INSTITUTE OF TROPICAL & INFECTIOUS DISEASES

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PREVALENCE OF DRUG MANIPULATION TO OBTAIN PRESCRIBED DOSE IN THE PAEDIATRIC IN-PATIENT UNITS IN KENYATTA NATIONAL HOSPITAL

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Declaration

Candidate:

This research project report is my original work and has not been presented elsewhere to the best of my knowledge.

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Dedication

This research is dedicated to my beloved parents and siblings for the immense support, prayers, encouragement and cheering on during the whole study period. This is for never letting me give up, when times got tough.

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List of abbreviations and acronyms

95% CI	95% Confidence interval
B	Beta
BNF-C	British National Formulary for Children
CI	Confidence interval
df	Degrees of freedom
DGH	District general hospital
DMARDS	Disease Modifying Agents in Rheumatoid Disorders
eMC	electronic Medicines Compendium
ERC	Ethics and research committee
EXP	Exponential
IBM	International Business Machines Corporation
ICU	Intensive care unit
IQR	Interquartile range
IV	Intravenous
KNH	Kenyatta National Hospital
NICU	Neonatal intensive care unit
NSAIMS	Non-steroidal Anti-inflammatory Medicines
OR	Odds ratio
P-value	Probability value
PICU	Paediatric intensive care unit
RCH	Regional children’s hospital
S.E	Standard error
SPC	Summary of product characteristics
SPSS	Statistical Package for the Social Sciences
STD	Standard deviation
UK	United Kingdom
UNICEF	United Nations Children's Fund
WHO	World Health Organization

Operational definitions

1. **Age-appropriate formulation** - a formulation whose pharmaceutical design makes it suitable for use in the target age group(s).
2. **Bioavailability –** the fraction of unchanged drug reaching the systemic circulation following administration by any route
3. **Compounding -**The bringing together into a homogenous mix of active ingredients, excipient and solvent components.
4. **Dosage Form** - A pharmaceutical product type (e.g., tablet, capsule, solution, cream) that contains a drug substance generally, but not necessarily, in association with excipients.
5. **Drug manipulation** - the physical alteration of a medicine dosage form for extracting a proportion of the drug amount or for ease of administration. Drug manipulation may include:
    a. Crushing a tablet
    b. Crushing a tablet or opening a capsule and adding all the resultant powder to food or liquid e.g. breast milk, formulae milk
    c. Cutting, breaking, splitting into smaller segments a tablet, suppository, patches
    d. Dispersing whole tablets with liquids
    e. Taking a proportion of a nebulizer contents
    f. Taking a proportion of an enema
6. **Drug manipulation to obtain the prescribed dose** - " physical alteration of a dosage form for the purpose of extracting a proportion of the drug amount (such as splitting a tablet, opening a capsule or splitting a suppository, measurement of small volumes of an oral liquid or injection – with the administration of a proportion of the dosage form)"
7. **Extemporaneous compounding** - the preparation, mixing, assembling, packaging and labelling of a medicinal product based on a prescription order from a licensed practitioner for the individual patient or modifying the concentration of a drug from that of the original manufacturer to fit the unique needs of a patient commonly undertaken by pharmacists in the pharmacy
8. **Extemporaneous preparation** – a product made through the process of extemporaneous compounding

9. **Formulation -**The composition of a dosage form, including the characteristics of its raw materials and the operations required to process it.
    - Further diluting readily prepared intravenous solutions (usually to allow a smaller dose to be administered).
    - Further diluting reconstituted oral solutions (usually to allow a smaller dose to be administered).
10. **Palatability** - overall appreciation of an (oral) medicine by organoleptic properties such as vision (appearance), smell, taste, aftertaste and mouth feel (e.g. texture, cooling, heating); determined by characteristics of the components (active substance and excipients). May also be relevant for other routes of administration (e.g. buccal, nasal, inhalation use) where the product may contact taste receptors indirectly.

Abstract

Background

Manipulation of drug dosage forms is frequently conducted in children due to lack of age appropriate formulations. Manipulation involves physical alteration of a dosage form to extract a proportion of the drug amount such as tablet splitting, opening a capsule or splitting a suppository to either obtain prescribed dose or make administration easier. In the United Kingdom, a resource rich setting, frequency of manipulation was 6.5% of drugs administered to children. Kenyatta National Hospital, a national referral hospital is a resource constrained setting. The study aimed at determining the prevalence of manipulation of drugs to obtain the prescribed dose in paediatric in-patient units in this hospital.

Method

An observational cross sectional study was conducted between 5th and 18th July 2016 in 4 general paediatric wards, oncology patients, specialized surgical ward, paediatric intensive care and newborn units. Medicines administration by nursing staff and clinicians to newly admitted children below 6 years of age was observed. This was to determine the frequency of drug manipulation. Informed consent was obtained from nursing staff and clinicians before observation. Collected data was recorded on drug manipulation observation form. Data was analyzed using chi-square test and independent samples t-test to determine association between the dependent and independent variables. Logistic regression was used to determine factors associated with drug manipulation.

Findings

249 medicines administrations were observed. Prevalence of drug manipulation to obtain the prescribed dose was 6.4%. Drug manipulation was frequently conducted in newborn unit (43.8%, $p < 0.01$). A drug's dosage form is significantly associated with occurrence of drug manipulation (56%, $p < 0.0001$). Folic acid 5mg tablet was commonly manipulated (31.3%). Manipulation involved tablet segmentation and dispersion (56%) and measurement of intravenous liquid volumes <0.2ml (44%). A drug's schedule ($p = 0.015$, OR = 1.195, 95%CI 1.035 - 1.379) was significantly associated with increasing odds of occurrence of drug manipulation.

Conclusion

The prevalence of drug manipulation to obtain the prescribed dose in Kenyatta National Hospital paediatric in-patient units is comparable to resource rich settings. Tablet manipulation involving tablet segmentation and dispersion was common. Development of a drug manipulation policy and procurement of age-appropriate formulations is recommended.

Chapter 1: Introduction

The lack of appropriate medicine dosage forms for children affects drug therapy in children in Africa (Gray, 2009). In Africa, there are limited resources that can be spent on health care, which further aggravates this issue. Many of the essential medicines are available in commercial dosage forms or strengths that are not suitable for use in children (Hoppu, Ranganathan, Dodoo, Sri Ranganathan, & Dodoo, 2011). In addition they are not appropriate in terms of dosing, dispensing and administration (Hoppu et al., 2011). Consequently, due to cost constraints, the practice is to split tablets of higher strengths to obtain lower strengths of a medicine.

The World Health Organization (WHO) launched a campaign called “Make Medicines Child Size” in 2007, in a bid to combat the issue of lack of appropriate medicines for children (“WHO to Launch New Initiative”, n.d.). This is aimed at increasing access to children of safe and effective medicines (“WHO to Launch New Initiative”, n.d.). The campaign advocates for and promotes the development and access to appropriate and quality medicines for children (“Accomplishments in the Area”, n.d.). In addition, WHO, has been developing and coming up with a Model List for Essential Medicines for Children in conjunction with the United Nations Children's Fund (UNICEF) from 2007 (“Accomplishments in the Area”, n.d; “WHO Model Lists”, n.d.). This Model List for Essential Medicines for Children is reviewed every 2 years, with the most up to date one having been published in June 2015 (“Accomplishments in the Area”, n.d; “WHO Model Lists”, n.d.). This model list is aimed at helping institutions or countries to come up with priority medicines for children to use in their settings (“Essential Medicines Lists”, n.d.). In 2010 (WHO), developed a Model Formulary for Children that health care workers can use to identify appropriate medicines to use for different diseases and conditions. In Kenya, an essential medicines list was published in 2010, but no essential medicines list for children has been published.

The paediatric population consists of neonates (0 - 28 days old), infants and toddlers (28 days - 23 months), children (2 - 11 years) and adolescents (12 - 18 years). This population is not homogenous as it ranges from the neonate to an adolescent. These sub-populations have differences physically and developmentally in regards

to pharmacokinetic and pharmacodynamic handling of drugs (WHO, 2012). Therefore, development of a drug formulation that is appropriate for all the age groups is a challenge. However, the goal of formulation development for this population is to cover as wide an age range as possible with a single formulation (WHO, 2012). Consequently, more than one dosage form of an active pharmaceutical ingredient or more than one strength of a dosage form may be required to cover the different paediatric age groups (WHO, 2012). This is because the intended dose volume or size should be appropriate for the target age group (WHO, 2012). In the paediatric population, the preferred and appropriate route of administration is the oral route (WHO, 2012). This is applicable across all the paediatric age groups if the medicine is administered in a suitable dosage form (WHO, 2012). Most children below the age of 6 years are not able to take or swallow tablets; therefore the liquid dosage form is preferred.

The practice of manipulation of drug dosage forms is widely carried out in the paediatric age group (Richey et al., 2012). This is aimed at achieving the prescribed dose or assisting in drug administration to the child (Richey et al., 2012). Manipulation occurs when the available drug is supplied in a much higher strength than the dose required or is in a dosage form that the child is not able to take. Richey et al. (2012), define drug manipulation to obtain the prescribed dose as "physical alteration of a dosage form for the purpose of extracting a proportion of the drug amount (such as splitting a tablet, opening a capsule or splitting a suppository – with the administration of a proportion of the dosage form)". Drug manipulation is also undertaken to enable administration of the drug such as crushing a tablet and adding all of the resultant powder to food or liquid to make it easier to administer (Richey et al., 2012). In other literature, the practice of manipulation has also been referred to as transformation of a drug for administration to children, when it's impossible to obtain the appropriate doses for children from the original form (Boztepe, Ozdemir, Karababa, & Yildiz, 2014).

Richey et al. (2013) reviewed inpatient prescriptions in different paediatric settings in 3 hospitals in the United Kingdom (UK). They found manipulation was a widespread practice intrinsic to paediatrics (Richey et al., 2013). In addition, manipulation of

dosage forms also occurs in other settings such as at home when the parents or the care - givers have to administer drugs to children.

Chapter 2: Literature review

2.1 Research conducted on manipulation of drug dosage forms

Few studies have been done to investigate the prevalence of drug manipulation to obtain the prescribed dose in the paediatric population. Three studies were done in the UK and 1 in Turkey. Three out of the four studies had investigated drug manipulation in the paediatric setting in different hospitals (Boztepe et al., 2014; Nunn et al., 2013: Richey et al., 2013). The fourth study was a poster presentation on research carried out on drug manipulation in neonatal units (Richey et al., 2011).

The first study was a poster presentation of research conducted in the neonatal setting (1 regional and 2 smaller neonatal settings) by Richey et al. (2011). It was a combination of an observational study and a national paediatric nurses survey. However, as this was a conference poster presentation, further details on the study were not available to obtain the overall extent or prevalence of manipulation in the neonatal setting.

The second study was conducted in a regional children's hospital (RCH), regional neonatal intensive care unit (NICU) and a district general hospital (DGH) in the UK. The estimates of manipulation required to obtain the prescribed dose was determined in different paediatric clinical settings namely; paediatric wards, high dependency cots/beds, neonatal units, NICU and paediatric intensive care unit (PICU) (Nunn et al., 2013). The study involved a review by an experienced paediatric clinical pharmacist of all paper based inpatient prescriptions. This was done over 5-day periods in a period of 5 months. The study estimated the type and frequency of manipulations and the drugs involved.

The previous authors conducted the third study in the same year. They looked at the scope of manipulations in paediatric practice specifically, the formulations that are manipulated and the specific drugs (Richey et al., 2013). In addition, reasons for undertaking manipulations and concerns raised by paediatric nurses in regards to manipulation were explored and described (Richey et al., 2013). The study used two methodology designs. The first was a structured undisguised, observation of drug manipulations in blocks of 2 weeks in the different paediatric clinical settings (Richey

et al., 2013). The second was a questionnaire survey to paediatric nurses throughout the UK (Richey et al., 2013). Potential drug manipulations to be observed were identified through two methods. The first was through daily review of prescriptions for potential drug manipulations. The second was through use of alert cards that paediatric nurses filled in on identification of a manipulation while administering drugs.

The fourth study was conducted in 2013 in a Children's Hospital in a Turkish University over a period of 1 day (Boztepe et al., 2014). The study determined the difficulties that paediatric nurses faced during preparation and administration of oral drugs in the inpatient setting. The investigators used two study designs, face-to-face interview and a quantitative survey. This study is however not directly comparable with the other 3 studies as it only looked at orally administered drugs. Nevertheless, the study provides information on the type of manipulations that are conducted for orally administered drugs. Drug manipulation was identified as a problem during drug administration. This is similar to the practice of drug manipulation as described previously.

2.2 Findings from studies on manipulation of drug dosage forms

2.2.1 Prevalence and type of manipulations

Nunn et al. (2013) through review of inpatient prescriptions assessed 5,375 drug administrations in the different clinical settings. Overall, 542 (10.1%) of these drug administrations were found to require drug manipulation to obtain the prescribed dose. From the 542 identified manipulations, 10 different types of manipulations were identified (Nunn et al., 2013). The most common type of manipulation across all the clinical settings was measurement of small volumes of oral liquids for doses between 0.1 and 0.2ml (26.4%, 143/542). This is an important finding, as it requires the inpatient setting to have measuring containers that can accurately measure small volumes less than 0.2 ml. Examples of such measuring containers are a measuring cup or an oral syringe. This does away with the practice of diluting the drug further, measuring a larger volume which is easier, to obtain the prescribed dose.

Table 2.1 Identified types of manipulations

Identified types of manipulations (Nunn et al., 2013)			
Type of manipulation		**%**	**Number of manipulations**
1.	Measurement of small volumes of oral liquids for doses between 0.1 and 0.2ml	26.4	143
2.	Measurement of small volumes of intravenous (IV) injections to obtain doses between 0.1 and 0.2ml	22.1	120
3.	Measurement of small volumes of IV injections to obtain doses less than 0.1ml	19.6	106
4.	Measurement of small volumes of oral liquids for doses less than 0.1ml	11.6	63
5.	Tablet segmentation	10.5	57
6.	Tablet dispersion	3.9	21
7.	Manipulation of nebuliser	3.1	17
8.	Manipulation of enema	1.1	6
9.	Suppository segmentation	0.7	4
10.	Intra-vesicular manipulation	0.6	3
11.	Others	0.4	2
	Total number of manipulations		**542**

In the study by Boztepe et al., (2014), 3 types of drug transformations were described. This are crushing of drugs given by oral routes, opening of capsules and dissolving the contents in fluid and dissolving of crushed powder from tablets in fluid and giving the solution to the child. The proportion of orally administered drugs that required transformation was 45.9% (406/884). For the drugs that were transformed, three different transformations were identified. This are crushing of full tablets, 44.8% (182/406), crushing of either a half or quarter tablet, 43.1% (175/406) and opening of capsules with dissolving of resulting powder in fluid to obtain the prescribed dose, 12% (49/406) (Boztepe et al., 2014). These transformations are similar to tablet dispersion and segmentation identified by Nunn et al. (2013). Tablet crushing was the most common type of manipulation of oral drugs (88%), which is in contrast to UK Hospitals where measurement of small volumes of oral liquids for doses between 0.1 and 0.2 ml was most common. However, it should be noted that in this study it was not clear whether the drug transformation done was to obtain the prescribed dose or to make drug administration to the child easy.

