood of generating erroneous medication orders. **Table 9** provides a detailed HFMEA worksheet for all the potential failure modes identified in the prescribing process.

**Table 9: HFMEA worksheet for prescribing intrathecal chemotherapy**

<table>
<thead>
<tr>
<th>Failure mode</th>
<th>Potential cause</th>
<th>Severity</th>
<th>Probability</th>
<th>Hazard score</th>
<th>Single point weakness Y/N</th>
<th>Action Type (Control, Accept or Eliminate)</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Inability to determine the date the preceding intrathecal chemotherapy (ITC) was administered.</td>
<td>3 Inappropriate documentation. (Day of treatment schedule or check mark instead of date of administration. )</td>
<td>3</td>
<td>4</td>
<td>12</td>
<td>No</td>
<td>Control</td>
<td>1. Clarification of terms of treatment: course, cycle, day and date of intrathecal chemotherapy administration. 2. Redesign of the chemotherapy prescription sheet to fully accommodate course, cycle, day and date of ITC administration.</td>
</tr>
<tr>
<td>2. Inadequate provision on the chemotherapy</td>
<td>3</td>
<td>3</td>
<td>9</td>
<td>No</td>
<td>Control</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Issue</td>
<td>Score</td>
<td>Control</td>
<td>Reason</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>----------------------------------------------------------------------</td>
<td>-------</td>
<td>---------</td>
<td>----------------------------------------------------------------------------------------------------------------------------------------</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| 2. Failure to relate a medication event to previously administered ITC. | 4 2 8 | No      | 1. Prescribers to develop a high index of suspicion of the potential effects of ITC medications for the patient profile and document on the patient records.  
2. Oncology pharmacist consultation for any suspected medication related events.  
|                                                                        |       |         | 1. Lack of awareness of the potential untoward effect of the ITC medication in relation to patient profile. |
| 3. Error in Intrathecal dose determination.                           | 3 2 6 | Yes     | 1. Provision of a prescription work sheet for documenting details of dosage calculations, dose adjustment and reason for adjustment.  
2. Measures to ensure dose determination is based on current parameters. E.g. weekly charting and documentation of patient weight. |
|                                                                        |       |         | 1. Use of outdated parameters to determine ITC Cytarabine dose. |
| 4. Inappropriate prescription: non adherence to good prescribing practices for High-alert medications and the current treatment protocol. | 3 4 12| No      | 1. Hospital policy and sensitization of prescribers on dangerous abbreviations for chemotherapy names and routes in full.  
2. Double-check of prescriptions for appropriateness before signing. |
|                                                                        |       |         | 1. Non standard abbreviations for medication names and route of administration. |
|                                                                        |       |         | 2. Mismatch between the prescription and treatment protocol. |
| 5. Incorrect medication order generated from the prescription.        | 3 2 6 | Yes     | 1. Double check prescriptions for adherence to treatment protocol before signing. |
4.5.4.2 Failure modes for dispensing intrathecal chemotherapy

Failure mode 6. Failure to thoroughly verify a medication order for completeness and appropriateness

This is likely to occur at the oncology pharmacy. The causes could be a combination of new or replacement staff in a high workload environment of a training institution with constant interruptions from staff and outpatients or illegible medication orders. This was the observation at the oncology pharmacy.

Failure mode 7. Failure to document and/or communicate changes or adjustments to intrathecal treatment

This failure mode can occur when prescribing, dispensing or administering intrathecal chemotherapy leading to inappropriate or missed treatment. The team attributed this to excessive workload and distractions and lack of a dedicated area on the prescription sheet to document unusual occurrence, deviations from treatment plan or observations throughout prescribing, dispensing and administering intrathecal chemotherapy.

Failure mode 8. Intrathecal medication stock out

The team observed that intrathecal medication stock-out has the potential to delay treatment for a patient and can also lead additional out of pocket expenditure. This can also lead to the purchase of preserved formulations of methotrexate and cytarabine. The hospital occasionally receives donations of preserved formulations of methotrexate and cytarabine. Such formulations are contraindicated for administration via the intrathecal route. Stock-outs can be attributed to poor inventory management practices in relation to restocking of supplies, a delay in availing stocks by suppliers or a delay in making funds available to facilitate purchase.
Failure mode 9. Dispensing unlabelled medication for intrathecal administration

Upon verification, medications are packed per patient, in a labelled medicine bag. This label contains the patient name, in-patient number and the ward number. The medications are only labelled in case of medicine bag stock out where the patient name is inscribed manually on the packaging material. The route of administration, dose and warning sign are not indicated on the medication. There are no standardized labels for chemotherapy medications and the packaging material is designed in a way that limits attaching a label. Poor labelling has the potential for confusion and medication related problems such as overdosing and under-dosing. Table 10 provides a detailed HFMEA worksheet for all the potential failure modes identified in the dispensing process

Table 10: HFMEA worksheet for dispensing intrathecal chemotherapy

<table>
<thead>
<tr>
<th>Failure mode</th>
<th>Potential cause</th>
<th>Severity</th>
<th>Probability</th>
<th>Hazard score</th>
<th>Single point weakness</th>
<th>Action Type (Control, Accept or Eliminate)</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>6. Failure to thoroughly verify a medication order for completeness and appropriateness</td>
<td>1. Excessive workload and distractions by staff and patients when verifying medication orders.</td>
<td>3</td>
<td>2</td>
<td>6</td>
<td>Yes</td>
<td>Control</td>
<td>1. Deployment of adequate staff to verify inpatient prescriptions in a dedicated area free from distractions.</td>
</tr>
<tr>
<td></td>
<td>2. Illegible handwriting, rendering the medication order obscure.</td>
<td>2</td>
<td>2</td>
<td>4</td>
<td>Yes</td>
<td>Eliminate</td>
<td>2. Double check of the verification process before proceeding.</td>
</tr>
<tr>
<td>7. Failure to document and/or communicate changes or adjustments to the requisitioning staff</td>
<td>1. Excessive workload and distractions from staff and patients.</td>
<td>4</td>
<td>1</td>
<td>4</td>
<td>Yes</td>
<td>Control</td>
<td>1. Computerized Prescriber Order Entry (CPOE) system to generate medication orders.</td>
</tr>
<tr>
<td></td>
<td>2. lack of provision on the prescription sheet to document adjustments and change.</td>
<td>3</td>
<td>1</td>
<td>3</td>
<td>Yes</td>
<td>Control</td>
<td>1. Provision for documenting unusual occurrence, deviations from treatment plan or observations on the prescription sheet.</td>
</tr>
<tr>
<td>8. Intrathecal medication stock out.</td>
<td>1. Poor inventory management in relation to restocking and supply.</td>
<td>2</td>
<td>2</td>
<td>4</td>
<td>Yes</td>
<td>Control</td>
<td>1. Automated 'dead stop' on the HMIS once a preset stock reorder level is reached.</td>
</tr>
</tbody>
</table>
4.5.4.3 Failure modes for preparation and administration of intrathecal chemotherapy

**Failure mode 10. Contamination of the preparation by operator, material or working environment in the procedure room**

In KNH, intrathecal chemotherapy is prepared prior to administration by specialist registrars and consultant paediatricians and haematologists. This is done in procedure rooms whose layout does not allow the preparation process to occur in a logical flow and in biological safety cabinets. This was attributed to the distance between the oncology pharmacy and the user wards. There are no standard operating procedures for preparation of intrathecal chemotherapy. The team also observed an inadequate availability of some essential personal protective equipment across all the preparation areas. The rubber tops of vials of intrathecal medication are not swabbed and allowed to dry. Any combination of these observations has the potential to introduce contaminant to the final preparation.

**Failure mode 11. Incomplete labelling of the intrathecal preparation**

The standard practice is to attach a labelled adhesive strapping on the prepared syringes indicating the patient name and the medication name. The strength, final volume of the preparation, storage conditions, warning sign and the dates of preparation and expiry are not indicated on the label. This has the potential for confusion.
Failure mode 12. Unsuccessful attempted administration of intrathecal chemotherapy

The complexity of a lumbar puncture for administration of chemotherapy qualifies it as a high risk procedure that involves high-alert medications. This failure mode was observed to emanate from patient discomfort during the procedure, even when sedated, limited familiarity with the procedure and the lack of lumbar puncture needles leading to improvisation through the use of 18 gauge needles. This can be mitigated by ensuring an adequate supply and availability of lumbar puncture needles at the paediatric wards.