2.2.2 Prevalence of manipulation per clinical setting

In the study by Nunn et al. (2013), where they reviewed inpatient prescriptions, the largest proportion of drug manipulations was identified in the DGH (see table 2.2) (Nunn et al., 2013). However it should be noted that the Regional PICU is a clinical setting in the RCH that was analyzed separately. If the findings from the regional PICU and RCH were to be combined, then the proportion of drug manipulations in the RCH would be 9.3% (339/3633).

Table 2.2 Proportion of manipulations by inpatient setting

Setting	**Total number of assessed drug administrations**	**Total number of identified manipulations**	**% Manipulations**
DGH	922	150	16.3
Regional PICU	1689	213	12.6
RCH	1944	126	6.5
Regional NICU	820	53	6.5
Total	**5375**	**542**	**10.1**

For each type of paediatric clinical setting, there was variation in the most frequent type of manipulation (see table 2.3). In the 2 intensive care units, the most frequently identified drug manipulation was measurement of small IV doses of less than 0.2 mls. For the RCH, tablet dispersion was most frequent (45.2%) and for the DGH it was measurement of small oral doses of between 0.1 and 0.2 mls (71.3%).

Table 2.3 Most frequent type of manipulation per clinical setting

Setting (Nunn et al., 2013)	**Most frequent type of manipulation**	**Number of Manipulations**	**% Manipulation**
DGH N= 150	Measurement of small volumes of oral liquids for doses between 0.1 and 0.2ml	107	71.3 %
Regional NICU N= 53	Measurement of small volumes of IV injections to obtain doses less than 0.1ml	32	60.4 %
Regional PICU N=213	Measurement of small volumes of IV injections to obtain doses between 0.1 and 0.2ml	86	40.4 %
RCH N= 126	Tablet dispersion	57	45.2 %

IV drug manipulations seem to occur most frequently in the specialist's areas as observed in the 3 studies by Nunn et al. (2013), Richey et al. (2013) and Richey et

al. (2011). In the observational component of the study by Richey et al. (2013), most of the IV drug manipulations occurred in specialist areas namely; specialist neonatal unit (60 %) and PICU (38.5 %). An almost similar scenario was reported in the national survey of paediatric nurses component of the same study; 68.2 % of IV drug manipulations in the neonatal areas. In the study by Nunn et al. (2013), most frequent manipulations in PICU and NICU that are specialist areas are reported. This are measurement of small volumes of IV doses between 0.1 and 0.2 mls (40.4%, 86/213) and less than 0.1 mls (60.4%, 32/53) respectively (Nunn et al., 2013). Lastly in the study by Richey et al. (2011), which focused on the neonatal setting, the most commonly manipulated dosage form was IV form (58%, N= 92). Consequently, the most common manipulation in the neonatal setting is manipulation of IV dosage forms.

The results stated previously show that the most common type of manipulation done varies with the type of inpatient setting. This is commensurate with the severity of the disease conditions that would be treated in the specific in-patient setting.

2.2.3 Types of dosage forms manipulated

In the study by Richey et al. (2013), in different paediatric clinical settings, potential manipulations were identified and studied through observation of drug administration. Manipulation was categorized based on the dosage form that was manipulated and not the type of manipulation that was done. The study by Nunn et al. (2013) identified the type of manipulations done. Therefore, the study by Nunn et al. (2013) and Richey et al. (2013) cannot be compared.

Richey et al. (2013) identified the most commonly manipulated dosage form to be tablets (61.6%, 191/310). The second most manipulated dosage form was IV injections (21%, 61/310). This was almost similar to the findings reported by the paediatric nurses in the national survey component of the same study. Tablets were most commonly manipulated dosage form (45.7%, 86/188). IV injections and nebuliser solutions were the second most frequently manipulated dosage forms (11.7%, 22/188). Out of the 310 identified manipulations, the authors were only able

to observe 54 manipulations occurring in practice, with 40 of them being tablet manipulations (74.1%, 40/54) (Richey et al., 2013).

2.2.4 Types of drugs and drug classes that are manipulated

The studies by Richey et al. (2011) and Nunn et al. (2013) identified the specific drugs that were manipulated while the study by Richey et al. (2013) identified the drug classes. In the study by Richey et al. (2011) done in the neonatal setting, the most commonly manipulated drugs were vancomycin, ranitidine and midazolam. In the study by Nunn et al. (2013) that reviewed inpatient prescriptions in different clinical settings, there was variation in the specific medicines that were most frequently manipulated (See Table 2.4).

Table 2.4 Specific medicines that were manipulated per clinical setting

Setting	**Type of drug most manipulated (Nunn et al., 2013)**
DGH	Measurement of oral domperidone liquid in doses of less than 0.2 mls in volume
RCH	Dispersion of diclofenac tablets and administration of a proportion of the resulting dispersion
Regional PICU	Measurement of doses of IV fentanyl of less than 0.1 mls in volume
Regional NICU	Measurement of doses of IV phenobarbital less than 0.1 mls in volume

Table 2.5 Most commonly manipulated drugs

Drug	**Hydrocortisone**	**Domperidone**	**Fentanyl**
	IV dose < 0.1 mls (28/77)	Oral < 0.1 mls (8/48	IV dose < 0.1 mls (35/46)
	IV dose 0.1 - <0.2ml (25/77)		
	Tablet Segmentation (24/77)	Oral dose 0.1 - < 0.2ml (40/48)	IV dose 0.1 - <0.2ml (11/46)
Total manipulations	**77**	**48**	**46**

Overall, in the study by Nunn et al. (2013), the 3 most commonly identified manipulated drugs were hydrocortisone, domperidone and fentanyl (see table 2.5).

In the study by Richey et al. (2013), the top five manipulated drug classes as per the British National Formulary for Children (BNF-C) classification were identified and are

outlined in table 2.6. The leading class in both the observational study and national nurses survey components of the study was the analgesic class (29.7% and 17.6%).

Table 2.6 Top five drug classes that are manipulated

Observational Study (n = 310 manipulations)			**National Nurses Survey (n = 188 manipulations)**		
Drug Class Manipulated	**Number**	**%**	**Drug Class Manipulated**	**Number**	**%**
Analgesic	92	29.7	Analgesics	33	17.6
Proton pump inhibitors	24	7.7	Proton pump inhibitors	24	12.8
Antimuscarinic	18	5.4	Bronchodilator	23	12.2
Antiemetic	17	5.5	Antimuscarinic	20	10.6
Alginate preparation	16	5.2	Steroid	12	6.4

2.3 Problem statement

In Kenyatta National Hospital (KNH), manipulation of drugs to obtain the prescribed dose and make drug administration easier is commonly done in the various paediatric inpatient units. The nursing staff has devised a way of documenting which drugs are manipulated before drug administration and how to go about it. This documentation is then utilized during orientation of new staff or nursing student who will be involved in drug administration. This documentation is attached to the drug trolley for ease of reference. However it's not a standard and uniform document across all the paediatric inpatient units. This may give rise to variability in the various ways of manipulation across the different units. At the pharmacy department level, the staff is aware of the drugs commonly manipulated. With this knowledge in mind, some drugs are prepared as extemporaneous preparations for the patient to make it easier for the nursing staff to measure and administer the drugs. However the exact magnitude of manipulation of drugs taking place in the inpatient settings is not known, it has not been quantified and there is no comprehensive knowledge of all the drugs that are manipulated.

2.4 Study justification

The justifications to conduct this study are varied. They include standardization of manipulation practices across the paediatric inpatient units by development of a drug manipulation policy and standard operating procedures to guide manipulation

practice. This will be for drugs which manipulation cannot be avoided all together due to the dose required or the formulation properties (WHO, 2012).

Determination of the extent to which manipulation occurs and the drugs that are manipulated will help in formulary review and change of prescribing practices. Recommendations will be made for the use of dose bands during prescribing for manipulated drugs, which are based on weight or body surface area. Another recommendation is use of rounded doses, based on available strengths and formulations in the hospital. This means that a prescriber will prescribe a dose from a dose band which will contain doses that can be easily obtained from a dosage form without manipulation to obtain the accurate dose. This will make drug administration easier for the nursing staff and prevent any medication and prescribing errors from occurring. During the formulary review, information on the extent and type of drugs that are manipulated will aid in coming up with recommendations for the purchasing team to procure drugs that are age-appropriate for the paediatric population. This would require procurement of drugs in the smallest dose strength available, solid dose forms that can be easily split into smaller uniform doses and liquid dosage forms in dose volumes that can be accurately measured. This will assist in limiting drug manipulation as much as possible.

Another justification is that manipulation of drugs might lead to over dosing or under dosing of a child. Over dosing may lead to toxic effects of the drug in a child or an adverse effect from the drug, which may be fatal. Under dosing may lead to lack of treatment response in a patient due to lack of efficacy. Drug manipulation may lead to change in the biophysical properties of a drug. This may affect a drug's bioavailability, release profile in the body for drugs with controlled release profiles and it's stability after manipulation. There could also be issues with acceptability or palatability of a drug such as change in taste of the resulting manipulated drug. This may result in the child refusing to take the drug, resulting in non-adherence to treatment.

There are numerous concerns associated with drug manipulation by nurses. These are that it's time consuming and requires a lot of concentration and skill to avoid

making any errors. Issues to do with whether drug manipulation is carried out in a clean area to avoid contamination. The risk of drug exposure to the nursing staff through inhalation of dust from opening of capsules and crushing of tablets. It's also an issue whether the nurses have appropriate tools for conducting drug manipulation such as tablet splitters, measuring syringes or spoons, small volume oral syringes. Lack of appropriate tools for drug manipulation may lead to inaccurate tablet splitting or segmentation during drug manipulation or use of a large volume oral syringe to measure a small volume of a liquid, which may result in errors in measurement of the prescribed dose. Drug manipulation that requires dilution of the resulting powder, solid or a liquid may result in under dosing, leading to lack of treatment response. This may occur through deposition of the drug at the bottom of the container that does not dissolve in the fluid, which may result in delivery of less than the required dose to the patient. In the scenario of opening of capsules, there could be loss of some of the drug during removal of the powder.

2.5 Research question

The research question was 'What is the extent of drug manipulation to obtain the prescribed dose in the paediatric in-patient units in KNH?'

2.6 Study objectives

2.6.1 Broad objective

The objective of the study was to determine the extent of drug manipulation to obtain the prescribed dose in the various paediatric in-patient units in KNH over a 1-month period.

2.6.2 Specific objectives

The specific objectives were:

1. To determine the frequency of manipulation of drugs to obtain the prescribed dose in paediatric in-patient units in KNH over a 1-month period
2. To describe the types of drug manipulations done in the paediatric in-patient units over a 1-month period.
3. To describe the drug schedules of manipulated drugs in the paediatric in-patient units over a 1-month period.

4. To describe the dosage forms and routes of administration of manipulated drugs in the paediatric in-patient units over a 1-month period.
5. To determine the factors associated with manipulation of drugs to obtain the prescribed dose in the paediatric in-patient units in over a 1-month period

Chapter 3: Methodology

3.1 Study design

A cross sectional observational study was conducted to identify drug manipulations that were carried out during administration of medicines over 1 month. This involved observation of drug administration by nursing staff and clinicians in the paediatric inpatient units. The variables recorded were; whether manipulation was done, type of manipulation done, specific drug that is manipulated, dosage form, route of administration, dose of the drug, patient details such as age, sex and diagnosis. A study period of 1 month was chosen as it was assumed that the period would be long enough to obtain the required sample size for the study.

3.2 Study site

The study was conducted in KNH, which is the national referral hospital that doubles up as the University Teaching Hospital for University of Nairobi's College of Health Sciences. The hospital has 50 wards, 22 outpatient clinics, 24 theaters with 16 of them being specialized, an accident and emergency department. The hospital has a total bed capacity of 1800. The general paediatric wards admit patients on a rotational basis, with one ward admitting per day. On average, one ward has 20 admissions per admitting day. KNH was chosen as the study site as the investigator was able to access the hospital, as it serves as the universities' teaching hospital. In addition, KNH is a national referral hospital; hence it was assumed that a large sample size would be easily obtained from this hospital.

Drugs are dispensed to the wards per patient for prescribed medicines by the designated satellite pharmacy. Emergency medicines are dispensed in minimal quantities to be kept in the wards. Drug administration times in the wards are specific depending on the frequency of administration for instance, for drugs administered thrice a day, they are given at 6.00am, 2.00pm and 10.00pm.

The paediatric inpatient units included in the study were, 4 general paediatric wards with an average capacity of 100 patients, newborn unit with 60 cots, which includes 6 cots for NICU, PICU with 6 beds and the paediatric surgical ward, which is a specialized paediatric ward. A second paediatric ward admitting oncology patients

(Ward IE) was to be included in the study but was excluded, as the children in the ward were older than 6 years old. The admitted oncology patients aged 6 years and below were admitted in the general paediatric wards, therefore the proposed sample size for the oncology patients was obtained from this ward.

3.3 Study population

Drug administration by nurses, registered clinical officers or medical doctors was observed for children between the ages of 0 - 6 years. This paediatric sub-population was chosen, as children aged above 6 years are able to swallow tablets and may not require manipulation of their medicines to obtain the prescribed dose. Nurses mainly undertook drug administration in the ward, but a registered clinical officer or a medical doctor also administered medicines especially in the case of oncology medicines.

3.3.1 Eligibility criteria

1. Newly admitted patients in each paediatric-inpatient unit per week.
2. New admissions that have been in the ward for less than 3 days to ensure newly admitted patients are not missed out.
3. Patients aged 0 - 6 years

3.3.2 Exclusion criteria

1. Drug manipulation undertaken to make it easier to administer the drug to the patient due to issues such as patient preference or ease of swallowing (aim is not to obtain the prescribed dose).
2. Extemporaneous preparations of drugs such as sildenafil, furosemide.

3.4 Sample size

Drug administrations were sampled and observed. The sample size calculation was based on the first objective to determine how common drug manipulation is in the paediatric inpatient units in KNH. The sample size formula used was the formula for a cross sectional study based on Cochran's formula (Czaja & Blair, 2005). In the literature review, the prevalence of drug manipulations ranged between 5 – 10%, which was in resource rich settings. KNH is a national referral hospital in a resource constrained setting with a larger catchment area; therefore an assumption was that

the prevalence of manipulations would be higher. With this assumption in mind, P was conservatively assumed to be 50% to get the largest sample size possible for this study.

Sample size formula for populations > 10,000:

$$n_o = \frac{Z^2 P(1-P)}{d^2}$$

n_o = desired sample size (for populations >10,000)

Z= normal standard deviate at 95%, confidence level = 1.96

P = estimated prevalence of 50%.

d^2 = error margin with which to estimate the P = 5%

$$n_o = \frac{1.96^2 \times 50\,(100-50)}{5^2}$$

n_o= 384 drug administrations

Estimating that the number of patients admitted at any time at full capacity in the wards to be studied was 384. Adjusting the sample size for finite populations the sample size formula used was as follows:

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

n = Sample size (for population < 10,000)

N = Population size, which is 384 (number of patients admitted at full capacity)

n_o = 384, the number of drug administrations

$$n = \frac{384 \times 384}{384 + (384-1)}$$

n= 192

In order to ensure that observation of drug administration was balanced among the 8 paediatric in-patient units that were studied, proportionate sampling was used to decide on the number of observations per unit. This was based on the total bed capacity per unit as follows.

Table 3.1 Sample sizes per inpatient unit

Paediatric in patient unit	Bed capacity	Sample of drug administrations to observe
General paediatric wards		
Ward 3A	60	30
Ward 3B	60	30
Ward 3C	60	30
Ward 3D	60	30
Specialist paediatric wards		
Ward 1E	28	14
Ward 4A- Paediatric Surgical	50	25
New Born Unit & NICU	60	30
PICU	6	3
Total	**384**	
Sample size		**192**

3.5 Data collection

3.5.1 Training procedures for data collection

Two pharmacist interns were engaged as research assistants. They were trained on data collection and protection of human research participants before starting data collection. The training on protection of human research participants was on ethics in research and was based on the National Institute of Health web-based training course 'protection of human research participants'. Confidentiality agreements were signed between the research assistant and the investigator before commencing data collection (appendix VI).

3.5.2 Pre-testing of data collection tool

The data collection tool was pre-tested on 4th July 2016 before data collection started. 5 drug administrations were observed and the data collection tool was found suitable for data collection and did not require any amendments.

3.5.3 Sampling approach

All paediatric patients 6 years old and below, admitted between 5th and 18th July 2016 in the various paediatric inpatient units were sampled. Any patient who had been in the ward for more than 3 days and had been sampled was not included. The list of new admissions for each in patient paediatric unit was prepared from the admission register. The general paediatric wards; 3A, 3B, 3C and 3D admit on a rotational basis during the week, therefore patients were selected on the post admission day for the respective ward. This was repeated for each of these wards until the estimated sample size was obtained. For wards 4A, NBU, oncology patients in the general wards and PICU, newly admitted patients were continuously identified during the two weeks of the study until the estimated sample size was achieved. Ward 1E, which is a paediatric oncology ward was not included in the sample as the patients in the ward were 6 years old and above. Patients who had an oncology related diagnosis in the general paediatric wards were sampled as previously described. Population sampling was used to avoid sampling a patient more than once as this population consisted of new admissions per week for each in-patient unit studied.

3.5.4 Selection of drug administrations to observe

The observed drug administrations were for all patients in the list described previously. A flow chart of the process of selection of patients and observation of medicines administration is highlighted in figure 3.1.

Before observation could be done, the names and in-patient numbers of patients who had been sampled were anonymized by use of a link log. This involved assigning them a unique study number, which was then recorded in the data collection tool. This link log was prepared for each in-patient unit that was studied. For each selected patient, drug administration by a nurse or a medical doctor in the case of administration of cancer medicines was observed. Informed consent was obtained from the concerned staff before commencing observation of drug administration.

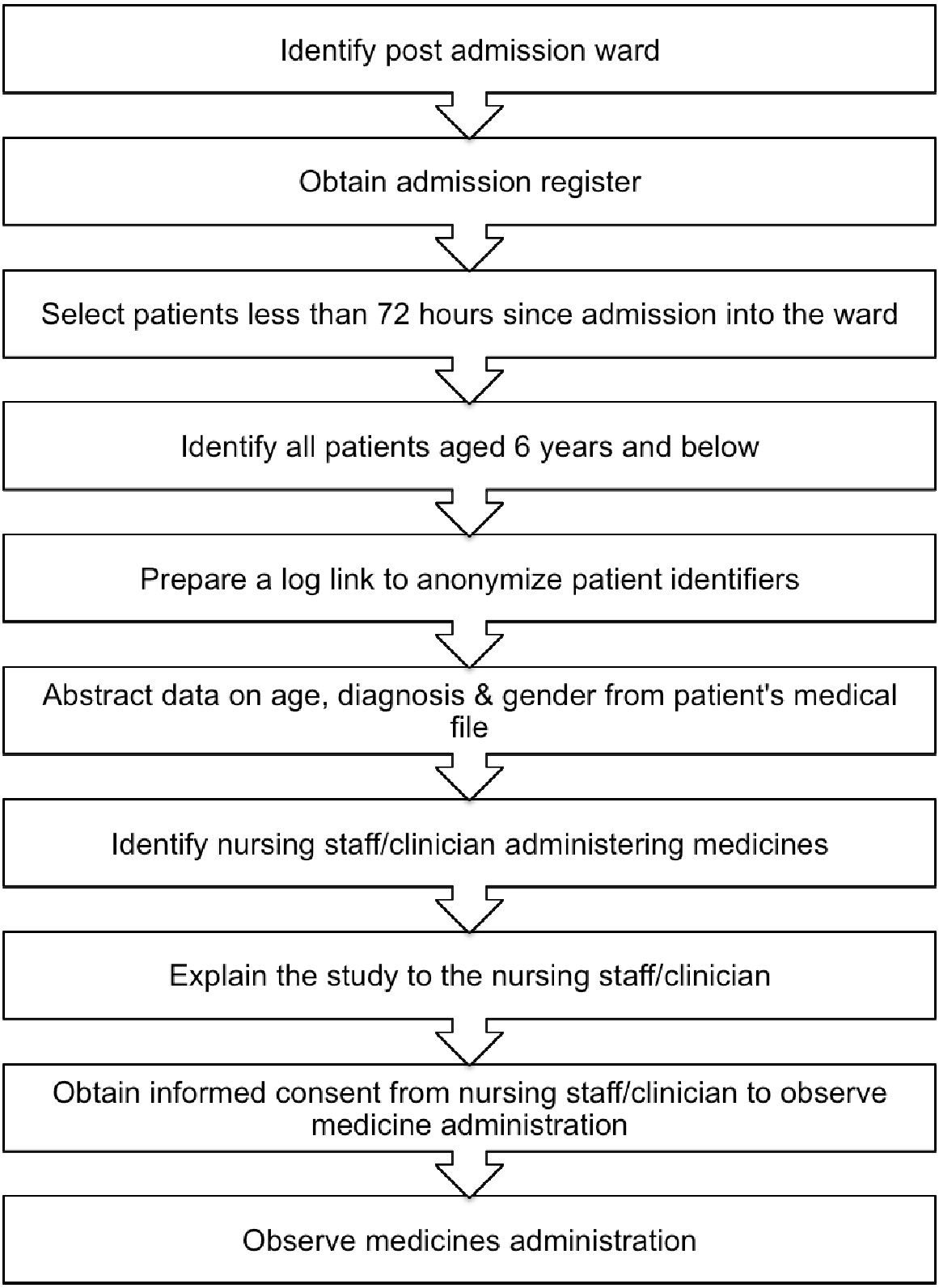

Figure 3.1 Simple flow chart of selection of patients to observe medicines administration

3.5.5 Observation

Observation of medicine administrations was done during morning, afternoon and evening drug rounds. A research assistant or the investigator observed the staff as they administered drugs to a patient. Data variables that were observed and recorded on the drug manipulation observation form (appendix IV) were the drug name, dose, dosage form being administered, route of administration, whether manipulation of a dosage form occurred to obtain the required dose to be administered to the patient and how the manipulation was done.

3.5.6 Data abstraction from patient records

Data obtained from the patient's medical file included age of patient, gender and diagnosis. Details of the drugs administered were obtained from the inpatient treatment sheet and included the drug name, dose and route of administration. These data variables were recorded on the drug manipulation observation form (appendix IV). The investigator who is a clinical pharmacist subsequently indicated the drug schedules for each observed drug as per the 2013, Kenyatta National Hospital formulary.

3.6 Data management and analysis

3.6.1 Data entry and cleaning

Collected data was entered into a password protected Microsoft Access database. The soft copy of the data was compared with the hard copy forms for completeness and accuracy. Exploratory data summaries were generated to assess inconsistency and the necessary corrections done.

3.6.2 Data analysis

The collected data was analyzed using IBM SPSS Statistics software version 24. Categorical variables were summarized using frequency tables while continuous variables were summarized using measures of central tendency and dispersion (mean, mode, median, standard deviations, and interquartile range). The frequency of drug manipulation was obtained by calculating the proportion of medicines administrations that were manipulated out of all observed medicines administrations. The association between whether a drug was manipulated or not and the ward the

observation was done, the drug schedule, dosage form, route of administration and the age category of the patients whose medicines administration was observed were demonstrated using chi-square test. The association between age of the patient whose medicines administration was observed and whether manipulation was observed was determined using the independent samples t- test.

Logistic regression through the backward elimination method was used to determine the independent factors that are associated with occurrence of drug manipulation. The independent factors that had statistical significance on bivariate analysis were included in the logistic regression model. These were age in days, drug schedule, dosage form and the in-patient area.

3.6.3 Quality assurance

The investigator assured quality by reviewing the completed data collection forms daily to ensure the data captured was complete. Any incomplete forms were identified and incomplete data recorded by going back to the inpatient units to verify the information with the staff observed and the patient records.

3.7 Ethical considerations

3.7.1 Ethical and administrative approval

Ethical approval was sought and given by the KNH/University of Nairobi Ethics and Research Committee (ERC) on 13th April 2016. The study was registered with the KNH research and programs department. The Chief pharmacist gave administrative approval to conduct the study. The paediatrics department and the specialized surgical services gave a letter authorizing data collection in their respective departments. The Senior Assistant Chief Nurses of the paediatrics and specialized surgical services were given a copy of the letters authorizing data collection in addition to the respective unit in-charges. (See appendices VI, VII, VIII and IX for copies of the approvals and registration certificates).

3.7.2 Informed consent

Written informed consent was obtained from the staff before observing any drug administration as stated previously. The aim and purpose of the study, study

procedure, storage of data and assurance of confidentiality was explained during the informed consent process. In addition, they were informed that participation was voluntary and that they may refuse to participate or withdraw during observation without any consequences. Lastly, they were allowed to ask questions or seek clarification before they could sign the informed consent form. Staff that agreed to participate was given a copy of the signed informed consent form and the study information sheet.

3.7.3 Data confidentiality

The investigator and the research assistants prepared a link log for each in-patient unit as described previously. This was to maintain and ensure patient confidentiality. All link logs were surrendered to the investigator after observation was complete in an in-patient unit for secure storage under lock and key and were only accessible to the investigator. Signed consent forms and confidentiality agreement forms were kept under lock and key and only accessible to the investigator. The drug manipulation observation forms that had been completed were only accessible to the investigator and data analyst and were kept under lock and key.

3.7.4 Risks and benefits of the study

It was anticipated that there would be no physical harm or injury to the staff during observation of drug administration. In addition, there was potential disclosure of patient and staff identity. Any patient or staff identifiers were anonymised and kept confidential to avoid disclosure.

There was no monetary benefit for staff participating in the study. This information was provided to the staff before study participation. The staff was also informed that the future benefits were in terms of assisting in obtaining information that would be used to improve medicines use in the paediatric inpatient units, reduction of any medication errors and improvement of patient safety.

3.7.5 Inappropriate practices

There were no inappropriate practices observed during the study.

Chapter 4: Results

4.1 Univariate analysis

4.1.1 Demographic characteristics

In the sample of paediatric patients whose medicines administration was observed, male patients 51.9% (68/131) were slightly more than female patients 48.1% (63/131) as highlighted in table 4.1.

Table 4.1 Demographic characteristics of paediatric patients in whom medicines administration was observed

Characteristic	Category	n	%
Gender	Male	68	51.9
	Female	63	48.1
	Total	**131**	**100**
Type of in - patient area	3A	23	17.6
	3B	20	15.3
	3C	20	15.3
	3D	33	25.2
	4A	10	7.6
	NBU	14	10.7
	PICU	4	3.1
	Oncology	7	5.3
	Total	**131**	**100**
Age group	0 – 12 months	84	64.1
	13 – 24 months	25	19.1
	25 – 36 months	8	6.1
	37 – 48 months	9	6.9
	49 – 60 months	3	2.3
	61 – 72 months	2	1.5
	Total	**131**	**100**

The mean age of the patients was 423 days (standard deviation 497, median 240) with the youngest patient being 1 day old and the oldest 2160 days. More than half of the patients 64.1% (84/131) were from the 0 – 12 months age group which constitutes neonates (1 - 28 days) and infants. Majority of the patients were drawn from the general paediatric wards (wards 3A, 3B, 3C and 3D).

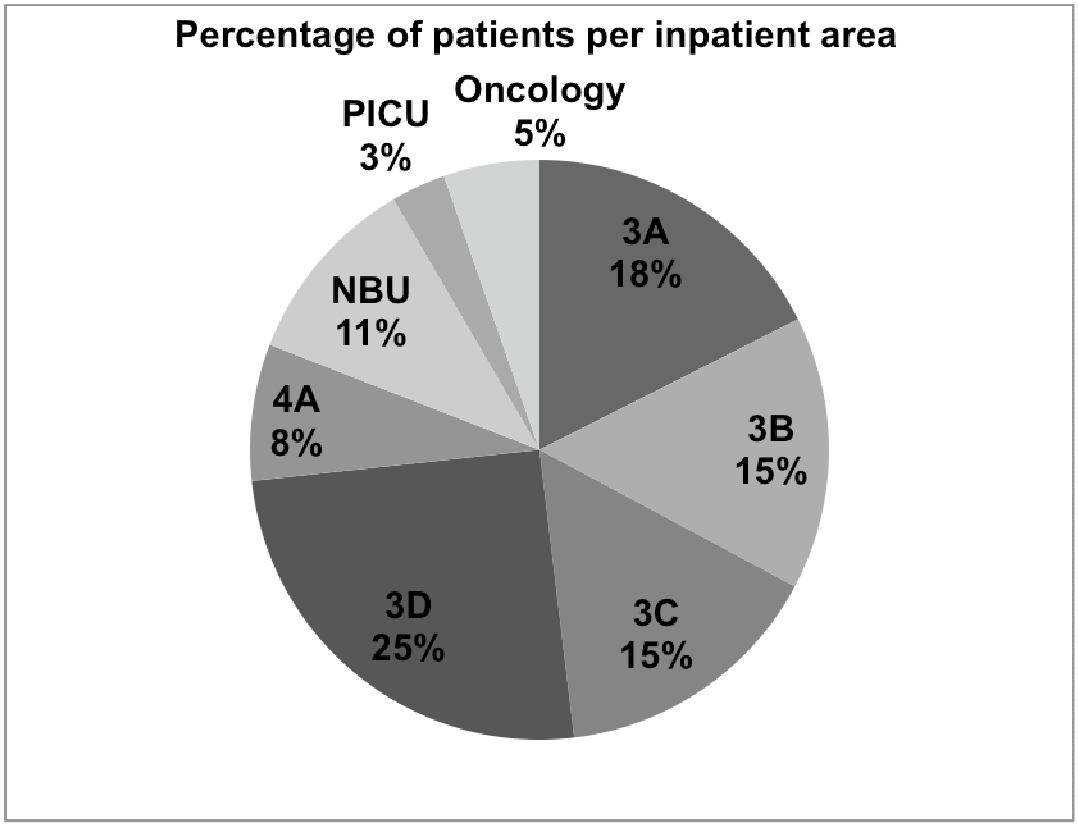

Figure 4.1 Proportion of patients per each sampled ward

The patients in the paediatric wards had 158 different types of diagnoses on admission. The most common diagnosis was pneumonia as highlighted in table 4.2.

Table 4.2 Top 8 diagnoses of patients in the wards

Disease condition	n	%
Pneumonia	36	22.78
Meningitis	13	8.23
Neonatal sepsis	8	5.06
Premature-risk of sepsis	6	3.80
Bronchitis	5	3.16
Convulsive disorder	5	3.16
Malnutrition	5	3.16
Rickets	5	3.16

4.1.2 Frequency of drug manipulation to obtain prescribed dose

The number of medicines administrations observed was 249 in 131 patients. This was much larger than the estimated sample size of 192 medicines administrations. 16 drug manipulations were observed. The frequency of drug manipulation to obtain

the prescribed dose was estimated to be 6.4%, (16/249) in the paediatric in-patient setting.