Failure mode 13. Inability to ascertain the volume of cerebro-spinal fluid withdrawn

The aim of withdrawing 3-5 ml of CSF into a collection bottle is to have available a sufficient sample for cytology and biochemistry evaluation. This is done with the hope of replacing it with an equivalent volume of diluted preservative free intrathecal medication. However, the sample bottle used for collecting CSF is uncalibrated, making it impossible to ascertain the required volume of preservative free 0.9% normal saline sufficient for the final volume. This becomes even more challenging when conducting double intrathecal methotrexate and cytarabine administration.

Failure mode 14. Administration of undiluted intrathecal medication

The treatment protocol for KNH, Kasilis Synopsis of the Management of Paediatric Cancers in Kenya, pg 55 requires one to:

“Dilute intrathecal methotrexate or cytarabine as follows: draw the required quantity of the drug and make up to 5 ml in preservative free 0.9% normal saline (never use water for injection. Note that some drugs come with their water for injection. These should not be used) in a 10 ml syringe and place on the trolley”

However, the observation was administration of undiluted small volumes of intrathecal medication with or without a follow up administration of the diluent. This was attributed to non-adherence to hospital protocol. Dilution serves to replace the volume of CSF withdrawn and to increase the volume of distribution of the medication in the CNS.
Failure mode 15. Inadvertent erroneous intrathecal administration of a medication in relation to the medication, formulation, dose, volume and timing

For a patient on intrathecal chemotherapy, it is possible that the prescribing, preparation and administration can all be performed by the same specialist registrar. Dispensing is an independent check for prescribing process. There are no independent checks for preparation and administration processes. The team observed that if the staff involved in preparation and administration is not aware of an inadvertent medication error, this would easily reach the patient. There is no documentation of the required volume of medication and diluent, total final volume and volume of CSF withdrawn. Independent double-checks and documentation by staff not involved in the preparation process are not carried out prior to administration. The system for reporting and feedback of chemotherapy medication errors, near-misses and deviations from aseptic technique is not active.

Failure mode 16. Spillage of cytotoxic medication.

This failure mode can occur during preparation of intrathecal chemotherapy and when clearing the working area after administration. It has the potential to expose both the patient and staff to the harmful effects of cytotoxic medications. The hospital has not provided sufficient spill kits in all wards.

Failure mode 17. Failure to document the date of intrathecal administration on the prescription sheet

This failure mode was also described as a cause for failure mode 1 above. Failure to document date of administration can lead to a failure to determine the date of the next intrathecal treatment and thus disrupting treatment tracking. Table 11 provides a detailed HFMEA worksheet for all the potential failure modes identified in the preparation and administration processes.
Table 11: HFMEA worksheet for preparation and administration of intrathecal chemotherapy

<table>
<thead>
<tr>
<th>Failure mode</th>
<th>Potential cause</th>
<th>Severity</th>
<th>Probability</th>
<th>Hazard score</th>
<th>Single point weakness Y/N</th>
<th>Action (Control, Accept or Eliminate)</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>10. Contamination of preparation by operator, material or working environment in the procedure room.</td>
<td>1. Wearing incomplete PPE during the preparation process.</td>
<td>3</td>
<td>4</td>
<td>12</td>
<td>No</td>
<td>Control</td>
<td>1. Ward in-charge to ensure adequate stocks of Liquid proof powder free nitrile protective gloves, Liquid proof disposable gowns, goggles in production areas.</td>
</tr>
<tr>
<td></td>
<td>2. Preparation in an non sterile working environment due to lack of essential production equipment i.e. Biologic Safety chambers.</td>
<td>3</td>
<td>4</td>
<td>12</td>
<td>No</td>
<td>Eliminate</td>
<td>1. Centralized production unit with externally ducted negative pressure isolators to ensure sterility of intrathecal preparations.</td>
</tr>
<tr>
<td></td>
<td>3. Failure to swab the rubber tops of the vials.</td>
<td>3</td>
<td>2</td>
<td>6</td>
<td>Yes</td>
<td>Eliminate</td>
<td>1. Policy requirement to swab the rubber tops of vials with alcohol based antiseptic and allow to dry in order to remove any residues.</td>
</tr>
<tr>
<td>11. Incomplete labelling of the intrathecal preparation.</td>
<td>1. Lack of standardized labels for syringes prepared for intrathecal chemotherapy.</td>
<td>3</td>
<td>4</td>
<td>12</td>
<td>No</td>
<td>Control</td>
<td>Colour coded label on a zip lock envelope for prepared medication.</td>
</tr>
<tr>
<td></td>
<td>2. Lack of the essential equipment i.e. Lumbar Puncture needles leading to improvisation.</td>
<td>3</td>
<td>4</td>
<td>12</td>
<td>No</td>
<td>Eliminate</td>
<td>2. Adequate supply and availability of Lumbar Puncture needles in the paediatric wards.</td>
</tr>
<tr>
<td>13. Inability to determine the volume of CSF withdrawn.</td>
<td></td>
<td>1</td>
<td>4</td>
<td>4</td>
<td>Yes</td>
<td></td>
<td>1. Provision of calibrated collection bottles to enable determination of volume of diluent to be used for dilution.</td>
</tr>
<tr>
<td>14. Inadvertent erroneous intrathecal administration in relation to the medication.</td>
<td>Use of uncalibrated sample collection bottles.</td>
<td>1</td>
<td>4</td>
<td>4</td>
<td>Yes</td>
<td>Eliminate</td>
<td>1. Provision of calibrated collection bottles to enable determination of volume of diluent to be used for dilution.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. An absent self-awareness of the error due to single point nature of prescribing, preparation and administration of paediatric chemotherapy in KNH.</td>
<td>3</td>
<td>3</td>
<td>9</td>
<td>No Control</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Provision of a preparation worksheet for documenting dose calculations, whether the volume of medication drawn provides the correct dose in mg, the required volumes of medication and diluent, total final volume of preparation, labelling and independent checks.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Lumbar puncture worksheet for documentation of number of attempts before a successful intrathecal access, volume and colour of CSF drawn, patient positioning during lumbar puncture, equipment used for procedure and independent checks and documentation of day and time of completion.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. Structured induction training program, assessment of competence, adequate deployment of staff and regular audit of intrathecal chemotherapy processes.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. Hospital policy for sequencing of intrathecal and intravenous chemotherapy on different days or intrathecal administration only after documented completion of intravenous administration.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6. A system for reporting and feedback of chemotherapy medication errors, near-misses and deviations from aseptic technique.</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<p>| | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Non-adherence to hospital protocol requirement for dilution of medication intended for IT administration.</td>
<td>2</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td>1. Sensitization of staff on need to dilute medication intended for intrathecal route as per the hospital protocol.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>16. Spillage of cytotoxic medication during clearing the working area.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Poor handling of cytotoxic waste and spills.</td>
<td>3</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>1. Sensitization of staff on safe handling of cytotoxic waste and management of spills.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>17. Date of</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>3</td>
<td>9</td>
</tr>
</tbody>
</table>
intrathecal administration not entered on the prescription sheet.

| 1. Inadequate provision on the prescription to make entries of dates of administration. | 3 | 3 | 9 | No | Control | 1. Redesign of the prescription sheet to facilitate complete documentation of date of administration and the day of treatment as per schedule. |

### 4.6. Recommendations

The observation that some of the failure modes are interrelated led to classification of the recommendations to avoid repetition. This classification covers; documentation and communication, equipment and material, induction training, organisational factors and internal assessment of resource needs. **Table 12** below provides a summary of the recommendations. It also highlights the responsible person/s.