4.1.3 Manipulated drugs and drug classes as per KNH Formulary, 2013

Seven drugs were manipulated as highlighted in table 4.3. The most commonly manipulated drug was folic acid 5mg tablet, 31.3% (5/16) with the least manipulated drug being aminophylline 250mg/10ml inj, 6.3% (1/16).

Table 4.3 Manipulated drugs

Drug	**Number of observed manipulations**	**%**
Folic acid 5mg tab	5	31.3%
Vitamin K 2mg/0.2ml inj	2	12.5%
Soluble insulin 100units/ml inj	2	12.5%
Phenobarbitone 30mg tab	2	12.5%
Gentamicin 80mg/2ml inj	2	12.5%
Clonazepam 0.5mg tab	2	12.5%
Aminophyllin250mg/10ml inj	1	6.3%
Total	**16**	**100.0%**

The manipulated drugs were drawn from 6 drug schedules as per the 2013, KNH formulary, as highlighted in table 4.4. The drug schedule with the most number of observed manipulations was vitamins and minerals 31% (5/16).

Table 4.4 Manipulated drug classes

Drug Schedule	**Drug Class**	**Number of observed manipulations**	**%**
N	Vitamins and minerals	5	31%
C	Movement disorder, antiparkinsonism, antiepileptic, antipsychotherapeutic and psychotherapeutic agents	4	25%
E[§]	Medicines affecting blood and cardiovascular medicines	2	13%
F	Anti-infective medicines-antibacterial	2	13%
J-B	Hormones, other endocrine medicines and contraceptives	2	13%
M	Medicines acting on the respiratory tract	1	6%
	Total	16	100%

[§]In the 2013 KNH formulary, Vitamin K is classified as a drug affecting blood (Schedule E).

4.1.4 Manipulated dosage forms and their routes of administration

Two dosage forms were manipulated to obtain the prescribed dose; tablet, 56% (9/16) and injectable liquids, 44% (7/16). The most frequently manipulated dosage form was a tablet (56%), with the oral route being the most commonly used route of administration, 56%. The oral, 56% (9/16) and the intravenous routes, 44% (7/16) were used for manipulated drugs.

4.1.5 Types of manipulation observed

Five types of manipulation were observed as highlighted in table 4.5. The most frequent type of manipulation was tablet segmentation and dispersion, 50% (8/16). In the category of other types of manipulation, this manipulation involved drawing up a larger than required volume of soluble insulin and diluting it with 5 mls of normal saline so as to be able to draw up the prescribed dose in a volume that is easier to measure out. In these 2 instances, 0.2 and 0.3 units of soluble insulin were required which were not measurable in the insulin syringes that were available in the inpatient unit. Two units of insulin was drawn and diluted with 5 mls of normal saline. Then a calculation was done to determine what volume to draw from the diluted insulin that would be equivalent to 0.2 and 0.3 units.

Table 4.5 Types of manipulations identified

Types of manipulations	**Number of observed manipulations**	**%**
Tablet segmentation & dispersion	8	50
IV vol less than 0.2mls	4	25
Other types of manipulation	2	13
Tablet segmentation	1	6
IV vol 0.2 - 0.1ml	1	6
Total	**16**	**100**

There were no observed drug manipulations in wards 3A, PICU, 4A and oncology patients. In ward 3D, only tablet segmentation and dispersion was observed (100%, 3). In ward 3B, dilution of small volumes of insulin to be able to measure out the required dose was commonly observed (67%, 2/3) followed by tablet segmentation and dispersion (33% 1/3). Tablet segmentation and dispersion (43%, 3/7) and measurement of intravenous volumes of intravenous drugs below 0.2ml (43%,3/7)

were commonly observed in NBU. 3 types of manipulation practices were observed in ward 3C. These were tablet segmentation, measurement of intravenous volumes of intravenous drugs below 0.2ml and tablet segmentation and dispersion. Measurement of IV volumes between 0.2 and 0.1 mls was observed in NBU.

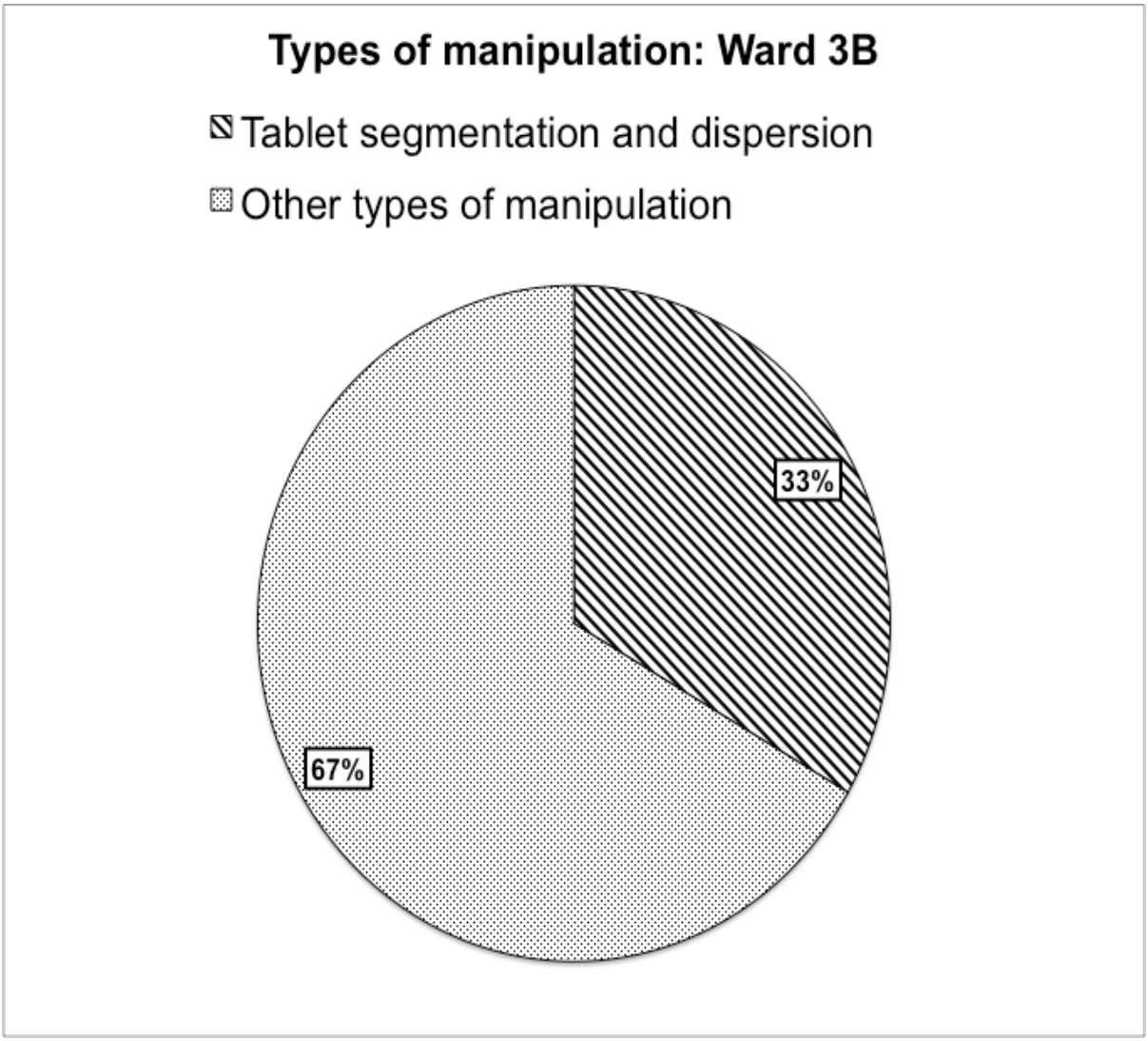

Figure 4.2 Types of observed drug manipulations in Ward 3B

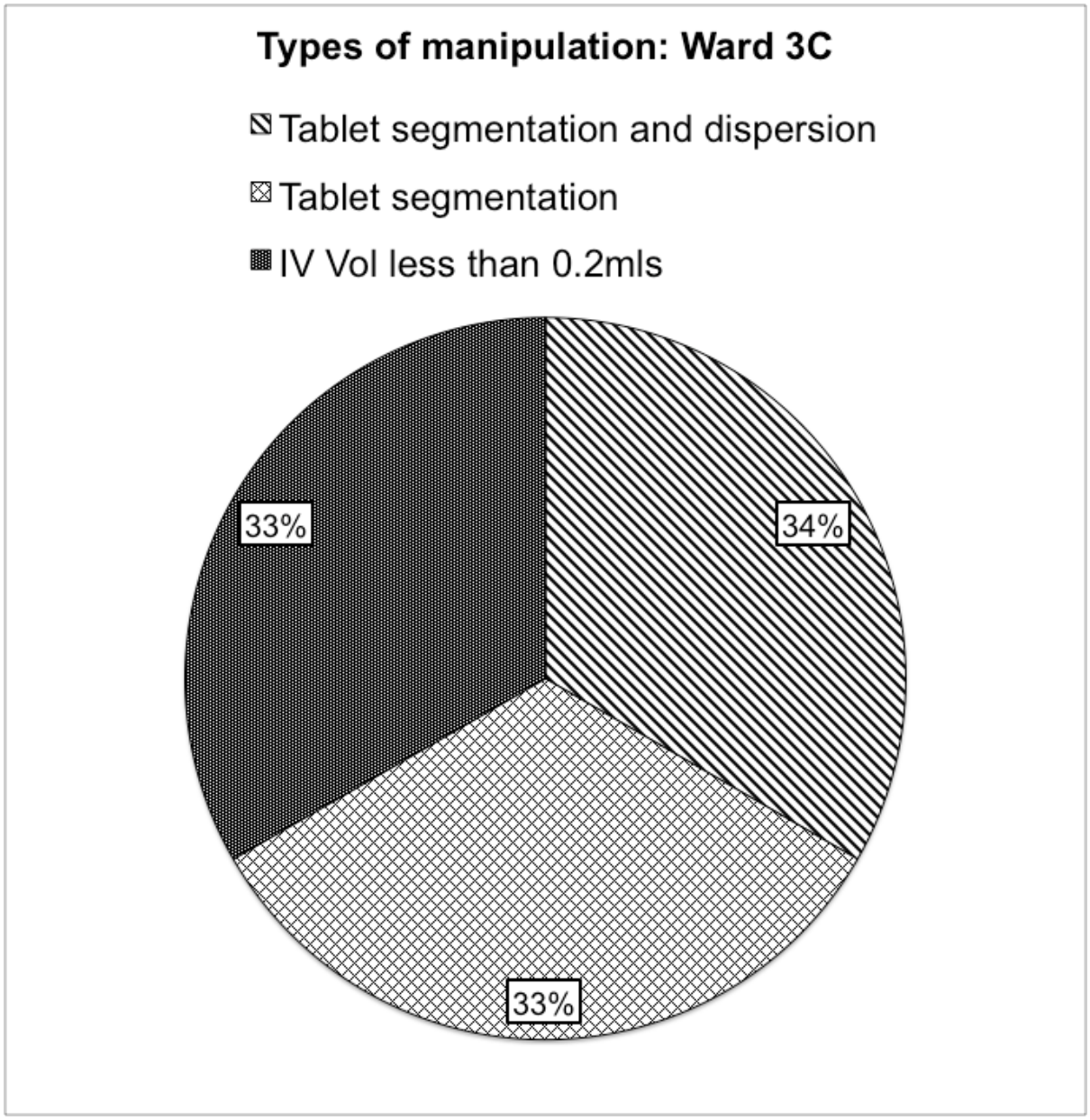

Figure 4.3 Types of observed drug manipulations in Ward 3C

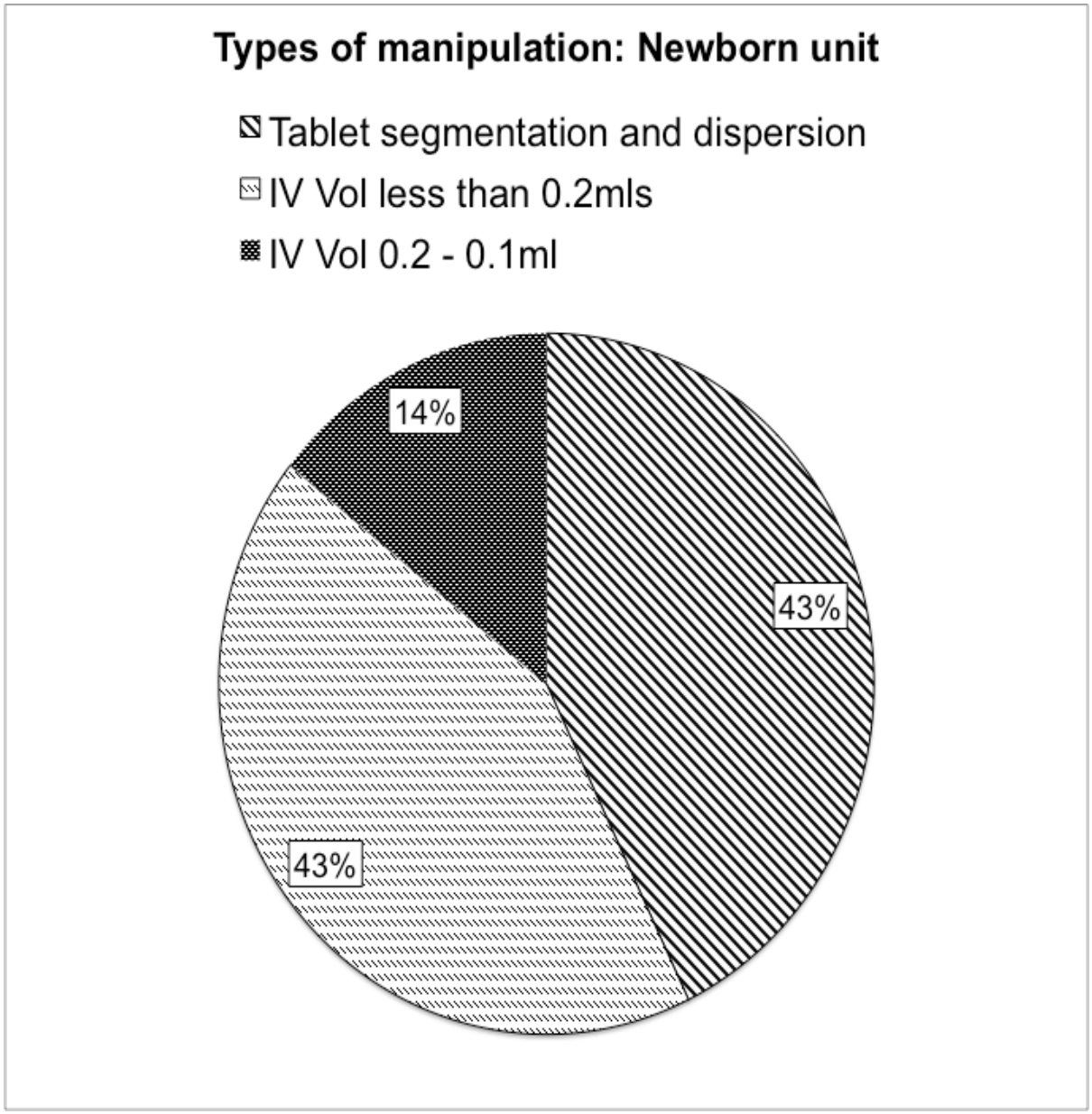

Figure 4.4 Types of observed drug manipulations in newborn unit

4.2 Bivariate analysis

4.2.1 Association between type of paediatric in-patient area and observed drug manipulations

Drug manipulation was commonly observed in NBU (43.8%, 7/16) in comparison to wards 3D, 3C and 3B (18.8%, 3/16 for each ward). This association was statistically significant (chi-square = 18.421, df = 7, p= 0.01) as highlighted in table 4.6. There

was no drug manipulation associated with oncology patients, PICU, wards 4A and 3A.