**Table 12: Summary of recommendations and responsibilities**

<table>
<thead>
<tr>
<th>Failure mode classification</th>
<th>Recommendation</th>
<th>Responsibility</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Documentation and communication</strong></td>
<td>1. Re-design of the oncology prescription sheet to facilitate treatment tracking, scheduling and sequencing of treatment, dosage calculations and weekly charting of weight and height.</td>
<td>Medicines and Therapeutic Committee</td>
</tr>
<tr>
<td></td>
<td>2. Computerized prescriber order Entry system</td>
<td>Director Corporate Services</td>
</tr>
<tr>
<td><strong>Training</strong></td>
<td>1. An induction training program relevant to the level of staff involvement in chemotherapy covering: a. Aseptic technique b. Good chemotherapy prescribing practices c. Good chemotherapy dispensing practices d. Safe handling of cytotoxic drugs and their waste products e. Lumbar puncture technique</td>
<td>1. Director Clinical Services 2. Head of cancer treatment centre 3. Head of oncology pharmacy</td>
</tr>
</tbody>
</table>
| **Equipment and materials** | 1. Adequate supply and availability of materials and equipment for intrathecal production at all times;  
   a. Personal protective equipment  
   b. Lumbar puncture needles  
   c. Biological safety chambers  
   d. Intrathecal medication  
   e. Spill kits  
   f. Calibrated CSF sample collection bottles  
   g. Standardized colour coded labels for medication and syringes  
   h. Zip lock envelopes for packaging of intrathecal preparations | 1. Procurement department  
2. Head of paediatric services  
3. Deputy Director Pharmacy |
| **Organizational factors** | 1. An integrated hospital policy on the safe use of (intrathecal) chemotherapy that also covers;  
   a. Scheduling of intravenous and intrathecal chemotherapy.  
   b. Active, non-punitive systems for reporting chemotherapy medication related problems and feedback.  
   c. Process defences and barriers like Independent double-checks for critical aspects of high risk processes in chemotherapy  
   d. Preparation of intrathecal chemotherapy by oncology pharmacy staff | 1. Director of Clinical Services  
2. Medicines and Therapeutics Committee  
3. Paediatric oncology protocol development team  
4. Head of oncology pharmacy |
| **Assessment of human and infrastructural resource needs for decision making** | 1. Adequate staffing  
2. Safe and conducive environment for prescribing, dispensing, preparation and administration of all chemotherapy. | 1. Deputy Director Human Resource  
2. Director Clinical Services |
5.0. CHAPTER FIVE: DISCUSSION, CONCLUSION AND RECOMMENDATIONS

5.1. The prevalence of intrathecal chemotherapy and intrathecal treatment related characteristics

This study identified retinoblastoma (27.4%), Wilm’s tumour (14.9%), non-Hodgkin’s lymphoma (13.1%) acute lymphoid leukaemia (8.9%) and Hodgkin’s lymphoma (7.1%) as the top 5 cancers, accounting for 71.4% of the paediatric cancer patients admitted in KNH in 2015. This observation is not consistent with the data in the Kenya National Guidelines [2] and the research by Mwanda in 1999 which identified leukaemia and lymphoma as the leading paediatric cancers in KNH[27]. However, it is consistent with the Kenya National Guidelines with regards to retinoblastoma and Wilm’s tumour ranking among the leading solid tumours in children [2]. The inconsistency can be explained by the fact that this study had access to 281(54.7%) of the records for paediatric oncology patients admitted in KNH in 2015. Of the missing records, 65 were duplicates of already retrieved files while 198 records could not be found at the Health Records and Information department.

The prevalence of intrathecal chemotherapy established it as common procedure among paediatric oncology patients in KNH. There are no facility-based studies on the prevalence of intrathecal chemotherapy. However, some hospital policies for intrathecal chemotherapy in the United Kingdom require documentation of the annual number of intrathecal chemotherapy prescribed, dispensed, prepared and administered [42]

For patients diagnosed with acute lymphoid leukaemia, males had 11 times the odds of receiving intrathecal chemotherapy when compared to females. This finding is suggestive of gender as a prognostic factor. A WHO report on childhood cancers shows a higher incidence of non-Hodgkin’s lymphoma, Hodgkin’s lymphoma, ependymomas, primitive neuroectodermal tumours and acute lymphoid leukaemia in males, and a higher incidence of thyroid carcinoma and malignant melanoma among females [58]. A study by Donadeu et al identified male gender as a predictor of poor outcome in childhood ALL in a French hospital in 1998 [(59)]. There is no evidence of gender as prognostic factors in paediatric NHL.
The patients who received intrathecal chemotherapy had a diagnosis of either ALL or NHL. This finding is consistent with the hospital policy for the management of paediatric cancers in KNH[11], the national guidelines for management of cancers in Kenya [2] and international hospital policies for the safe handling of intrathecal chemotherapy [13,39] where it is used for prophylaxis or treatment of CNS infiltration.

The finding that intrathecal chemotherapy was administered to 63.3% of NHL and 63.6% of ALL patients on chemotherapy shows that close to two thirds of ALL and NHL paediatric patients on chemotherapy had a high risk of CNS infiltration and were in need of intrathecal prophylaxis or had a confirmed CNS disease and needed intrathecal treatment. It further corroborates the observation that in Kenya, many paediatric cancers are diagnosed late leading to late initiation of treatment [2].

Intrathcal chemotherapy was administered to patients in induction, consolidation and maintenance phases of treatment, this is consistent with hospital protocol, Kenya national guidelines for the management of cancer [2,11]. The same approach, using intrathecal methotrexate and cytarabine or liposomal cytarabine is practiced internationally in for management of ALL and NHL. In solid tumours that have a confirmed CNS metastasis, the use of intrathecal methotrexate and/or cytarabine is limited by the narrow antitumour activity. Thiotepa and investigational drugs like topotecan, mafosfamide, busulfan have been used for intrathecal chemotherapy. [12,13]

There was a significant difference between the role of intrathecal chemotherapy and whether a patient was a first time chemotherapy patient or retreatment patient. All retreatment patients were on intrathecal chemotherapy for the treatment of confirmed CNS disease, and first time chemotherapy patients were on intrathecal chemotherapy for prophylaxis against CNS infiltration. All patients on prophylactic intrathecal treatment were treated using methotrexate while those treated with combined intrathecal chemotherapy involving methotrexate and cytarabine had confirmed CNS disease. This shows that children who relapse are treated with more intensive and potentially toxic drugs. It is further supported by Kerr et al, who states that intrathecal cytarabine is primarily used as treatment for CNS lymphomas and leukaemias while
intrathecal methotrexate can be used either alone or in combination with cytarabine and hydrocortisone for prevention or treatment of CNS infiltration [13]

5.2. The intrathecal chemotherapy processes in paediatric oncology in KNH

In KNH, the intrathecal chemotherapy processes of prescribing, ordering, dispensing, transportation, preparation and administration are conducted through a multi-disciplinary approach that involves specialist registrars, nursing staff and pharmacy staff under the supervision of consultant paediatricians, haematologists and clinical pharmacist.

The lack of a hospital policy for safe use of intrathecal chemotherapy is a source of potential medication errors due to absence of standardized techniques. Where policies exist, for example in the UK, hospitals are required to have a policy document for intrathecal chemotherapy covering: an induction training program for aseptic technique, safe handling of intrathecal cytotoxic products and their waste, regular competence assessment and documentation of intrathecal chemotherapy processes [38]

5.2.1. The prescribing process

Intrathecal chemotherapy is prescribed by medical officers in paediatric specialist training, also known as specialist registrars under the supervision of consultant paediatricians and haematologists. This practice compares well with that highlighted in hospital policies in many western countries [35,38,40,41]

The prescriptions are generated based on a review of a patient’s fitness for treatment and in accordance to the hospitals protocol for management of paediatric cancers. It incorporates the results of diagnostic screening tests like complete blood counts, radiological test results, patient’s general condition, need for supportive treatment for pain, toxicity and infections, tolerability of chemotherapy medications and co-morbidities, nature and extent of disease. Intrathecal chemotherapy is prescribed according to the hospital’s treatment protocol and together with other anticancer medication. The details of the prescription are handwritten onto a purpose-specific chemotherapy prescription sheet in the patient’s medical notes. Medication
names and routes of administration are seldom written in full. The hospital protocol does not forbid the use of abbreviations when prescribing chemotherapy.

The Institute of Safe Medication Practices (ISMP) recommends the prescribing of high-alert medications names and routes of administration in full[14]. This recommendation has been adopted by hospital policies for the safe use of intrathecal chemotherapy in many western countries. In KNH, there is no specific policy document to addresses the safe use of intrathecal chemotherapy. To generate a medication order, the prescription is copied into a duplicate requisitioning form (S11) and a non-schedule form by a requisitioning nurse. The American Society of Hospital Pharmacists (ASHP) guidelines for prevention of medication errors in chemotherapy recommend the use of a Computerized Physician Order Entry (CPOE) system when prescribing anticancer medication. A CPOE system improves safety by having safety-checks that are not possible with a paper based system. In addition, it improves efficiency and reduces workload. In low resource settings, a pre-printed order system can also be adopted to improve order legibility, standardization of practice across prescribers, scheduling and sequencing of chemotherapy[37]

5.2.2. The dispensing process

Kenyatta national hospital utilizes a centralized system for dispensing all anticancer medications through the oncology pharmacy. The pharmacy serves both adult and paediatric inpatients and outpatients. It is a single room located approximately 300 meters from the paediatric oncology ward 1E, the highest consumer of intrathecal chemotherapy services in KNH.

Dispensing process is carried out by 2 pharmacists and 3 pharmaceutical technologists under the supervision of a consultant oncology pharmacist. It entails verification of prescriptions for appropriateness in relation to the diagnosis, schedule of treatment and treatment protocol. These clinical pharmacy verifications include patient demographics of age, height, weight and body surface area for dose calculation, possible drug allergies and interactions, full blood counts and need for dose adjustments. This practice is in line with the British Oncology Pharmacists Association (BOPA) standards of verification of chemotherapy prescriptions [58]. The BOPA
standards provide for the need to verify the compatibility of diluents to be used for preparation of intrathecal chemotherapy and their volume.

In the UK, the national guidelines for safe administration of intrathecal chemotherapy require the pharmacist to dispense appropriately labelled medication and only after ensuring that medication for intravenous route has been administered [38]; this includes a legible warning sign on the prepared syringe that the medication is “FOR INTRATHECAL USE ONLY”. This is not the practice in KNH because intrathecal medications are dispensed in their vials for preparation by specialist registrars in the wards and on the same day as for medications intended for administration via intravenous route.

5.2.3. Preparation and administration processes

There is a dedicated chemotherapy preparation room in KNH located next to the oncology pharmacy where the pharmacy staff prepare intravenous medications only. This is due to the high workload. When preparing intrathecal chemotherapy, there are no provisions for independent double checks given that preparation and administration procedures are done by the same specialist registrar. The production environment in the paediatric wards does not guarantee safety to the staff involved and sterility of the final product. It lacks biologic safety cabinets, adequate personal protective equipment, orderly and logical positioning of equipment or material and is prone to interruptions by inpatients. Quality assurance of aseptic preparations requires that a pharmacist should verify aseptic preparations. This verification involves checks and documentation of compatibility of components for production, stability of formulation and that the product is in the correct presentation for intrathecal route [61].

Key aspects of the preparation procedure are not documented on the patient’s records including whether the volume of medication drawn into a syringe gives the required dose and how the final volumes of the medication and diluents were arrived at. In the UK and New Zealand, national guidelines for safe use of chemotherapy recommend hospitals to adopt policies that require preparation of intrathecal chemotherapy by trained pharmacy staff, in controlled aseptic environment[25,38,39]. In 2012, a review of circumstances leading to medication errors in the aseptic manufacturing unit of a hospital in the UK recommended and adopted the use of
preparation worksheets. The worksheets are used for calculation of doses and documentation of volumes of chemotherapy medications and diluents and dates of production and expiry of intrathecal preparations [62]. The prepared syringes should be labelled to show the total volumes of medication, diluents used for production and legible warning sign that the preparation is ‘FOR INTRATHECAL USE ONLY’ [63]

In KNH, intrathecal chemotherapy is administered to all patients via a lumbar puncture. Studies have shown that intraventricular administration through Omaya reservoirs offer greater intrathecal drug concentrations for CNS relapse patients when compared to intralumbar administration[13]. Intravenous and intrathecal chemotherapy is administered on the same day and time and therefore increasing the likelihood of inadvertent intrathecal administration of medications for intravenous route like vincristine. Such incidences have led to recommendations for separate transportation, storage, preparation, adequate labelling and administration of all intrathecal and intravenous chemotherapy. Additionally, independent double-check of the preparation and administration of intrathecal preparations can minimize the potential errors and improve patient safety. [16,18]

Optimum administration involves the use of the correct equipment to administer at least 6mls of diluted intrathecal medication so as to achieve a better distribution in the CNS, reduce pain and improve success rates of lumbar puncture procedures [64].

5.3. CONCLUSION

Intrathecal chemotherapy is a component of the multiple chemotherapy of paediatric ALL and NHL in KNH. 16.7% (C.I 13.0-21.3) of 198 paediatric oncology patients on chemotherapy received intrathecal chemotherapy involving methotrexate alone or in combination with cytarabine either as prophylaxis or treatment of CNS infiltration.

The current practice of intrathecal chemotherapy at KNH does not provide adequate safeguards to ensure patient and provider safety. The use of a prospective risk assessment tool via a multi-disciplinary team enabled this study to identify potential gaps, their cause and effect. These gaps, in the form of potential failure modes were spread across the processes of prescribing, dispensing, preparation and administration processes of intrathecal chemotherapy. The
recommendations made by the multi-disciplinary team comprised of key process users can improve the safety and efficiency of intrathecal chemotherapy among paediatric oncology patients in KNH. The magnitude of improvement can be measured using a follow up HFMEA upon implementation of recommendations.

**5.4. RECOMMENDATIONS**

**5.4.1. Recommendations for policy and practice**

The multi-disciplinary team developed recommendations for improving efficiency and safety of intrathecal chemotherapy among paediatric oncology patients in KNH. These covered communication, documentation, training, organizational factors, equipment, materials and assessment of needs.

There is need for a customized hospital policy on the safe use of intrathecal chemotherapy and other commonly used anticancer medication, a platform for effective documentation and communication of all aspects of a patient’s medication and management plan, a comprehensive induction training program for staff involved in chemotherapy that is relevant to their level of involvement, regular competence assessment, adequate staffing and stocking of medication, personal protective equipment, lumbar puncture needles and adequate production areas that guarantee asepsis.

The preparation of intrathecal chemotherapy should be a centralized function of the oncology pharmacy so as to maintain standards of practice, guarantee asepsis of preparations and the safety of staff involved in production.

The oncology pharmacy should consider stocking liposomal cytarabine in place of the standard cytarabine for intrathecal chemotherapy due to its long duration of action; 168 hours compared to 24 hours.

In cases of relapse of CNS disease, KNH should consider intraventricular administration of drugs in place of intralumbar route because it offers greater intrathecal concentrations.

At the Health Records and Information unit, an electronic filing system is recommended to ease access to patient’s medical notes.
5.4.2. Recommendations for future studies

Upon implementation of the recommendations, a follow up HFMEA should be conducted to inform the effectiveness of the mitigation strategies identified in this study.

The HFMEA approach can be utilized to assess the potential risks in other high risk surgical procedures, infusion and high-alert medications like insulin, heparin and other anticoagulants, potassium and concentrated electrolytes, narcotics and anti-infectives.

The finding that over one third of ALL (36.4%) and NHL (36.7%) paediatric patients on chemotherapy did not receive intrathecal chemotherapy highly recommends a prospective study into the cause of missed doses and clinical characteristics of these patients.

This study can be conducted in other facilities that offer intrathecal chemotherapy in Kenya for comparison and inform national decision making.

Study Limitations

For the quantitative phase, data abstraction through a retrospective approach was a challenge due to missing patient records. The poor documentation practices limited the determination of the actual number of intrathecal doses administered.

HFMEA does not measure actual failure rates or medication errors. Due to lack of incidence reports relating to intrathecal chemotherapy in KNH, determination of effects of failure modes was based on experience and a sense of what happens in KNH.
REFERENCES


49. DeRosier J, Stalhandske E, Bagian JP et al. Using Health Care Failure Mode and Effect


APPENDICES
APPENDIX 1A: SCREENING AND ELIGIBILITY FORM

All subjects enrolled must meet eligibility criteria based on the inclusion and exclusion criteria detailed in the application approved by the KNH-UoN Ethics and Research Committee.

I. Study Information

Study Title: Proactive risk assessment of intrathecal chemotherapy in paediatric oncology in Kenyatta National Hospital.

Principal Investigator: Wilson Major Nyamai.

Signature……………………………………..Date of screening………………………………..