Table 4.6 Association between type of inpatient area and number of observed drug manipulations

In-patient area	Was drug manipulated?				Chi-square test		
	Yes		No				
	n	%	n	%	$\chi 2$	df	p-value
NBU	7	43.8	27	11.6	18.421	7	0.01
3D	3	18.8	48	20.6			
3C	3	18.8	29	12.4			
3B	3	18.8	35	15			
Oncology	0	0	17	7.3			
PICU	0	0	11	4.7			
4A	0	0	33	14.2			
3A	0	0	33	14.2			
Total	**16**	**100**	**233**	**100**			

4.2.2 Association between occurrence of drug manipulation and route of drug administration

Drug manipulation was commonly associated with drugs administered via the oral route (56%, 9/16), followed by the intravenous route (44%, 7/16) in comparison to the other routes of administration; however, this association was not statistically significant (chi-square = 4.162, df = 3, p= 0.244) as highlighted in table 4.7. The inhalation and per rectal routes of administration were not associated with drug manipulation.

Table 4.7 Associations between occurrence of drug manipulation and route of drug administration

	Was drug manipulated?				Chi-square test		
	Yes		No				
Route of administration	n	%	n	%	$\chi 2$	df	p-value
Inh	0	0	2	1	4.162	3	0.244
P.R	0	0	2	1			
I.V	7	44	155	66			
P.O	9	56	74	32			
Total	**16**	**100**	**233**	**100**			

4.2.3 Association between occurrence of drug manipulation and dosage form

Drug manipulation was strongly associated with tablets (56%, 9/16) in comparison to injectable liquids (44%, 7/16). This association was strongly statistically significant (chi-square = 105.478, df = 8, p<0.0001) as highlighted in table 4.8. There was no association with the other dosage forms namely; nebulizer solutions, sachets, suppositories, capsules, oral liquids, injectable powders and oral suspensions.

Table 4.8 Association between occurrence of drug manipulation and the drug dosage form

	Was drug manipulated?				**Chi-square test**		
	Yes		**No**				
Dosage form	**n**	**%**	**n**	**%**	$\chi 2$	**df**	**p-value**
Tab	9	56.3	4	1.7	105.478	8	p<0.0001
Inj liq	7	43.8	36	15.5			
Inj powd	0	0	118	50.6			
Nebs	0	0	2	0.9			
Sachet	0	0	1	0.4			
Supp	0	0	2	0.9			
Cap	0	0	1	0.4			
P.O Liq	0	0	12	5.2			
P.O Susp	0	0	57	24.5			
Total	**16**	**100**	**233**	**100**			

4.2.4 Association between occurrence of drug manipulation and the drug's schedule

Drug manipulation was commonly associated with drugs from schedule N (vitamins and minerals) (31.3%, 5/16). There was also an association with drugs from schedules C, J-B, F, E and M. The details of the drug classes are outlined in table 4.9. This association was strongly statistically significant (chi-square 63.289, df 10, p<0.0001) as highlighted in table 4.9. Drugs from schedules S, H, G, D, and B were not associated with drug manipulation.

Table 4.9 Association between occurrence of drug manipulation and drug schedule

		Was drug manipulated?				Chi-square test		
Drug schedule	**Drug class**	**Yes**		**No**				
		n	**%**	**n**	**%**	$\chi 2$	**df**	**p-value**
N	Vitamins and minerals	5	31.3	12	5.2	63.289	10	p<0.0001
C	Movement disorder, antiparkinsonism, antiepileptic, antipsychotherapeutic and psychotherapeutic agents	4	25.0	8	3.4			
J-B	Hormones, other endocrine medicines and contraceptives	2	12.5	1	0.4			
F	Anti-infective medicines - antibacterials	2	12.5	133	57.1			
E	Medicines affecting blood and cardiovascular medicines	2	12.5	6	2.6			
M	Medicines acting on the respiratory act	1	6.3	5	2.1			
S	Plasma substitutes and fractions, solutions correcting water and electrolyte imbalance and parenteral nutrition	0	0.0	1	0.4			
H	Antineoplastic, immunosuppresives and medicines affecting bone metabolism	0	0.0	15	6.4			
G	Other anti-infective medicines	0	0.0	6	2.6			
D	Gastrointestinal medicines	0	0.0	13	5.6			
B	Analgesics, antipyretics, Non-steroidal Anti-inflammatory Medicines (NSAIMS), medicines used to treat gout and disease modifying agents in rheumatoid disorders (DMARDS)	0	0.0	33	14.2			
Total		**16**	**100.0**	**233**	**100.0**			

4.2.5 Association between occurrence of drug manipulation and age of the patients whose medicines administration was observed

The mean age of patients whose drugs were manipulated to obtain the prescribed dose was 130 days (standard deviation 167.75) and for those whose drugs were not manipulated was 502.62 days (standard deviation 542.980). There was a statistically significant difference between the mean ages of patients whose drugs were manipulated and those that were not (mean difference = - 372.612, t statistic = -6.776, df = 42.912, p - value < 0.0001, 95% confidence interval - 483.526 to - 261.710). This means that infants aged around 4 months were significantly more likely to have their medicines subjected to drug manipulation compared to older infants and children between 2 and 6 years.

4.2.6 Association between occurrence of drug manipulation and age category of the patients whom medicines administration was observed

Drug manipulation commonly occurred in the lowest age group of 0 – 12 months (87.5%, 14/16) however this was not statistically significant (chi-square= 6.145, df = 5, p=0.292) as highlighted in table 4.10. Manipulation was also less frequently associated with the age group, 13 -24 months (12.5%, 2/16). Manipulation was not associated with older children aged 25 months to 72 months.

Table 4.10: Association between age group and occurrence of drug manipulation

Age group in months	Age groups in days	Was drug manipulated				Chi-square test		
		Yes		No				
		n	%	n	%	$\chi 2$	df	p-value
0 – 12	1 - 360	14	87.5	136	58.4	6.145	5	0.292
13 – 24	361 - 720	2	12.5	42	18.0			
25 – 36	721 - 1079	0	0.0	15	6.4			
37 – 48	1080 - 1439	0	0.0	29	12.4			
49 – 60	1440 - 1799	0	0.0	9	3.9			
61 – 72	1800 - 2160	0	0.0	2	0.9			
Total		**16**	**100.0**	**100**	**100.0**			

4.3 Multivariate analysis

The independent variables that were included in the model were age in days, the drug's schedule, dosage form and type of in-patient area or ward. This is because they showed a statistically significant association with occurrence of drug manipulation on bivariate analysis. Three models were generated and the model including all the independent variables (step 1) had the highest likelihood of predicting the association of the independent variables with occurrence of drug manipulation by 19.9% (chi-square = 19.577, df = 4, p value = 0.01, Nagelkerke R square 0.199) as highlighted in tables 4.11 and 4.12.

Table 4.11 Omnibus tests of model coefficients

		Chi-square	df	Sig.
Step 1	Step	19.577	4	.001
	Block	19.577	4	.001
	Model	19.577	4	.001
Step 2[a]	Step	-.111	1	.739
	Block	19.466	3	.000
	Model	19.466	3	.000
Step 3[a]	Step	-.439	1	.508
	Block	19.027	2	.000
	Model	19.027	2	.000

a. A negative Chi-squares value indicates that the Chi-squares value has decreased from the previous step.

Table 4.12 Model summary

Step	-2 Log likelihood	Cox & Snell R Square	Nagelkerke R Square
1	99.208[a]	.076	.199
2	99.319[a]	.075	.198
3	99.758[a]	.074	.194

a. Estimation terminated at iteration number 7 because parameter estimates changed by less than .001.

From the model in step 1, the drug's schedule (wald = 5.920, df = 1, p-value = 0.015) is significantly associated with increasing odds of occurrence of drug manipulation as highlighted in table 4.13. In addition, the drug's schedule is 1.195 times or 20% more likely to result in occurrence of drug manipulation (OR = 1.195, 95% CI 1.035 -

1.379). The ward (p=0.739) and the dosage form (p=0.551) are not significantly associated with occurrence of drug manipulation. Age in days is statistically associated with occurrence of drug manipulation (p=0.029), however change in age does not result in occurrence of drug manipulation (OR = 0.997, 95% CI 0.994 - 1).

Table 4.13 Factors associated with drug manipulation

Variables in the Equation									
		B	S.E.	Wald	df	p-value	Exp(B)/ OR	95% C.I. for EXP (B)/OR	
								Lower	Upper
Step 1[a]	Ward	0.053	0.161	0.111	1	0.739	1.055	0.770	1.445
	Drug schedule	0.178	0.073	5.920	1	0.015	1.195	1.035	1.379
	Dosage form	-0.077	0.130	0.355	1	0.551	0.925	0.717	1.194
	Age in days	-0.003	0.001	4.749	1	0.029	0.997	0.994	1.000
	Constant	-3.075	1.196	6.605	1	0.010	0.046		
Step 2[a]	Drug schedule	0.181	0.072	6.292	1	0.012	1.199	1.040	1.381
	Dosage form	-0.085	0.127	0.447	1	0.504	0.918	0.716	1.179
	Age in days	-0.003	0.001	4.824	1	0.028	0.997	0.994	1.000
	Constant	-2.839	0.955	8.840	1	0.003	0.059		
Step 3[a]	Drug schedule	0.196	0.071	7.703	1	0.006	1.217	1.059	1.398
	Age in days	-0.003	0.001	4.845	1	0.028	0.997	0.994	1.000
	Constant	-3.322	0.668	24.721	1	0.000	0.036		
a. Variable(s) entered on step 1: Ward, Drug schedule, Dosage form, Age in days.									

Chapter 5: Discussion and conclusion

5.1 Discussion

The observational cross sectional study carried out over two weeks was aimed at determining the prevalence of drug manipulation to obtain the prescribed dose in the various paediatric in-patient units in KNH. The study further determined the specific drugs that are manipulated, drug schedules, dosage forms and routes of administration of drugs that are manipulated in addition to the types of manipulations that are carried out. Lastly, the study examined the factors associated with manipulation of drugs to obtain the prescribed dose.

5.1.1 Frequency of manipulation of drugs to obtain the prescribed dose in paediatric in-patient units

The frequency of manipulation of drugs to obtain the prescribed dose of drugs being administered to patients in the various paediatric in-patient units in KNH was found to be 6.4% (16/249). This is comparable to 6.5% (126/1944), which was estimated for a regional children's hospital in the UK in the study by Nunn et al. (2013). However, the number of assessed drug administrations in the UK study was much more in comparison to the study's sample size of 249 medicines administration. In addition, the study design was different as it involved review of paper based in-patient treatment sheets by an experienced paediatric clinical pharmacist over a longer period of 3, 5-day periods over 5 months in contrast to the present's study observational study design over 2 weeks. Bearing these differences in mind, it can be postulated that the prevalence of drug manipulation in KNH could be much higher if the study was conducted over a much longer period. There are various reasons, which could result in manipulation of drugs in this setting, which will be highlighted in the following sections.

5.1.2 Types of manipulations observed per paediatric in-patient area

Five types of manipulations were observed, which was less in comparison to 10 types of manipulations observed in the study by Nunn et al. (2013). Half of the observed manipulations involved tablet segmentation and dispersion. This practice is broadly similar to the practice described in two studies in the literature review by Nunn et al. (2013) and Botzepe et al. (2014) where the tablets either in full, halves or

quarters are crushed and dispersed in liquid and then a volume of liquid corresponding to the required dose is drawn and given to the child. In the study by Nunn et al. (2013) the most common manipulation in the regional children's hospital was tablet dispersion (45.2%, 57/126), which is comparable to the observed practice in KNH, where the practice is more common in the 3 general paediatric wards in comparison to NBU. A probable explanation for this practice being common in the general paediatric wards is that a large number of children admitted in this ward are not severely ill and are therefore able to take oral medications.

The most common type of manipulation in NBU, which is a specialist area, was IV drug manipulations (57%, 4/7). This result is similar to past results from past research work, where measurement of small intravenous volumes was found in specialist areas such as the neonatal unit with the prevalence ranging from 40.4 % to 68.2% (Richey et al., 2011; Nunn et al., 2013; Richey et al., 2013). This result was expected, as the NBU is a clinical area where neonates receive intensive and specialists care after birth, they are critically sick and most of their medicines are administered via the intravenous route.

The NBU was found to be strongly associated with occurrence of drug manipulation (43.8%) in comparison to wards 3D, 3B and 3C. As explained previously, this is an expected finding due to the nature of the patients found in NBU and the nature of care given to such patients.

5.1.3 Manipulated drugs, their drug classes, dosage forms and routes of administration

The 7 drugs that were manipulated were drawn from 6 broad drug schedules or classes as per the KNH Formulary (2013). Three orally administered drugs were manipulated through tablet segmentation with and without dispersion. These were folic acid 5mg, clonazepam 0.5mg and phenobarbitone 30mg tablets. In most instances, the prescribed dose was half the strength of the tablet, hence the need to manipulate the tablet to get the prescribed dose. This manipulation was most common for folic acid tablets.

Tablet segmentation to obtain the prescribed dose is associated with a concern on whether dose or weight uniformity is achieved in the resulting segments especially for drugs with a narrow therapeutic index (Verrue, Mehuys, Boussery, Remon, & Petrovic, 2011). This leads to concerns on dose accuracy due to loss of some of the drug during segmentation or unequal tablet segments. This could be problematic when tablets are split by hand and one is not able to obtain equal segments especially in instances where a tablet does not have a score line to aid in splitting the tablet. This may inadvertently result in over dosage or under dosage, which may lead to toxicity, occurrence of adverse effects or treatment failure. In resource - rich hospitals or pharmacy departments, they may be able to acquire tablet splitters or cutters, which may assist in splitting the tablets and having a better chance of obtaining, tablet segments of equal weight or dose. This was demonstrated in a study that compared and quantified the mean deviation from theoretical weight and the mean weight loss of tablets split with a kitchen knife, a tablet splitter and by hand, where a tablet splitter had the least weight loss in weight than the other methods (Verrue et al., 2011). With this in mind, caution should be exercised when segmenting tablets especially by hand.

Dispersion of tablets in liquids is associated with a number of concerns associated with the dosage form. These are unpredictable or variable pharmacokinetic properties of the manipulated drug affecting the drugs bioavailability, site and rate of absorption of the drug into the body and possible changes to the location where the drug exerts its effect. Drugs that are insoluble will not dissolve in water or the liquid used for dispersion resulting in a patient receiving a variable and inaccurate dose due to settling of the insoluble components at the bottom of the container especially if proper mixing is not done prior to drawing the volume containing the required dose or administration of the resulting solution. Folic acid is a crystalline yellowish powder that is very slightly soluble in water (International Pharmacopoeia, 2015). Dispersion of folic acid tablets may be problematic as it’s not soluble in water and could result in variable dosing in the patients receiving the drug. Other effects that could occur with tablet segmentation and dispersion in liquids are an unpleasant taste and acceleration of the destruction rate of the drug.