II. Patient Information

Participant Code Number…………………………

III. Inclusion/Exclusion Criteria (Tick where appropriate)

<table>
<thead>
<tr>
<th>Inclusion Criteria.</th>
<th>YES</th>
<th>NO</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Items 1 to 3 must be answered YES for eligibility)</td>
<td></td>
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</tr>
<tr>
<td>1. Paediatric oncology patient either male or female.</td>
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<tr>
<td>2. Patient admitted in paediatric wards in KNH between 1\textsuperscript{st} of January 2015 and 31\textsuperscript{st} of December 2015.</td>
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<tr>
<td>3. Patient aged below 13 years on admission.</td>
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</table>

<table>
<thead>
<tr>
<th>Exclusion Criteria.</th>
<th>YES</th>
<th>NO</th>
</tr>
</thead>
<tbody>
<tr>
<td>(items 1 or 2 need to be answered YES for exclusion)</td>
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<td></td>
</tr>
<tr>
<td>1. Missing information on patient diagnosis</td>
<td></td>
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<tr>
<td>2. Missing information on the prescribed treatment for the patient.</td>
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APPENDIX 1B. DATA COLLECTION FORM

Participant Code Number: ..........................

I. Participant Demographics.

1. Date of Birth: Day………… Month………… Year…………
2. Gender: Male ☐  Female ☐
3. Weight (kgs) ……….
4. Height (cms) ……….  Body Surface Area (BSA) ……….

II. Participant’s Chemotherapy History.

1. Date of admission: Day………..Month…………Year………………
2a. Diagnosis

……………………………………………………………………………………………………………………
……………………………………………………………………………………………………………………
……………………………………………………………………………………………………………………

2b. Staging of diagnosis where applicable

……………………………………………………………………………………………………………………

3. Was chemotherapy prescribed to the participant? YES ☐  NO ☐

4. a) New chemotherapy patient ☐  b) Retreatment ☐
Table 1: Summary of participant’s prescribed chemotherapy.

<table>
<thead>
<tr>
<th>Medication name</th>
<th>Prescribed dose</th>
<th>Route of administration</th>
<th>Frequency of administration</th>
<th>Duration of treatment</th>
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<tbody>
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</tbody>
</table>

5. Was Intrathecal Chemotherapy a component of the prescribed regimen? (Fill where appropriate) **YES** [ ] **NO** [ ]

6. Name and Dosage of Intrathecal medication prescribed?

............................................................................................................................

............................................................................................................................

............................................................................................................................

............................................................................................................................
Table 2: Summary of participant’s intrathecal chemotherapy.

<table>
<thead>
<tr>
<th></th>
<th>Induction</th>
<th>Consolidation</th>
<th>Maintenance</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dates of intrathecal chemotherapy prescription</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dates of intrathecal chemotherapy administration</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of intrathecal doses administered</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total number of doses</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

7. Purpose for intrathecal chemotherapy? (Fill where appropriate)

Treatment of Central Nervous System disease

Prophylaxis for Central Nervous System involvement

8. Date of discharge? Day .......... Month .............. Year ..........
APPENDIX 2: PRIOR INFORMED CONSENT FORM FOR HEALTHCARE WORKERS

UNIVERSITY OF NAIROBI

COLLEGE OF HEALTH SCIENCES

SCHOOL OF PHARMACY

DEPARTMENT OF PHARMACOLOGY AND PHARMACOGNOSY

P. O. Box 19676, NAIROBI, 00202 TEL. 0202 725099

Serial Number……………………..

Study Title: Proactive risk assessment of intrathecal chemotherapy in paediatric oncology in Kenyatta National Hospital.

Principal Investigator: Dr. Wilson Major Nyamai, postgraduate student (Pharmacoepidemiology and Pharmacovigilance) P.O. Box 33-60100, Embu.

Mobile: +254720467350.

Supervisors: Dr. Eric .M. Guantai, Department of Pharmacology and Pharmacognosy, School of Pharmacy, University of Nairobi.

Dr. Peggotty Mutai, Department of Pharmacology and Pharmacognosy, School of Pharmacy, University of Nairobi.

I am Dr. Nyamai Major, conducting the above mentioned study to partly fulfil the requirements for a Master Degree of Pharmacy in Pharmacoepidemiology and Pharmacovigilance of the University of Nairobi.
Ethical Approval: Kenyatta National Hospital- University of Nairobi Ethical Research Committee, P.O.BOX 20723-00100, Nairobi. Tel 2726300 / 2716450 Ext 44102

What is the purpose of this study?

The purpose of this study is to systematically examine the prescribing, dispensing, preparation and administration of intrathecal chemotherapy among paediatric oncology patients in Kenyatta National Hospital with the aim to consultatively identify the potential sources of hazards to the patients and make the appropriate recommendations.

Why have I been invited to participate?

You have been approached as a participant based on your knowledge, training and experience in paediatric oncology chemotherapy in KNH.

What is expected of me as a participant?

Should you agree to participate in the study, your expertise shall be sought as a member of a Healthcare Failure Mode and Effect Analysis (HFMEA) multidisciplinary team. This team shall individually identify the main processes and sub-processes (and their corresponding intended outcome), develop a refined and detailed flow diagram of the overall process of intrathecal chemotherapy use in paediatric oncology patients at KNH. The developed process flow diagram shall be subjected to a risk/hazard analysis to determine the different ways that a process or sub-process can fail to provide the anticipated result and the most likely outcomes for each failure mode. Further, the HFMEA multi-disciplinary team will categorize the severity (how serious the outcome of the failure is likely to be) and probability (how often the failure is likely to occur) of each potential failure mode using the Severity Rating Table and the Probability Rating Table.

The HFMEA Hazard Scoring Matrix will then be used to assign a hazard score to each potential failure mode based on its severity and probability. Failure modes with a hazard score of 8 or more will be subjected to HFMEA Decision Tree analysis to determine whether the failure mode warrants further action on the basis of criticality, absence of effective control measures and lack of detectability. Finally, this decision tree analysis will be summarized and presented
in the form of a HFMEA Work Sheet and causes of failure mode categorized as eliminate, control or accept.

HFMEA multi-disciplinary team will then make recommendations for action for each failure mode cause that will be eliminated or controlled.

**How will I be engaged for this study?**

This study will utilize the idea generation technique of brainstorming sessions to trigger ideas and solutions through intensive and non-restricted group discussions. There will be a minimum of 7 sessions scheduled after every 2 weeks. Each session will last for not more than 2 hours. The first session will be an introduction to Healthcare Failure Mode and Effect analysis, a proactive risk assessment method that helps identify the potential risks in any high risk process, their potential cause and the appropriate mitigation strategies. All your queries and concerns about the method will be adequately addressed during this session. Following this session, you will be expected to independently visit your work station to observe the relevant processes and sub-processes under your jurisdiction in the prescribing, dispensing, preparation and administration of intrathecal chemotherapy in paediatric oncology in KNH. Consultation with process users will help you gain additional input. This will help you developed a detailed logical flow diagram of all the steps involved in the process that you will identify.

The second session will be a collective process of consolidation and refining of the flow diagrams into one final comprehensive process flow diagram. This will be followed by a brainstorm and listing of the potential failure modes of the processes and sub-processes of intrathecal chemotherapy. In preparation for the third session, you will be expected to consult process users in your work site for additional failure modes or accurate and/or complete capture of failure modes.

During the third session, we will collectively refine the failure modes based on input from process users and the advisory panel. We will further identify all the causes of failure modes and effects on the process of intrathecal chemotherapy. You will be assigned to consult process users for additional input into the causes and effects of failure modes.
The fourth session will be utilized to refine the failure mode causes and their effects on the process of intrathecal chemotherapy. This will be followed by a collective process of hazard analysis of each failure mode by determining and assigning them a severity and a probability score and finally hazard score. A severity rating scale, probability rating scale and a hazard scoring matrix will be provided during the session. In the case of a disagreement on a rating, a vote will be held to provide a conclusive rating.

The team will use the fifth session to conduct a decision tree analysis to determine whether the failure mode warrants further action on the basis of criticality (whether the entire system will fail if this part of the process fails), absence of effective control measures (steps or actions that eliminates or significantly reduces the likelihood of the failure occurring), and lack of detectability (likelihood of detecting failure or the effect of failure before it occurs).

Where the team decision will be to proceed, all the failure mode causes will be listed and categorized as eliminate, control or accept during the sixth session. Those categorized for elimination or control will form the basis for team recommendations and action. The need for additional session/s to complete any pending tasks will be reviewed by the team. A date for such session/s will be assigned upon consensus. The final session will be used to draft the final report.

**Who will have access to the data collected?**

All data collected during this analysis shall be available only to the principle investigator and the HFMEA multidisciplinary team. All information obtained from you will be kept in confidence. It shall be entered into a password protected computer to maintain confidentiality. It shall be availed to the KNH-UoN Ethics and Research Committee upon request.

**Must I participate?**

Your participation is completely voluntary. You are free to withdraw your participation at any point in the study without any form of jeopardy and without necessarily giving a reason for withdrawal.

**Are there any benefits for participating?**
There are no financial incentives or other direct benefits to you. However, the findings will be useful in improving the quality of care to paediatric oncology patients on intrathecal chemotherapy by proactively minimising risks to patient safety through a systematic process of identifying gaps and development of action plans to make the process more efficient and safe.

What are the risks associated with my participation?

There are no risks or harm anticipated during the course of this study. All information obtained will be treated in utmost confidence. Your opinion and contribution will be held in high regard during the entire course of this study.

STATEMENT OF CONSENT

I _______________________________ willingly give my consent to participate in this study. Dr. Nyamai Major has explained the nature of the study, my responsibilities as a participant and all the inconveniencies associated with voluntary participation.

Respondent Signature_________________________ Date________________________

I confirm that I have explained the nature and effect of the study to this participant and encouraged them to ask questions which I took time to answer to their satisfaction. I am adequately convinced that the participant fully understands all aspects of the research as discussed.

Signature_________________________ Date________________________

In case of any concern, you may contact the principle investigator on E-mail: wnmajor2@gmail.com or mobile: +254720467350 or KNH-UoN Ethics and Research Committee Secretary: Prof. Mark Chindia Tel +254 207 726300 ext. 44355, E-mail uonknh.erc@uonbi.ac.ke
APPENDIX 3: TABLE OF OPTION A MANAGEMENT OF ALL IN KNH

Adapted from Kasilis synopsis (11)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage and route</th>
<th>Duration of therapy.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vincristine</td>
<td>1.5mg/m² (max 2.0 mg), IV</td>
<td>Days 1, 8, 15, 22 (or weekly X 4)</td>
</tr>
<tr>
<td>Daunorubicin/Doxorubicin</td>
<td>25mg/m², IV</td>
<td>Days 1, 8, 15, 22 (or weekly X 4)</td>
</tr>
<tr>
<td>Prednisone</td>
<td>40mg/m²/day</td>
<td>For 28 days in 3 divided dose, then taper to zero over 7 days</td>
</tr>
<tr>
<td>Intrathecal methotrexate</td>
<td>Once weekly for 5 doses</td>
<td>Age related doses (1-2 years 5.5mg; 3-5 years 7.5mg; 5-7 years 10mg; &gt; 7 yrs 12.5mg)</td>
</tr>
</tbody>
</table>

2. **Consolidation** Starts 10-14 days after completing induction

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage and route</th>
<th>Duration of therapy.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclophosphamide IV</td>
<td>1000 mg/m² in saline over 8 hrs</td>
<td>On day 1 and 8</td>
</tr>
<tr>
<td>Vincristine IV</td>
<td>1.5mg/m²</td>
<td>Days 1 and 8, Give second course after 10-14 days as determined by level of blood counts</td>
</tr>
<tr>
<td>Cytarabine</td>
<td>75mg/m² SC</td>
<td>Days 1-4, 22-25, 29-32</td>
</tr>
</tbody>
</table>

3. **Maintenance** For 24 months. Starts 4 weeks after completing consolidation and is still remission
<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage</th>
<th>Schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-Mercaptopurine</td>
<td>75mg/m²/day, PO</td>
<td>Daily for 24 months</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>25mg/m²/week, PO</td>
<td>Weekly for 24 months</td>
</tr>
<tr>
<td>Vincristine</td>
<td>1.5mg/m² IV</td>
<td>Day 1 monthly for 24 months</td>
</tr>
<tr>
<td>Intrathecal methotrexate</td>
<td>Dose for age.</td>
<td>Every 8 weeks for 1st year for those without CNS disease</td>
</tr>
<tr>
<td>Adriamycin</td>
<td>25mg/m²</td>
<td>Every three months for 24 months</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>300mg/m²</td>
<td>Every three months for 24 months.</td>
</tr>
<tr>
<td><strong>Re-induction - (4 weeks)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vincristine</td>
<td>1.5mg/m² IV</td>
<td>Days 1, 8, 15 and 22</td>
</tr>
<tr>
<td>Daunorubicin</td>
<td>25mg/m², IV</td>
<td>Days 1, 8, 15 and 22 (Echo cardiogram done before each dose)</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>4 mg/m²/day, orally</td>
<td>Days 1-22, then taper to zero from day 22 to 29</td>
</tr>
<tr>
<td>Intrathecal methotrexate</td>
<td>Dose for age</td>
<td>Day 1 every week for 4 weeks</td>
</tr>
<tr>
<td><strong>Re-consolidation.</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>650 mg/m² (maximum 1000mg) IV</td>
<td>Starting on day 28 then every two weeks times 3.</td>
</tr>
<tr>
<td>Intrathecal methotrexate</td>
<td>(dose for age)</td>
<td>Day 31, 38, 45 and 52 weekly for three weeks</td>
</tr>
<tr>
<td>6-Mercaptopurine</td>
<td>60mg/m²/day, orally</td>
<td>Days 29-57 ( for 28 days )</td>
</tr>
<tr>
<td>Cytarabine</td>
<td>75mg/m², SC</td>
<td>Starting day 30 daily for four days and</td>
</tr>
</tbody>
</table>
APPENDIX 4: TABLE OF OPTION B MANAGEMENT OF ALLIN KNH

Adapted from Kasilis Synopsis(11)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage and route</th>
<th>Duration of therapy.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prednisone</td>
<td>60mg/m² orally</td>
<td>Days 1 to 28</td>
</tr>
<tr>
<td>Vincristine</td>
<td>1.5mg/m² (max. 2.0mg) IV</td>
<td>On days 1,8,15 and 22</td>
</tr>
<tr>
<td>Daunorubicin</td>
<td>25mg/m² IV</td>
<td>On days 1,8,15 and 22</td>
</tr>
<tr>
<td>L-Asparaginase</td>
<td>5000 units/m² IV</td>
<td>On days 1 to 14. (Dose may be adjusted downward at 3,000 unit/m² when given together with anthracycline).</td>
</tr>
</tbody>
</table>

Consolidation: Phase II

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage and route</th>
<th>Duration of therapy.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclophosphamide</td>
<td>650 mg/m² (maximum 1000mg) IV</td>
<td>Starting on day 28 then every two weeks times 3.</td>
</tr>
<tr>
<td>Intrathecal methotrexate</td>
<td>(dose for age)</td>
<td>Day 31, 38, 45 and 52 weekly for three weeks</td>
</tr>
<tr>
<td>6-Mercaptopurine</td>
<td>60mg/m²/day</td>
<td>PO days 29-57 for 28 days.</td>
</tr>
<tr>
<td>Cytarabine</td>
<td>75mg/m², SC</td>
<td>Starting day 30 daily for four days and repeating every week</td>
</tr>
</tbody>
</table>
for 3 weeks.

**Re-induction: Phase I**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dexamethasone</td>
<td>10mg/m² orally</td>
<td>On days 1 to 28.</td>
</tr>
<tr>
<td>Vincristine</td>
<td>1.5mg/m² (max. 2.0mg) IV</td>
<td>On days 1, 8, 15 and 22</td>
</tr>
<tr>
<td>Doxorubicin</td>
<td>25mg/m² IV</td>
<td>On days 1, 8, 15 and 22</td>
</tr>
</tbody>
</table>

**Re-consolidation: Phase II**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclophosphamide</td>
<td>650 mg/m² (maximum 1000mg)</td>
<td>Starting on day 28 then every two weeks times 3.</td>
</tr>
<tr>
<td></td>
<td>IV</td>
<td></td>
</tr>
<tr>
<td>Intrathecal methotrexate</td>
<td>(dose for age)</td>
<td>Day 31, 38, 45 and 52 weekly for three weeks.</td>
</tr>
<tr>
<td>6-Mercaptopurine</td>
<td>60mg/m²/day</td>
<td>Days 29-57 for 28 days</td>
</tr>
<tr>
<td>Cytarabine</td>
<td>75mg/m², SC</td>
<td>Starting day 30 daily for four days and repeating every week for 3 weeks.</td>
</tr>
</tbody>
</table>

**Maintenance**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-Mercaptopurine</td>
<td>60mg/m² orally daily</td>
<td>On weeks 10 to 18 and 29 to 130</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>20mg/m² orally or IV weekly</td>
<td>On weeks 10 to 18 and 29 to 130</td>
</tr>
</tbody>
</table>
## APPENDIX 5: TABLE OF CHOP REGIMEN FOR MANAGEMENT OF BURKITTS LYMPOMA IN KNH