Possible safety concerns arise with tablet segmentation and dispersion as a manipulation practice. This could include occupational health and safety issues to the health professional manipulating the tablet due to risk of skin contact or inhalation of dust with may be potentially noxious. Manipulation in unsanitary conditions may lead to contamination of the drug and unintended intake of contaminants with potential adverse effects. Lastly, there could be gastroesophageal irritation due to the drug's irritant effect, which had been protected by the drug's original formulation.

Possible reasons as to why folic acid, clonazepam and phenobarbitone were manipulated are lack of liquid formulations and tablets of smaller strengths in this setting. Formulation of a liquid dosage form of folic acid in the past has been problematic due to stability issues leading to non-availability of a liquid formulation of folic acid (Vignesh, Sivakumar, Parkavi, Selvakumar, & Joysa Ruby, 2012). However, there are available liquid formulations of folic acid, clonazepam and phenobarbitone commercially with strengths that allow a user to obtain small doses for use in children.

Three drugs were manipulated through measurement of small volumes for intravenous administration below 0.2ml. These were gentamicin 80mg/2ml, aminophylline 250mg/10ml and vitamin K 2mg/0.2ml. Possible reasons for measurement of small volumes is lack of formulations with lower strengths or concentrations to allow measurement of larger volumes and lack of syringes with small volumes to allow measurement of small measurements. Aminophylline 250 mg/10ml is the formulation currently available commercially, while vitamin K 2mg/0.2ml is the paediatric formulation available.

The manipulation of soluble insulin 100 units/ml was due to the requirement to administer doses less than 1 unit of insulin. During the study, the observed medicines administrations required 0.2 and 0.3 units of soluble insulin. This volume that was not measurable in the unit as the size of insulin syringe they had was the 1ml insulin syringe (100 units) resulting in the previously described manipulation.

This can be avoided by supplying insulin syringes of smaller volumes such as the ½ ml/50 units insulin syringe the 3/10 ml/30 units.

In KNH, only two types of dosage forms were manipulated, with tablet manipulation accounting for 56% of the manipulations and intravenous liquids for the remaining manipulations (44%). This was similar to a previous study by Richey et al. (2013) where manipulation of tablets ranged from 45.7 % to 74.1%, however for intravenous drugs, the proportion was lower (11.7% to 21%) in comparison to KNH. This is because in the previous study, 7 dosage forms were manipulated in comparison to 2 in KNH. A possible reason for the difference is different prescribing policies and hospital formularies in the two settings. KNH is a public national referral hospital in a resource limited setting while the hospital in the past study is in a resource rich country.

Comparison of the drug classes and drugs manipulated in KNH with past studies shows distinct differences. The most common drug class in the study by Richey et al. (2013) was analgesics in comparison to vitamins and minerals in KNH. The most commonly manipulated drug in KNH was folic acid in comparison to hydrocortisone in the study by Nunn et al. (2013). This could be due to the explanation offered in the previous paragraph in regards to differences in prescribing policies, the type of patients being treated, amount of resources and the clinical conditions that are treated and managed in KNH. The clinical conditions in KNH would largely be drawn from poverty related diseases such as malnutrition and infectious diseases as highlighted in table 4.2 which would not be similar to a resource rich setting.

5.1.4 Factors associated with manipulation of drugs to obtain the prescribed dose in the paediatric in-patient units

The study demonstrated that the age of a patient, the drug schedule and the route of administration of the drug were strongly associated with a drug being manipulated. A possible explanation of this association is because ordinarily, the dose of a drug to use in a neonate or a paediatric patient would be estimated based on what drug or drug class is being prescribed, the age of a patient which would determine the level of development, maturity and weight of a child and the route of administration of the

drug. These factors in addition to others would ordinarily be considered to determine dosing of a drug. It was interesting to note that the dosage form and the type of paediatric in-patient unit were not factors strongly associated with occurrence of drug manipulation, which had been expected to be the predictors of occurrence of drug manipulation since the lack of an age appropriate formulation or dosage form leads to use of other formulations designed for adults or older children to be used in younger children, infants and neonates.

Infants aged 4 months were more likely to have their medicines subjected to drug manipulation compared to older children and neonates. This is an interesting finding worth highlighting, as this was not identified in the literature review that was conducted. Past research studies did not study association of manipulation with the different paediatric ages. However this finding should be interpreted with caution as the sample size of the study was based on drug administration as the sample and not a person.

5.1.5 Study limitations

The study was based on an observational cross sectional study design, which only gives an estimate of the prevalence of drug manipulations over a specific period, which may not be representative of the actual frequency in the real setting. In addition, the sample size calculation was based on observations of drug administrations and not persons, which makes the study not powered to predict association of manipulation with age accurately.

Other limitations encountered were that the observational study was prone to selection and observer bias by the investigator and the research assistants during sampling and observation of medicines administration to determine if drug manipulation occurred. This could reduce the validity of the findings making them not generalizable to other hospital settings. As the study involved observation of nursing and clinical staff, there was a possibility that they could change their medicine administration practices during observation resulting in not being able to observe the actual practice in the ward, hence reducing the reliability of the study results. An effect that could have affected the study are the research participants

being very keen to show that they manipulate drugs, in an attempt to meet the expectations of the researcher which could reduce the validity of the study findings. Lastly, during data analysis, there could be confounding factors in the study that were not identifiable or controlled for that could reduce the validity of the study findings.

5.1.6 Recommendations for future research

In this study it was not possible to explore the reasons for drug manipulation, perceptions and concerns of the nursing staff and clinicians who are involved in the practice of drug manipulation in the wards and also whether they knew the possible consequence of the practice to the patient. This would have required use of questionnaires and interviews either as a qualitative or quantitative study, which would not have been possible in the time that was available. These are future research studies that can be conducted.

This study can be extended to determine whether the drugs that are manipulated are associated with any medication errors that occur in these paediatric in-patient units. Another suggested study would be to determine how frequent medicines are used in an off- label or unlicensed manner in these paediatric in-patient units due to the peculiarities associated with dosing of medicines in the paediatric population, lack of licensed indications or uses for medicines in the paediatric population. Lastly, it would be useful to identify what are the perceptions and concerns of the pharmacy staff in regards to drug manipulation and what would be their suggestions.

5.1.7 Recommendations for future practice

Based on the findings of this study, it's recommended to develop a policy and guideline for guiding drug manipulation in the paediatric wards in KNH. The policy and guidelines would assist in standardizing the practice of drug manipulation by limiting drug manipulation to the drugs that have been reviewed and confirmed to require drug manipulation. This would ensure that paediatric patients are getting the required dose to avoid treatment failure or over dosage, which may have adverse consequences on the patient. It would also assist in reducing the dosage and safety concerns associated with manipulation of drugs. The manipulation policy and

guidelines would state the drugs that can be manipulated, how to conduct the manipulation, storage and stability of the manipulated drugs. It would also provide for the procurement of medicines administration devices such as measuring spoons and cups, oral syringes for measurement of very small oral volumes less than 1ml, tablet cutters and the appropriate small sizes of insulin syringes such as the ½ ml/50 units insulin syringe and the 3/10 ml /30 units with full and half mark graduations.

Manipulation of a drug from its original dosage form may have legal implications for any health care professional undertaking the manipulation. This is because there is modification of the drug from the dosage form that is registered or licensed by the drug regulatory authority to another form. Any harm, untoward or adverse effects that could result from use of a manipulated drug would mean that the health care professional is held responsible and not the company that holds the registration certificate for the drug unless the drug manufacturer has indicated in the product details that a drug may be modified from its original dosage form during use. This should be borne in mind when developing the policy and guidelines for drug manipulation and the Pharmacy and Poisons Act should be referred to.

In instances where, age - appropriate formulations can be procured, it's recommended to stock this formulations in the pharmacy department to reduce drug manipulation. This would result in manipulation being done for the drugs, where it has been demonstrated that in the commercial Kenyan market, there is no age appropriate formulation available. This would either be because it's not possible to develop a formulation that is appropriate for the paediatric ages due to the physicochemical properties of the drugs or the paediatric age appropriate formulations are not available in the Kenyan market despite being available in other countries internationally. A paediatric formulation is available for gentamicin injection in the 20mg/2ml strength.

In the case of folic acid, clonazepam and phenytoin tablets, it's recommended to source for liquid formulations appropriate for the paediatric age to avoid tablet segmentation and dispersion. There are liquid formulations of clonazepam, phenobarbitone and folic acid available in some international markets such as the United Kingdom. Folic acid is available as a 2.5mg/5ml oral solution (Electronic

Medicines Compendium (eMC), 2016b; eMC, 2016a). Clonazepam is available as 0.5mg/5ml and 2mg/5ml oral solution, while phenobarbitone is available as an elixir of 15mg/5ml (eMC, 2016c; eMC, 2016d; eMC, 2013). However, special attention should be paid to the excipients used in these liquid formulations to avoid toxicity associated with excipients. An example is propylene glycol that is used as a solvent in liquid dosage forms which is associated with central nervous system adverse effects in neonates (1 - 28 days old) and children on administration of large volumes such as those that would be taken in oral liquids or suspensions (Rowe, Sheskey, & Quinn, 2009). Information on the safety and toxicity data of excipients used in paediatric formulations can be accessed from the ' Safety and Toxicity of Excipients for Paediatrics' ("STEP") database which is accessible from the website http://pharmacyapp-a.ucl.ac.uk:8080/eupfi.

Preparation of extemporaneous preparation from the pharmacy department in KNH is recommended as a last resort if there are no available liquid formulations in the Kenyan market for clonazepam, folic acid and phenobarbitone. This would prevent manipulation of these tablets to obtain the required dose. The website www.pharminfotech.co.nz provides a monograph that can be used to prepare liquid formulations of folic acid and phenobarbitone in the pharmacy as extemporaneous preparations.

Lastly, the findings of this study may be used to lobby pharmaceutical manufacturers and suppliers to supply age appropriate formulations for folic acid, clonazepam and phenobarbitone in addition to other drugs that are currently being supplied as extemporaneous preparations in KNH. On the other hand, the Pharmacy and Poisons Board in Kenya may use these findings to encourage pharmaceutical manufacturers and suppliers to import or manufacture age appropriate formulations for the paediatric population in Kenya.

5.2 Conclusion

The prevalence of manipulation of drugs to obtain the prescribed dose in the paediatric in-patient units in KNH was 6.4%, which was comparable to past research studies in the same area. Drug manipulation was frequently conducted in the new born unit (43.8%, $p < 0.01$) in comparison to the general paediatric wards 3D

(18.8%), 3B (18.8%) and 3C (18.8%). Drug manipulation was not observed in one general ward: 3A, the specialized paediatric surgical ward (4A), paediatric intensive care unit and in oncology patients. A drug's dosage form was significantly associated with occurrence of drug manipulation, with tablets being commonly manipulated (56%, p< 0.0001). Drugs belonging to the class of vitamins and minerals were frequently associated with occurrence of drug manipulation (31.3%, p< 0.0001). The most commonly manipulated drug was folic acid 5mg (31.3%). Tablet segmentation and dispersion (56%) and measurement of small intravenous liquid volumes of less than 0.2ml (44%) were the types of manipulation observed in the paediatric in-patient units in KNH. Infants were frequently associated with manipulation of drugs administered to them (mean age 130 days, p <0.0001). The drug's schedule was significantly associated with increasing odds of occurrence of drug manipulation and was 20% more likely to result in occurrence of drug manipulation (OR = 1.195, 95% CI 1.035 - 1.379).

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Appendix I: Budget

	Item	Unit	No. of Days	Unit Price (KShs)	Total Cost (KShs)
1	Ethics and research review fees	1	N/A	2,000	2,000
2	Training costs	1	2	10,000.00	20,000.00
3	Dissemination costs	1		20,000.00	20,000.00
	Personnel				
1	Data analysis	1	30	2,000.00	60,000.00
2	Research assistant	4	14	250.00	14,000.00
	Sub-total				**74,000.00**
	Operating Expenses				
1	Printing costs	170	N/A	10.00	1,700.00
2	Photocopying	700	N/A	3.00	2,100.00
3	Binding	6	N/A	120.00	720.00
4	Airtime - data & voice	4	N/A	1,000.00	4,000.00
	Sub-total				**8,520.00**
	Supplies				
1	USB Drive 16GB	1	N/A	700.00	700.00
2	External hard disk drive	1	N/A	9,500.00	9,500.00
3	A4 printing papers	3	N/A	500.00	1,500.00
4	HB Pencil	6	N/A	20.00	120.00
5	Ball Pens	10	N/A	25.00	250.00
6	Marker pen	4	N/A	70.00	280.00
7	Stapler	1	N/A	500.00	500.00
8	Staple pins- pack	1	N/A	250.00	250.00
9	Paper punch	1	N/A	500.00	500.00
10	A4 Fool scaps- rim	1	N/A	400.00	400.00
	Sub-total				**14,000**
	Transport Costs				
1	Transport to Kenyatta National Hospital	1	15	500.00	**7,500.00**
	Total				**146,020.00**
	Plus 10% contingency				14,602.00
	Grand Total				**160,622.00**

Appendix II: Timeline of study activities

Timeline of Activities - Prevalence of drug manipulation to obtain prescribed dose in the paediatric inpatient units study																
			Month													
	Task	**Duration**	**Oct 2015**	**Nov 2015**	**Dec 2015**	**Jan 2016**	**Feb 2016**	**Mar 2016**	**Apr 2016**	**May 2016**	**Jun 2016**	**Jul 2016**	**Aug 2016**	**Sept 2016**	**Oct 2016**	**Nov 2016**
PREPARATION PHASE																
1	Research proposal preparation	4 months														
2	Ethical Approval	6 – 12 weeks														
DATA COLLECTION, ANALYSIS & REPORT WRITE UP																
1	Training of research assistants	2 days														
2	Pre-test of data collection tool	2 days														
3	Data collection	4 weeks														
4	Data analysis	2 weeks														
5	Report write up	3 months														
6	Project defense	2 months														
7	Final report submission	1 month														

Appendix III: Participant information sheet and informed consent form for observation

PREVALENCE OF DRUG MANIPULATION TO OBTAIN REQUIRED DOSE IN THE PAEDIATRIC IN-PATIENT UNITS IN KENYATTA NATIONAL HOSPITAL

PARTICIPANT INFORMATION SHEET AND INFORMED CONSENT FORM FOR OBSERVATION OF DRUG ADMINISTRATION IN THE PAEDIATRIC INPATIENT UNITS

A. Introduction

.....

(Name of investigator/research assistant)

is carrying out a study in the paediatric inpatient units/wards in Kenyatta National Hospital. The study will be looking at medicines that are changed or manipulated from the original form by either nursing staff, registered clinical officers or medical doctors to be able to get the prescribed dose before administering the medicine to a child. Manipulation means practices such as tablet splitting, tablet crushing and dissolving of resulting powder in liquid, opening of capsules, measurement of very small volumes of injections or oral liquids.

B. Purpose of study

The aim of the study is to determine how common the practice of manipulation is and how it is done in the paediatric inpatient units in Kenyatta National Hospital. In addition, we shall be able to identify the drugs that are commonly manipulated. The information that we shall obtain, will be used to come up with a policy and standard procedures for manipulation of drugs in the hospital, review of the hospital formulary, change of prescribing practices and identify drugs that should be sourced that are appropriate and easy to use in children.

C. Study procedures/ what will the study involve?

The study will involve identification of new admissions in each ward every week and then observing the nursing staff, registered clinical officer or medical doctor as they administer medicines to these patients during the drug round. During observation, the investigator will be looking for medicines that have to be manipulated or changed from the original form dispensed to get the prescribed dose before giving it to the patient. The investigator will also note down details regarding the medicines given and the patient.

D. What is the study duration?
The study will be conducted over 3 weeks after which the obtained data will be analyzed and a report written.

E. Your participation is voluntary
Your participation in this study is voluntary. You may refuse to participate or withdraw from being observed at any time without any consequence.

F. Will my taking part in this study be kept confidential?
During observation of medicines administration, your name and other personal details will not be recorded. We shall only record the drugs being administered and what happens during administration of the drug. Any information collected during the study will be kept confidential and only accessible to the investigator. Your participation in the study will not be disclosed.

G. What are the benefits of the study?
The study will assist in obtaining information that will be used to improve medicines use in the paediatric inpatient units and also reduce any medication errors and improve patient safety.

H. What are the risks of the study?
There could be a potential for loss of confidentiality, however during observation, your name and other personal details will not be recorded on the data collection form.

I. Who do I contact if I have questions about the study?
If you have any questions or desire further information about this study before or during participation, you can contact the following persons:

Investigator:
Dr. Hilda Nderitu
Postgraduate Diploma in Research Methodology Student▫
Institute of Tropical Infectious Disease (UNITID), University of Nairobi
Telephone Contact: 0722 234 852

Project supervisors:
Dr. Kefa O. Bosire
Department of Pharmacology & Pharmacognosy

University of Nairobi
Telephone Contact: 0733 241332

Dr. Irene Weru
Clinical Pharmacist - Kenyatta National Hospital
Telephone Contact:0732 490240

J. Who do I contact if I have any questions or concerns about being observed during the study?

If you have any concerns about participation during the study, you can contact the *Kenyatta National Hospital - University of Nairobi Ethics and Research Committee Secretary on 020-2726300 ext.44102, e-mail address uonknh_erc@uonbi.ac.ke*

CONSENT STATEMENT

By signing this form, I declare that I have read and understood this consent form and that I freely give my consent to be observed.

I have had sufficient time to consider the information provided and to ask for advice if necessary.

I have had the opportunity to ask questions and have received satisfactory responses to my questions.

I understand that all of the information collected during observation will be kept confidential and that the results will only be used for purposes of the study.

I understand that my agreement to be observed is voluntary and that I am completely free to refuse to be observed or to withdraw from being observed at any time without any consequences.

I understand that I am not waiving any of my legal rights as a result of signing this consent form.

I understand that there is no guarantee that this study will provide any benefits to me

I have been told that I will receive a dated and signed copy of this form.

.....	.....	…….....
Name	Signature	Date
.....	.....	.....
Investigator/designate	Signature	Date

Draft Version 2: *20/10/2015*

Appendix IV: Data collection tool

DRUG MANIPULATION OBSERVATION FORM

Date of Observation:……../……/…… **Study Number: ……**

Age of patient:……..... **Gender:☐Male ☐Female**

Diagnosis:……

DRUG ADMINISTRATIONS OBSERVED						
No	**Drug**	**Dosage form**	**Route of Administration**	**Dose**	**Manipulation YES or NO?**	**Type of manipulation**
1.	Name: Drug Schedule: ☐ A ☐ B ☐ C ☐ D ☐ E ☐ F ☐ G ☐ H ☐ J-A ☐J-B ☐ K ☐ L ☐ M ☐ N ☐ P ☐ R ☐ S ☐ T ☐ V ☐ U	☐ P.O Susp ☐ P.O Liq ☐ Tab ☐ Cap ☐ Inj Liq ☐ Inj powd ☐ Supp ☐ Sachet ☐ Nebs ☐ Drops ☐ Liquid	☐ P.O ☐ I.M ☐ I.V ☐ S.C ☐ SL ☐ P.R ☐ Inh ☐ Topical ☐ Eye ☐ Ear	____ (Qty) ____ (Units)	☐ Yes ☐ No	☐ Tab segmentation & dispersion ☐ Tab segmentation ☐ Tab crushing & dispersion ☐ Cap opening ☐ Cap opening & dispersion ☐ Supp segmentation ☐ P.O vol <0.2mls ☐ P.O vol 0.2 – 0.1 mls ☐ IV vol <0.2mls ☐ IV vol 0.2 – 0.1 mls ☐ Manipulation of Nebs ☐ Manipulation of enema ☐ Other (specify) …… …… ……
2.	Name:	☐ P.O Susp ☐ P.O Liq	☐ P.O ☐ I.M	____ (Qty)	☐ Yes	☐ Tab segmentation & dispersion ☐ Tab segmentation

DRUG ADMINISTRATIONS OBSERVED						
No	**Drug**	**Dosage form**	**Route of Administration**	**Dose**	**Manipulation YES or NO?**	**Type of manipulation**
	Drug Schedule: ☐ A ☐ B ☐ C ☐ D ☐ E ☐ F ☐ G ☐ H ☐ J-A ☐J-B ☐ K ☐L ☐ M ☐ N ☐ P ☐ R ☐ S ☐ T ☐ V ☐ U	☐ Tab ☐ Cap ☐ Inj Liq ☐ Inj powd ☐ Supp ☐ Sachet ☐ Nebs ☐ Drops ☐ Liquid	☐ I.V ☐ S.C ☐ SL ☐ P.R ☐ Inh ☐ Topical ☐ Eye ☐ Ear	____ (Units)	☐ No	☐ Tab crushing & dispersion ☐ Cap opening ☐ Cap opening & dispersion ☐ Supp segmentation ☐ P.O vol <0.2mls ☐ P.O vol 0.2 – 0.1 mls ☐ IV vol <0.2mls ☐ IV vol 0.2 – 0.1 mls ☐ Manipulation of Nebs ☐ Manipulation of enema ☐ Other (specify) …… …… ……
3.	Name: Drug Schedule: ☐ A ☐ B ☐ C ☐ D ☐ E ☐ F ☐ G ☐ H ☐ J-A ☐J-B ☐ K ☐L ☐ M ☐ N ☐ P ☐	☐ P.O Susp ☐ P.O Liq ☐ Tab ☐ Cap ☐ Inj Liq ☐ Inj powd ☐ Supp ☐ Sachet ☐ Nebs ☐ Drops ☐ Liquid	☐ P.O ☐ I.M ☐ I.V ☐ S.C ☐ SL ☐ P.R ☐ Inh ☐ Topical ☐ Eye ☐ Ear	____ (Qty) ____ (Units)	☐ Yes ☐ No	☐ Tab segmentation & dispersion ☐ Tab segmentation ☐ Tab crushing & dispersion ☐ Cap opening ☐ Cap opening & dispersion ☐ Supp segmentation ☐ P.O vol <0.2mls ☐ P.O vol 0.2 – 0.1 mls ☐ IV vol <0.2mls ☐ IV vol 0.2 – 0.1 mls ☐ Manipulation of Nebs ☐ Manipulation of enema ☐ Other (specify) …… ……

DRUG ADMINISTRATIONS OBSERVED						
No	**Drug**	**Dosage form**	**Route of Administration**	**Dose**	**Manipulation YES or NO?**	**Type of manipulation**
	R ☐ S ☐ T ☐ V ☐ U					……
4.	Name: Drug Schedule: ☐ A ☐ B ☐ C ☐ D ☐ E ☐ F ☐ G ☐ H ☐ J-A ☐J-B ☐ K ☐L ☐ M ☐ N ☐ P ☐ R ☐ S ☐ T ☐ V ☐ U	☐ P.O Susp ☐ P.O Liq ☐ Tab ☐ Cap ☐ Inj Liq ☐ Inj powd ☐ Supp ☐ Sachet ☐ Nebs ☐ Drops ☐ Liquid	☐ P.O ☐ I.M ☐ I.V ☐ S.C ☐ SL ☐ P.R ☐ Inh ☐ Topical ☐ Eye ☐ Ear	____ (Qty) ____ (Units)	☐ Yes ☐ No	☐ Tab segmentation & dispersion ☐ Tab segmentation ☐ Tab crushing & dispersion ☐ Cap opening ☐ Cap opening & dispersion ☐ Supp segmentation ☐ P.O vol <0.2mls ☐ P.O vol 0.2 – 0.1 mls ☐ IV vol <0.2mls ☐ IV vol 0.2 – 0.1 mls ☐ Manipulation of Nebs ☐ Manipulation of enema ☐ Other (specify) …… …… ……
5.	Name:	☐ P.O Susp ☐ P.O Liq ☐ Tab ☐ Cap ☐ Inj Liq ☐ Inj powd ☐ Supp ☐ Sachet ☐ Nebs ☐ Drops ☐ Liquid	☐ P.O ☐ I.M ☐ I.V ☐ S.C ☐ SL ☐ P.R ☐ Inh ☐ Topical ☐ Eye ☐ Ear	____ (Qty) ____ (Units)	☐ Yes ☐ No	☐ Tab segmentation & dispersion ☐ Tab segmentation ☐ Tab crushing & dispersion ☐ Cap opening ☐ Cap opening & dispersion ☐ Supp segmentation ☐ P.O vol <0.2mls ☐ P.O vol 0.2 – 0.1 mls ☐ IV vol <0.2mls ☐ IV vol 0.2 – 0.1 mls ☐ Manipulation of Nebs

DRUG ADMINISTRATIONS OBSERVED						
No	**Drug**	**Dosage form**	**Route of Administration**	**Dose**	**Manipulation YES or NO?**	**Type of manipulation**
	Drug Schedule: ☐ A ☐ B ☐ C ☐ D ☐ E ☐ F ☐ G ☐ H ☐ J-A ☐J-B ☐ K ☐L ☐ M ☐ N ☐ P ☐ R ☐ S ☐ T ☐ V ☐ U					☐ Manipulation of enema ☐ Other (specify) …… …… ……
6.	Name: Drug Schedule: ☐ A ☐ B ☐ C ☐ D ☐ E ☐ F ☐ G ☐ H ☐ J-A ☐J-B ☐ K ☐L ☐ M ☐ N ☐ P ☐ R ☐ S ☐ T ☐ V ☐ U	☐ P.O Susp ☐ P.O Liq ☐ Tab ☐ Cap ☐ Inj Liq ☐ Inj powd ☐ Supp ☐ Sachet ☐ Nebs ☐ Drops ☐ Liquid	☐ P.O ☐ I.M ☐ I.V ☐ S.C ☐ SL ☐ P.R ☐ Inh ☐ Topical ☐ Eye ☐ Ear	____ (Qty) ____ (Units)	☐ Yes ☐ No	☐ Tab segmentation & dispersion ☐ Tab segmentation ☐ Tab crushing & dispersion ☐ Cap opening ☐ Cap opening & dispersion ☐ Supp segmentation ☐ P.O vol <0.2mls ☐ P.O vol 0.2 – 0.1 mls ☐ IV vol <0.2mls ☐ IV vol 0.2 – 0.1 mls ☐ Manipulation of Nebs ☐ Manipulation of enema ☐ Other (specify) …… …… ……
7.	Name:	☐ P.O Susp ☐ P.O Liq ☐ Tab ☐ Cap ☐ Inj Liq ☐ Inj powd ☐ Supp ☐ Sachet	☐ P.O ☐ I.M ☐ I.V ☐ S.C ☐ SL ☐ P.R ☐ Inh ☐ Topical	____ (Qty) ____ (Units)	☐ Yes ☐ No	☐ Tab segmentation & dispersion ☐ Tab segmentation ☐ Tab crushing & dispersion ☐ Cap opening ☐ Cap opening & dispersion ☐ Supp segmentation ☐ P.O vol <0.2mls ☐ P.O vol 0.2 – 0.1 mls

DRUG ADMINISTRATIONS OBSERVED						
No	**Drug**	**Dosage form**	**Route of Administration**	**Dose**	**Manipulation YES or NO?**	**Type of manipulation**
	Drug Schedule: ☐ A ☐ B ☐ C ☐ D ☐ E ☐ F ☐ G ☐ H ☐ J-A ☐J-B ☐ K ☐L ☐ M ☐ N ☐ P ☐ R ☐ S ☐ T ☐ V ☐ U	☐ Nebs ☐ Drops ☐ Liquid	☐ Eye ☐ Ear			☐ IV vol <0.2mls ☐ IV vol 0.2 – 0.1 mls ☐ Manipulation of Nebs ☐ Manipulation of enema ☐ Other (specify) …… …… ……
8.	Name: Drug Schedule: ☐ A ☐ B ☐ C ☐ D ☐ E ☐ F ☐ G ☐ H ☐ J-A ☐J-B ☐ K ☐L ☐ M ☐ N ☐ P ☐ R ☐ S ☐ T ☐ V ☐ U	☐ P.O Susp ☐ P.O Liq ☐ Tab ☐ Cap ☐ Inj Liq ☐ Inj powd ☐ Supp ☐ Sachet ☐ Nebs ☐ Drops ☐ Liquid	☐ P.O ☐ I.M ☐ I.V ☐ S.C ☐ SL ☐ P.R ☐ Inh ☐ Topical ☐ Eye ☐ Ear	____ (Qty) ____ (Units)	☐ Yes ☐ No	☐ Tab segmentation & dispersion ☐ Tab segmentation ☐ Tab crushing & dispersion ☐ Cap opening ☐ Cap opening & dispersion ☐ Supp segmentation ☐ P.O vol <0.2mls ☐ P.O vol 0.2 – 0.1 mls ☐ IV vol <0.2mls ☐ IV vol 0.2 – 0.1 mls ☐ Manipulation of Nebs ☐ Manipulation of enema ☐ Other (specify) …… …… ……
9.	Name:	☐ P.O Susp ☐ P.O Liq ☐ Tab ☐ Cap ☐ Inj Liq	☐ P.O ☐ I.M ☐ I.V ☐ S.C ☐ SL	____ (Qty) ____	☐ Yes ☐ No	☐ Tab segmentation & dispersion ☐ Tab segmentation ☐ Tab crushing & dispersion ☐ Cap opening ☐ Cap opening & dispersion

DRUG ADMINISTRATIONS OBSERVED						
No	**Drug**	**Dosage form**	**Route of Administration**	**Dose**	**Manipulation YES or NO?**	**Type of manipulation**
	Drug Schedule: ☐ A ☐ B ☐ C ☐ D ☐ E ☐ F ☐ G ☐ H ☐ J-A ☐J-B ☐ K ☐L ☐ M ☐ N ☐ P ☐ R ☐ S ☐ T ☐ V ☐ U	☐ Inj powd ☐ Supp ☐ Sachet ☐ Nebs ☐ Drops ☐ Liquid	☐ P.R ☐ Inh ☐ Topical ☐ Eye ☐ Ear	(Units)		☐ Supp segmentation ☐ P.O vol <0.2mls ☐ P.O vol 0.2 – 0.1 mls ☐ IV vol <0.2mls ☐ IV vol 0.2 – 0.1 mls ☐ Manipulation of Nebs ☐ Manipulation of enema ☐ Other (specify) …… …… ……
10.	Name: Drug Schedule: ☐ A ☐ B ☐ C ☐ D ☐ E ☐ F ☐ G ☐ H ☐ J-A ☐J-B ☐ K ☐L ☐ M ☐ N ☐ P ☐ R ☐ S ☐ T ☐ V ☐ U	☐ P.O Susp ☐ P.O Liq ☐ Tab ☐ Cap ☐ Inj Liq ☐ Inj powd ☐ Supp ☐ Sachet ☐ Nebs ☐ Drops ☐ Liquid	☐ P.O ☐ I.M ☐ I.V ☐ S.C ☐ SL ☐ P.R ☐ Inh ☐ Topical ☐ Eye ☐ Ear	____ (Qty) ____ (Units)	☐ Yes ☐ No	☐ Tab segmentation & dispersion ☐ Tab segmentation ☐ Tab crushing & dispersion ☐ Cap opening ☐ Cap opening & dispersion ☐ Supp segmentation ☐ P.O vol <0.2mls ☐ P.O vol 0.2 – 0.1 mls ☐ IV vol <0.2mls ☐ IV vol 0.2 – 0.1 mls ☐ Manipulation of Nebs ☐ Manipulation of enema ☐ Other (specify) …… …… ……