Adapted from Kasilis Synopsis(11)

### Induction.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage and route</th>
<th>Duration of therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclophosphamide</td>
<td>500mg/m² IV</td>
<td>On day 1 and weekly for 6 weeks</td>
</tr>
<tr>
<td>Adriamycin/Doxorubicin</td>
<td>50mg/m², IV</td>
<td>On day 1, 21 and 43</td>
</tr>
<tr>
<td>Vincristine</td>
<td>1.4mg/m², IV</td>
<td>On day 1 and weekly for 6 weeks.</td>
</tr>
<tr>
<td>Prednisone</td>
<td>40mg/m², orally</td>
<td>Daily for 4 weeks tail off to zero from week 5</td>
</tr>
<tr>
<td>Intrathecal Methotrexate</td>
<td>12.5mg/m²</td>
<td>Twice weekly during induction and consolidation.</td>
</tr>
</tbody>
</table>

### Consolidation

Starts 10-14 days after completing induction

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage and route</th>
<th>Duration of therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclophosphamide</td>
<td>IV 1200 mg/m² in saline over 8 hrs</td>
<td>On day 1 and 8</td>
</tr>
<tr>
<td>Adriamycin</td>
<td>60mg/m², IV</td>
<td>Day 1.</td>
</tr>
<tr>
<td>Cytarabine</td>
<td>75mg/m², SC</td>
<td>Days 1-4, 22-25, 29-32</td>
</tr>
</tbody>
</table>

Second course is given after 7 to 10 days of day 8. This does not include Adriamycin.

### Maintenance

For 24 months. Starts 4 weeks after completing consolidation and is still remission.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage and route</th>
<th>Duration of therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-Mercaptopurine</td>
<td>75mg/m²/day, PO</td>
<td>Daily for 24 months.</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>25mg/m²/week, PO</td>
<td>Weekly for 24 months</td>
</tr>
<tr>
<td>Vincristine</td>
<td>1.5mg/m², IV</td>
<td>Day 1 monthly for 24 months</td>
</tr>
<tr>
<td>Intrathecal methotrexate</td>
<td>Dose for age</td>
<td>Every 8 weeks for 1st year for those without CNS disease.</td>
</tr>
<tr>
<td>Adriamycin</td>
<td>25mg/m²</td>
<td>Every three months for 24 months</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>300mg/m²</td>
<td>Every three months for 24 months</td>
</tr>
</tbody>
</table>
APPENDIX 6: TABLE OF CHOP-BLEO REGIMEN FOR MANAGEMENT OF NON HODGKINS LYMPHOMA IN KNH

Adapted from Kasilis Synopsis(11).

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage and route</th>
<th>Duration of therapy.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclophosphamide</td>
<td>1000mg/m², IV</td>
<td>On day 1 and weekly for 6 weeks</td>
</tr>
<tr>
<td>Doxorubicin</td>
<td>50mg/m², IV</td>
<td>On day 1, 21 and 43</td>
</tr>
<tr>
<td>Vincristine</td>
<td>2mg IV</td>
<td>On days 1 and 5 and weekly for 6 weeks</td>
</tr>
<tr>
<td>Prednisone</td>
<td>40mg orally</td>
<td>Daily for 4 weeks tail off from week 5</td>
</tr>
<tr>
<td>Bleomycin</td>
<td>15 units IV</td>
<td>On days 1 and 5 during induction and consolidation</td>
</tr>
<tr>
<td>Intrathecal Methotrexate</td>
<td>Dose for age</td>
<td>Should be given twice weekly as in option A for BL</td>
</tr>
</tbody>
</table>
### APPENDIX 7: HFMEA WORK SHEET

<table>
<thead>
<tr>
<th>FAILURE MODE</th>
<th>POTENTIAL CAUSE</th>
<th>SCORING</th>
<th>DECISION TREE ANALYSIS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Severity</td>
<td>Probability</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>2.</td>
<td></td>
</tr>
</tbody>
</table>

### APPENDIX 8: HFMEA Severity Rating Scale

<table>
<thead>
<tr>
<th>Rank</th>
<th>Outcome category</th>
<th>Outcome description</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>Catastrophic</td>
<td>Death, major permanent loss of sensory, motor, physiologic or intellectual function, Surgery/procedure on the wrong patient or wrong body part.</td>
</tr>
<tr>
<td>3</td>
<td>Major</td>
<td>Permanent lessening of bodily function, disfigurement, patient requires surgical intervention, patient requires increased level of care for 3 or more days.</td>
</tr>
<tr>
<td>2</td>
<td>Moderate</td>
<td>Event, occurrence, or situation which could harm the patient but doesn’t cause permanent injury or lessening of bodily function or additional health care services.</td>
</tr>
<tr>
<td>1</td>
<td>Minor</td>
<td>Minor injury to the patient, failure not likely to affect the patient, failure doesn’t necessitate changes in delivery of health care.</td>
</tr>
</tbody>
</table>
## APPENDIX 9: HFMEA probability rating scale

<table>
<thead>
<tr>
<th>Rating</th>
<th>Description</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>Frequent</td>
<td>Failure may occur once in every 5 attempts</td>
</tr>
<tr>
<td>3</td>
<td>Occasional</td>
<td>Failure may occur once in every 50 attempts</td>
</tr>
<tr>
<td>2</td>
<td>Uncommon</td>
<td>Failure may occur once in every 100 attempts</td>
</tr>
<tr>
<td>1</td>
<td>Remote</td>
<td>Failure may occur once in over 200 attempts</td>
</tr>
</tbody>
</table>

## APPENDIX 10: HFMEA HAZARD SCORING MATRIX

<table>
<thead>
<tr>
<th>Probability</th>
<th>Severity</th>
<th>Catastrophic</th>
<th>Major</th>
<th>Moderate</th>
<th>Minor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequent</td>
<td>16</td>
<td>12</td>
<td>8</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Occasional</td>
<td>12</td>
<td>9</td>
<td>6</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Uncommon</td>
<td>8</td>
<td>6</td>
<td>3</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Remote</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>
APPENDIX 11: Healthcare Failure Mode and Effect Analysis (HFMEA) TRAINING MANUAL

What is HFMEA?

It is a systematic, proactive method for evaluating a process to identify where and how it might fail and to assess the relative impact of different failures, in order to identify the parts of the process that are most in need of change. HFMEA includes review of the following:

Steps in the process

Failure modes (What could go wrong?)

Failure causes (Why would the failure happen?)

Failure effects (What would be the consequences of each failure?).

What is the objective of HFMEA?

The main objective of HFMEA is to prevent problems and errors before they can occur in any high risk process.

Applications of HFMEA

It can be applied in the design of medical processes in order to prevent errors, accidents and adverse reactions. Examples of field of application are the design of the process of treatment and therapy administration.

What are the requirements for conducting a HFMEA?

Trained personnel

HFMEA tools (the relevant tools will be provided)

Selected process description (e.g. flowchart)

Special team combined of key users of the process or experienced personnel related to methods and techniques used in the chosen process, advisor/s and a team leader.
Possible process error and problem awareness.

**What are the benefits of conducting a HFMEA?**

- Reduction of errors, accidents and adverse reactions
- Increase knowledge and understanding of possible failures
- Strengthen teamwork
- Improve quality of care.

**How to conduct a HFMEA**

This analysis is conducted though a series of brainstorming sessions involving the multi-disciplinary team members. Each participant is encouraged to give their unrestricted opinion concerning the topic of discussion. The agreed deliberations of each session should build into the next session. The steps for conducting a HFMEA are as follows:

**Select the process:** The first thing the user has to do is to select the process to analyze. The topic to be reviewed should be a high-risk or high-vulnerability area, to merit the investment of time and resources by the HFMEA multi-disciplinary team.

**Assemble a team:** A multidisciplinary team should include subject matter expert(s), an advisor/s, and a team leader. A multidisciplinary team ensures that various viewpoints are considered. By having a subject matter expert, the team will gain insights into how the process is actually carried out. The advisor acts as a consultant, helping the leader accomplish necessary tasks and stepping in as appropriate to keep the team on target. The team leader ensures that the team functions effectively.