GUIDE TO FILLING DRUG MANIPULATION STUDY OBSERVATION FORM			
Dosage forms			
• P.O Susp – Oral suspension • P.O Liq – Oral liquid • Tab – Tablet	• Inj – Liq – injectable liquid • Inj Powd – Injectable powder	• Cap – capsule • Nebs – Nebuliser solution • Supp – suppository	• Sach - Sachet • Eye oint – Eye ointment • Oint - Ointment
Routes of administration			
• p.o – per oral • i.m – intramuscular	• i.v - intravenous • s.c - subcutaneous	• s.l - sublingual • p.r – per rectal	Inh – inhalation
How to fill in dose; e.g. 500 mg or 1000,000 IU ____ (Qty) ____(Units) = **500** (Qty) **mg** (Units) or **1000,000** (Qty) **IU** (Units)			
Possible manipulations 1. Supp segmentation – segmentation or splitting of a suppository 2. P.O vol <0.2mls – measurement of small oral liquid volumes less than 0.2mls 3. P.O vol 0.2 – 0.1 mls - measurement of small oral liquid volumes between 0.1 and 0.2mls 4. IV vol <0.2mls - measurement of small injectable liquid volumes less than 0.2mls 5. IV vol 0.2 – 0.1 mls - measurement of injectable liquid volumes between 0.2 and 0.1mls 6. Manipulation of nebs – manipulation of nebulizer solution			

Drug Schedules as per the Kenyatta National Hospital Formulary, 2013

Schedule	Drug Class
A	Anaesthetics and other theatre agents
B	Analgesics, antipyretics, Non-steroidal Anti-inflammatory Medicines (NSAIMS), medicines used to treat gout and Disease Modifying Agents in Rheumatoid Disorders (DMARDS)
C	Movement disorder, antiparkinsonism, antiepileptic, antipsychotherapeutic and psychotherapeutic agents
D	Gastrointestinal medicines
E	Medicines affecting blood and cardiovascular medicines
F	Anti-infective medicines-antibacterials

Schedule	Drug Class
G	Other anti-infective medicines
H	Antineoplastic, immunosuppresives and medicines affecting bone metabolism
J-A	Antidotes and other substances used in Poisoning
J-B	Hormones, other endocrine medicines and contraceptives
K	Topical dermatological preparations
L	Opthalmological, ear preparations, nose and oropharynx
M	Medicines acting on the respiratory tract
N	Vitamins and minerals
P	Dialysis solutions
R	Disinfectants and Antiseptics
S	Plasma substitutes and Fractions, Solutions Correcting Water and electrolyte Imbalance and Parenteral Nutrition
T	Miscellaneous
V	Immunologicals
U	Oxytocics and Antioxytotics

Appendix V: Research assistant confidentiality agreement

Prevalence of Drug Manipulation to Obtain Required Dose in The Paediatric In-patient Units in Kenyatta National Hospital

This is a study in the paediatric inpatient units/wards in Kenyatta National Hospital looking at medicines that are changed or manipulated from the original form by either the nursing staff, registered clinical officers or medical doctors to be able to get the prescribed dose before administering the medicine to a child.

The study aims at determining how common the practice of manipulation is, how it is done in the paediatric inpatient units and commonly manipulated drugs. The findings will be used to come up with a policy and standard procedures for manipulation of drugs in the hospital, review of the hospital formulary, change of prescribing practices and identify drugs that should be sourced that are appropriate and easy to use in children.

I, ……[name of research assistant], agree to assist the investigator with this study by taking part in:

- Selecting patients from the admissions register in whom drug administration will be observed as outlined
- Obtaining informed consent from either nursing staff, registered clinical officers or medical doctors who will be observed conducting drug administration to selected patients
- Observation of drug administration to selected patients and recording the observations on the drug manipulation observation form
- Review of patient's in-patient prescription form and medical file to abstract required data and record on the drug manipulation observation form
- I agree to maintain full confidentiality when performing the above research tasks.

Specifically, I agree to:

1. Keep all research information shared with me confidential by not discussing or sharing the information in any form or format with anyone other than the investigator.

2. Hold in strictest confidence the identification of any research participant or patient that may be revealed during the course of performing the research tasks.

3. Not make copies of any raw data unless specifically requested to do so by the investigator.

4. Not make copies of the log link unless specifically requested to do so by the investigator

5. Keep the long link secure while it is in my possession.

6. Give, all raw data and link logs to the investigator when I have completed data collection for an inpatient unit.

7. Destroy all research information in any form or format that is not returnable to the investigator upon completion of the research tasks.

…….……. ……..……
Name Address Mobile Number

……
Signature Date

…… …… ……
Investigator Signature Date

Investigator: **Dr. Hilda Nderitu**, Postgraduate Diploma in Research Methodology Student. Institute of Tropical and Infectious Disease (UNITID), University of Nairobi. Telephone Contact: 0722 234852

Project supervisors:

Dr. Kefa O. Bosire
Department of Pharmacology & Pharmacognosy
University of Nairobi
Telephone Contact: 0733 241332

Dr. Irene Weru
Clinical Pharmacist
Kenyatta National Hospital
Telephone Contact: 0732 490240

If you have any questions about this study, you can contact the *Kenyatta National Hospital - University of Nairobi Ethics and Research Committee Secretary on 020-2726300 ext.44102, e-mail address uonknh_erc@uonbi.ac.ke*

Appendix VI: Kenyatta National Hospital-University of Nairobi ERC Approval

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

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

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

KENYATTA NATIONAL HOSPITAL APPROVED 13 APR 2016 KNH/UoN-ERC P.O.BOX 20723-00202 NAIROBI

Ref: KNH-ERC/A/129

13th April, 2016

Dr. Hilda E. W. Nderitu
Reg. No. W61/74995/2014
Institute of Tropical and Infectious Diseases (UNITID)
College of Health Sciences
University of Nairobi

Dear Dr. Nderitu,

Revised Research Proposal: Extent of Drug Manipulation to Obtain Prescribed Dose in the Paediatric Inpatient Units in Kenyatta National Hospital (P97/02/2016)

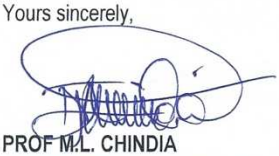
This is to inform you that the KNH- UoN Ethics & Research Committee (KNH-UoN ERC) has reviewed and **approved** your above proposal. The approval period is from 13th April 2016 – 12th April 2017.

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**

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 Director, UNITID, UoN
Supervisors: Dr. Kefa Bosire, Dr. Irene Weru

Appendix VII: KNH research programs study registration certificates

KNH/R&P/FORM/01

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

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

Study Registration Certificate

1. Name of the Principal Investigator/Researcher
   DR. HILDA E. W. NDERITU
2. Email address: nderithuhilda@gmail.com Tel No. 0722-234852
3. Contact person (if different from PI) N/A
4. Email address: N/A Tel No. N/A
5. Study Title
   EXTENT OF DRUG MANIPULATION TO OBTAIN PRESCRIBED DOSE IN THE PAEDIATRIC INPATIENT UNITS IN KENYATTA NATIONAL HOSPITAL.
6. Department where the study will be conducted PAEDIATRICS
   (Please attach copy of Abstract)
7. Endorsed by Research Coordinator of the Department where the study will be conducted.
   Name: ..... Signature ..... Date .....
8. Endorsed by Head of Department where study will be conducted.
   Name: Dr. J. Imwana Signature ..... Date 3/05/16
9. KNH UoN Ethics Research Committee approved study number P97/02/2016 (KNH-ERC/A/129
   (Please attach copy of ERC approval)
10. I HILDA E. W. NDERITU 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 3/05/2016
11. Study Registration number (Dept/Number/Year) Paediatrics / 46 / 2016
    (To be completed by Research and Programs Department)
12. Research and Program Stamp

KENYATTA NATIONAL HOSPITAL H.O.D. RESEARCH & PROGRAMS 04 MAY 2016 NAIROBI

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

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

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

Study Registration Certificate

1. Name of the Principal Investigator/Researcher
   DR. HILDA E. W. NDERITU
2. Email address: nderituhilda@gmail.com Tel No. 0722-234352
3. Contact person (if different from PI) N/A
4. Email address: N/A Tel No. N/A
5. Study Title
   EXTENT OF DRUG MANIPULATION TO OBTAIN PRESCRIBED DOSE IN THE PAEDIATRIC INPATIENT UNITS IN KENYATTA NATIONAL HOSPITAL
6. Department where the study will be conducted SPECIALISED SURGERY
   (Please attach copy of Abstract)
7. Endorsed by Research Coordinator of the Department where the study will be conducted.
   Name: Essan Ja Signature ..... Date 12/7/16
8. Endorsed by Head of Department where study will be conducted.
   Name: ..... Signature ..... Date .....
9. KNH UoN Ethics Research Committee approved study number P97/02/2016 (KNH-ERC/A/129)
   (Please attach copy of ERC approval)
10. I HILDA E. W. NDERITU 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 06/07/2016
11. Study Registration number (Dept/Number/Year) Surgery / 36 / 2016
    (To be completed by Research and Programs Department)
12. Research and Program Stamp

KENYATTA NATIONAL HOSPITAL H.O.D. RESEARCH & PROGRAMS P.O. Box 20723 NAIROBI

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

Appendix VIII: Permission to collect data in paediatrics department

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

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

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

Date: 6th May, 2016

Dr. Hilda E.W. Nderitu
Institute of Tropical and Infectious Diseases [UNITID]
College of Health Sciences
University of Nairobi

Dear Dr. Nderitu

RE: PERMISSION TO COLLECT DATA IN PAEDIATRICS DEPARTMENT

Following approval by the KNH/UON-Ethics & Research Committee for your Research Proposal, this is to inform you that authority has been granted to collect data in **Paediatrics Department** on your study titled ***"Extent of Drug Manipulation to obtain Prescribed dose in the Paediatrics Inpatient Units in Kenyatta National Hospital"***.

Kindly liaise with the Senior Assistant Chief Nurse, Paediatrics for facilitation and forward to this office a report of your findings.

DR. IRENE INWANI
ASSISTANT DIRECTOR, PAEDIATRICS

Cc. SACN, Paediatrics

Appendix IX: Approval to conduct a study at the KNH ward 4A

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

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

Ref: KNH/AD/SP-SURG/35/VOL.I

Date: 15th July, 2016

Dr. Hilda Nderitu
Institute of Tropical and Infectious Diseases
UNITID
College of Health Sciences
University of Nairobi

RE: APPROVAL TO CONDUCT A STUDY AT THE KNH WARD 4A

Following approval of your study by the KNH/UoN ERC and completion of the KNH study registration form, permission is hereby granted for you to collect data from Ward 4A at the Kenyatta National Hospital to enable you complete your study on ***"Extent of drug manipulation to obtain prescribed dose in the Paediatric inpatient units Kenyatta National Hospital"***.

Kindly liaise with the Senior Assistant Chief Nurse incharge of Specialized Surgical Services for facilitation. By a copy of this letter, the SACN is informed and requested to facilitate.

Kindly, note that we would like you to forward a copy of the study report to the department after completion of the study.

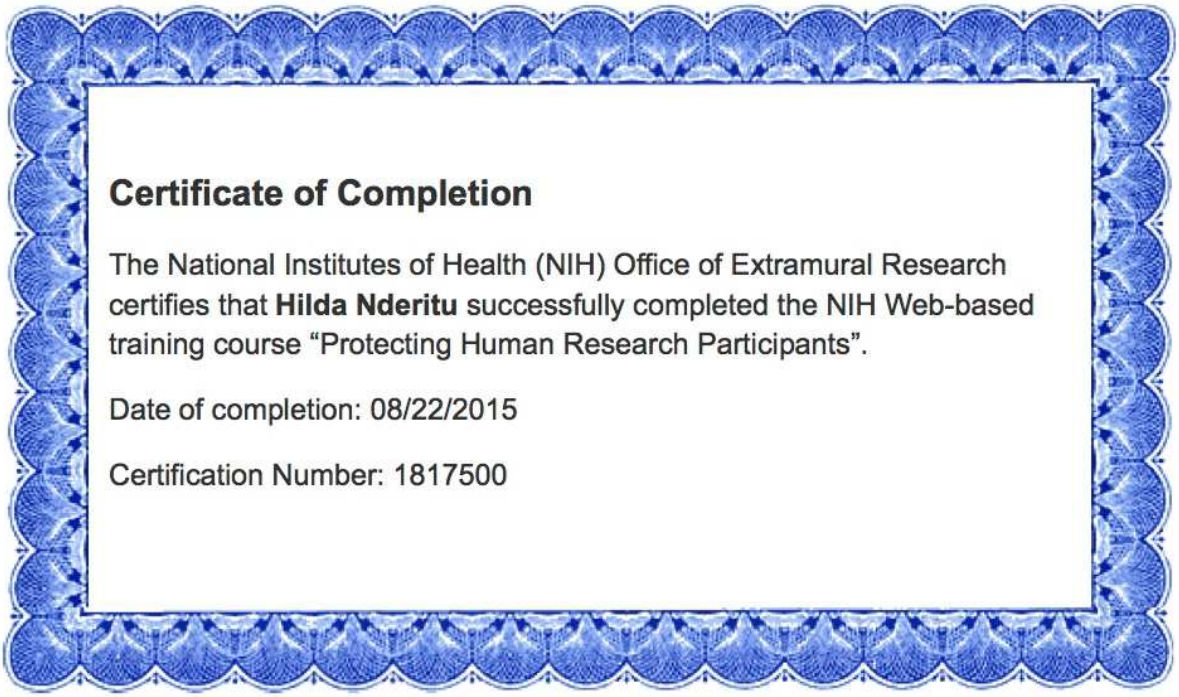
Gacheri
AD/SPECIALIZED SURGERY
KENYATTA NATIONAL HOSPITAL
DR. JOEL LESSAN
AD SPECIALIZED SURGICAL SERVICES

Copy to: SACN, Specialized Surgical Services
KNH

Vision: A world class patient-centered specialized care hospital

ISO 9001: 2008 CERTIFIED

Appendix X: National Institute of Health web-based training course certificates



Certificate of Completion

The National Institutes of Health (NIH) Office of Extramural Research certifies that **Hilda Nderitu** successfully completed the NIH Web-based training course “Protecting Human Research Participants”.

Date of completion: 08/22/2015

Certification Number: 1817500

Certificate of Completion

The National Institutes of Health (NIH) Office of Extramural Research certifies that **jackson onguko** successfully completed the NIH Web-based training course "Protecting Human Research Participants".

Date of completion: 07/08/2016.

Certification Number: 2108747.

Certificate of Completion

The National Institutes of Health (NIH) Office of Extramural Research certifies that **stephen oloo** successfully completed the NIH Web-based training course "Protecting Human Research Participants".

Date of completion: 06/22/2016.

Certification Number: 2098893.