**Review the process:** The process is analyzed and described in a flowchart. Also, have the team members individually observe the process and consult process users where necessary so that all members can become familiar with the way it works. To aid the team in discussing the flow diagram, consecutively number each process step (for example, 1, 2, 3...).
Next, brainstorm all sub-processes under each block of this flow diagram and consecutively letter these sub-process steps (that is, 1A, 1B . . . 3A, 3B . . .). Members can consult process users for additional input. The team will find it extremely beneficial to identify all sub-process steps before proceeding with further team work. For example PSA Test, the process steps are as follows; 1. ordering the PSA test, 2. drawing the sample, 3. analyzing the sample, 4. reporting the results to the physician, 5. filling the results in the medical records. The sub-process steps during sample analysis will be as follows; 3A. Review order. 3B. Centrifuge Specimen 3C. Verify Calibration 3D. Run Quality Control 3E. Run sample 3F. Report result 3G. Enter into the daily activity register. The team members should meet and develop, verify and refine the final detailed process flow diagram.

**Brainstorm potential failure modes:** Look at each stage of the process and identify ways it could potentially fail, things that might go wrong. For the part of the process that the team is examining, list all possible/potential failure modes for each of the sub-processes and consecutively number these failure modes (1A(1), 1A(2). . . 3E(1), 3E(2). . .). Failure modes are operationally defined as the different ways that a particular process or sub-process step can fail to accomplish its intended purpose. For example, under the sub-process 3A. Review order, the potential failure modes may include: 3A(1). Wrong test ordered 3A(2). Order not received in the lab, 3A(3). Incomplete order. Under the sub-section 3B. Centrifuge specimen, the potential failure modes may include: 3B(1). Centrifuge equipment broken, 3B(2). Wrong centrifugal speed, 3B(3). Wrong test tube used for centrifuge. Members can consult process users for additional input. The identified failure modes should be recorded into a HFMEA work sheet (Appendix 7 will be provided).

An additional example, if the sub-process step is confirming known drug allergies during the process of prescribing, failure modes would include the following: (1) not recording drug allergies and (2) incompletely capturing drug allergies.

**Brainstorm potential causes and effects of each failure mode:** Deliberate all the failure mode causes for each failure mode. Consult process users, medication error reporting system for additional input. A failure mode may have multiple causes and therefore each should be listed in
a separate row as follows: 1A(1)a, 1A(1)b. Examples of possible failure mode causes for the process step of confirming known drug allergies may include inexperienced staff, lack of competencies, failure to delineate task responsibilities, workload pressures, poor support from automated systems, and lack of checklists or cognitive aids. List the potential effect of each failure next to the failure. If a failure has more than one effect, write each in a separate row. When determining the effect, choose the most likely outcome and not the worst case scenario. Examples of effects a failure mode includes: adverse effects, delays in treatment, injury to the patient, treatment failure. All causes identified will be entered into a HFMEA work sheet (Appendix 7) will be provided during a team session.

Assign a severity rating for each effect: Give each effect its own severity rating (from 1 to 4, with 4 being the most severe). A severity rating scale (Appendix 8) will be provided. If the team cannot agree on a rating, hold a vote.

Assign an occurrence (probability) rating for each failure mode: Determine how likely it is for a failure to occur and assign an appropriate rating (from 1 to 4, with 4 being the most likely). A probability rating scale (Appendix 9) will be provided. If the team cannot agree on a rating, hold a vote.

Calculate the hazard score for each effect: Multiply the severity rating by the occurrence rating. A hazard scoring matrix (Appendix 10 will be provided) will be provided. Each score should be entered into the blank HFMEA work sheet (Appendix 7 will be provided) during a team session.

Prioritize the failure modes for action: Decide which items need to be worked on right away. For this exercise, failure modes with a score of 8 or more will be prioritized for further action. This means that the failure mode occurs often, has the potential for harm and is likely to result in catastrophic or major harm.

Decision tree analysis: This presents the steps to follow when evaluating a particular failure mode or failure mode cause. The decision tree serves as a triaging function, identifying areas where the team needs to mitigate vulnerabilities and areas not needing attention because they
are not critical, they are highly detectable, or they already have an effective control measure. It
determines whether the failure mode warrants further action on the basis of criticality, absence
of effective control measures, and lack of detectability: A single point weakness (Critically)
measures whether the entire system will fail if this part of the process fails. An effective control
measure eliminates or significantly reduces the likelihood of the failure occurring. An obvious
hazard (Detectability) is defined as the likelihood of detecting failure or the effect of failure
before it occurs. Team responses to the 3 aspects of the analysis should be recorded into the
HFMEA work sheet (Appendix7 will be provided) during the session.

**HFMEA Decision Tree**

**NOTE: THIS DECISION TREE IS TO BE USED AFTER THE HFMEA HAZARD SCORING MATRIX**

Where the team decision will be to proceed, all the failure mode causes should be listed and
categorized as eliminate, control or accept.
Take action to eliminate or reduce the high risk failure modes: Those categorized for elimination or control will form the basis for team recommendations and action.

If the failure is unlikely to be detected, the team can consider: identifying other events that may occur prior to the failure mode and can serve as “flags” that the failure mode might happen, adding a step to the process that intervenes at the earlier event to prevent the failure mode. For example, addition of pharmacy rounds to remove medications from patient care units.

If the failure is likely to cause severe harm, the team may consider: identifying early warning signs that a failure mode has occurred, and train staff to recognize them for early intervention. For example, use drills to train staff by simulating events that lead up to failure, to improve staff ability to recognize these early warnings, provide information and resources, such as a reversal agents or antidotes, at points of care for events that may require immediate action.

If the failure mode is likely to occur, the team may consider: an evaluation of the causes and see if any or all of them can be eliminated. Addition of a forcing function i.e. a physical constraint that makes committing an error impossible, addition of a verification step, such as independent double-checks, process completion documentation, modifying other processes that contribute to causes of failure.

The team will develop a description of action for them, identify outcome measures, and identify a single person responsible for completing or ensuring completion of each action. This will be presented inform of a table.

For this study, there will be a minimum of 7 brainstorming sessions, scheduled after every 2 weeks. Each session will last for at least 2 hours.
APPENDIX 12: KNH-UoN ERC REGISTRATION
Ref: KNH-ERC/A/357

Wilson Major Nyamai  
Reg. No:US1/81440/2015  
Department of Pharmacology and Pharmacognosy  
School of Pharmacy  
College of Health Sciences  
University of Nairobi

Dear Wilson

REVISED RESEARCH PROPOSAL: PROACTIVE RISK ASSESSMENT OF INTRATHecal CHEMOTHERAPY IN PAEDIATRIC ONCOLOGY IN KENYATTA NATIONAL HOSPITAL  
(P611/08/2016)

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 14th September 2016 – 13th September 2017.

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 Deputy Director, CS, KNH
     The Assistant Director, Health Information, KNH
     The Chair, KNH- UoN ERC
     The Dean, School of Medicine, UoN
     The Chair, Dept. of Psychiatry, UoN
     Supervisors: Prof. Wangari Kuria, Dr. Manasi Kumar

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APPENDIX 13: KNH STUDY REGISTRATION CERTIFICATE
KENYATTA NATIONAL HOSPITAL
P.O. Box 20723-00202 Nairobi

Study Registration Certificate

1. Name of the Principal Investigator/Researcher
   WILSON MAJOR NYAMAI

2. Email address: whnmajor@gmail.com
   Tel No. 0720469350

3. Contact person (if different from PI): N/A
   Email address: Tel No.

4. Study Title
   PROACTIVE RISK ASSESSMENT OF INTRATHECAL
   CHEMOTHERAPY IN PAEDIATRIC ONCOLOGY IN KENYATTA
   NATIONAL HOSPITAL.

5. Department where the study will be conducted: PAEDIATRICS
   (Please attach copy of Abstract)

6. Endorsed by Research Coordinator of the Department where the study will be conducted.
   Name: ___________________________ Signature ___________________________ Date __________

7. Endorsed by Head of Department where study will be conducted.
   Name: ___________________________ Signature ___________________________ Date __________

8. KNH UoN Ethics Research Committee approved study number P611/08/2016
   (Please attach copy of ERC approval)

9. I WILSON MAJOR NYAMAI 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 19.10.2016

10. Study Registration number (Dept/Number/Year) PAEDIATRICS 1721/2016
    (To be completed by Research and Programs Department)

11. Research and Program Stamp

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.

Version 2: August, 2014