PREVALENCE AND FACTORS ASSOCIATED WITH MEDICATION ERRORS IN PATIENTS WITH CHRONIC KIDNEY DISEASE AT MOI TEACHING AND REFERRAL HOSPITAL

BY

RHODA MARION MUTUNDU GATUTHA

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DECLARATION

DECLARATION BY STUDENT

I declare that this thesis is my original work and has not been presented for a degree in any other university. No part of this thesis may be reproduced without prior written permission of the author and or Moi University.

Rhoda Marion Mutundu Gatutha – SM/PGCP/03/17

Signature:…… Date:…….

DECLARATION BY THE SUPERVISORS

This thesis has been submitted for examination with our approval as university supervisors:

Dr. Zipporah Kamuren

Chair of Department of Pharmacology and Toxicology, Moi University School of Medicine

Signature _____ Date _____

Dr. Cheptinga Kipkurui Philip

Department of Renal Service, Moi Teaching and Referral Hospital

Signature_____ Date_____

Sonak Pastakia, PharmD

Associate Professor, Purdue University College of Pharmacy,

Visiting Lecturer, Moi University School of Medicine, Department of Pharmacology and Toxicology

Signature ___  Date_____23/9/2021__

DEDICATION

I dedicate this research work to the Almighty God by whom all things exist and to my parents Mr. and Mrs. Gatutha who successfully supported me to became the person that I am.

ABSTRACT

Background: Medication errors (MEs) refer to preventable events that may cause inappropriate medication use or patient harm. MEs are a global patient safety issue that cause morbidity, mortality and increase health care costs. A study in Kenya had a 100% prevalence of MEs in Chronic Kidney Disease (CKD) patients (Njeri et al., 2018). CKD is a complex illness requiring frequent contact with various prescribers and several medications which predispose patients to MEs. To avoid medication errors in CKD patients, medication should be prescribed based on estimated glomerular filtration rate (eGFR) and evidence-based recommendation. UpToDate® and Micromedex® are evidence based online medical and drug references which are accepted and used widely by health care professionals.

Objectives: The study determined the prevalence and factors associated with medication over dosage, under dosage, and inappropriate medication based on GFR, concomitant comorbidities and potential drug-drug interactions (DDI) in adult CKD patients at Moi Teaching and Referral Hospital (MTRH).

Methods: A cross-sectional census study was carried on 132 eligible adult patients with CKD stage 3 to 5 for six months. MEs were determined based on Kidney Disease Improving Global Outcomes (KDIGO) guidelines, UpToDate® and Micromedex. Statistical software STATA version 13 SE was used to analyze the data collected on MEs. Association between MEs and demographic, clinical as well as medication variables was assessed using logistic regression models. Odds ratios and the corresponding 95% confidence intervals were reported and P-values < 0.05 considered statistically significant.

Results: The median age was 53.5 (IQR: 39.0, 65.0) years and 55.3% of the population were males. There were 94 (71.2%) patients in CKD stage 5; hypertension was the most common comorbidity at 72.7% and 63.6% of the patients had more than five medications at the time data was collected. Prevalence of MEs included: over dosage 47 (35.6%), under dosage 36 (27.3%), inappropriate medication combination with major DDIs 19 (14.4%) and inappropriate medication prescription 16 (12.1%). Multivariate logistic regression showed that being on more than 5 medications (adjusted odds ratio (AOR)=2.93; 95% confidence interval (CI):1.28-6.71) and hematinic drugs (AOR=2.58; 95% CI: 1.06- 6.28) were independently associated with a higher probability of medication dosage errors. CKD stage 5 (AOR=5.26; 95% CI:1.70-16.29), being on an anti-infective (AOR=4.93; 95% CI:1.29-18.81) and hematinic drugs (AOR= 2.85; 95% CI:1.28-9.54) were independently associated with a higher probability of inappropriate medication.

Conclusions: Medication dosing errors and inappropriate medication were prevalent in CKD adult patients at MTRH. There was higher prevalence of medication dosing errors as compared to inappropriate medication errors. Polypharmacy, hematinic, anti-infectives and severity of CKD were associated with medication errors in general.

Recommendations: To prevent MEs in CKD patients, prescribers should; ensure appropriate medication and dosage prescription by estimation of eGFR, routinely use evidence-based reference tools such as UpToDate in prescribing medication and observe caution when prescribing to patients with more severe CKD, more than five medications, hematinics and anti-infective agents.

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ABBREVIATIONS AND ACRONYMS

ACEI	Angiotensin Converting Enzyme Inhibitor
ARB	Angiotensin Receptor Blocker
CG	Cockcroft- Gault
CKD- EPI	Chronic Kidney Disease Epidemiology
CKD	Chronic Kidney Disease
CO	Clinical Officer
CVD	Cardiovascular disease
DDI	Drug- drug Interactions
DRP	Drug Related Problem
DWR	Daily Ward Round
eGFR	Estimated Glomerular Filtration Rate
EPO	Erythropoietin
ESRD	End Stage Renal Disease
GFR	Glomerular Filtration Rate
GLP- 1	Glucagon- Like Peptide 1 receptor
HIV	Human Immunodeficiency Virus
KDIGO	Kidney Disease Improving Global Outcomes
KNH	Kenyatta National Hospital
MDRD- 4	Modification of Diet in Renal Disease Four Variable
MEs	Medication Errors
MO	Medical Officer
MRP	Medication Related Problem
MTRH	Moi Teaching and Referral Hospital

NCCMERP	National Coordinating Council for Medication Error Reporting and Prevention
NKF –KDOQI	National Kidney Foundation – Kidney Disease Outcomes Quality Initiative
NSAID	Non-Steroidal Anti-inflammatory Drug
PCNE	Pharmaceutical Care Network Europe
PUD	Peptic ulcer Disease
SGLT2	Sodium Glucose Co- Transporter 2
WHO	World Health Organization

OPERATIONAL DEFINITION OF TERMS

Medication Error- "Any preventable event that may cause or lead to inappropriate medication use or patient harm while medication is in the control of a health care professional, patient, or consumer" (NCCMERP, 2001).

Medication Related Problems- Event or a circumstance involving drug therapy that actually or potentially interferes with desired health outcomes.

Polypharmacy- "The concurrent use of multiple medications. Although there is no standard definition, polypharmacy is often defined as the routine use of five or more medications" (WHO, 2019).

Chronic Kidney Disease (CKD) - Abnormalities of kidney structure or function, present for three or more months, with implications for health.

CKD Staging - The classification of CKD based on estimated glomerular filtration rate (eGFR) where CKD stage 3; eGFR is (30-44) ml/min/1.73m^2, CKD stage 4; eGFR is (16-29) ml/min/1.73m^2 and CKD stage 5; eGFR is $\leq$ 15ml/min/1.73m^2.

Inappropriate Medication -The selected drug is improper disregarding a patient's eGFR concomitant comorbidities or drug- drug interactions.

Medication dosage errors – Inappropriate (amount, frequency and duration) of drug based on eGFR over dosage or drug under dosage or presence of both.

Medication over dosage – The selected dose is too high or the regimen too frequent.

Medication under dosage- The selected dose is too low or the regimen not frequent enough.

CHAPTER ONE: INTRODUCTION

1.1 Background

World Health Organization (WHO), in March 2017 launched the third Global Patient Safety Challenge: Medication Without Harm, with aim to reduce medication related errors by 50% by the year 2022 (Sheikh et al., 2017). An adverse drug event is harm arising from medical intervention during clinical practice which may be drug related or drug use-related. It may be categorized into two; adverse drug reaction and medication error. An adverse drug reaction is an unintended harmful response to a drug which occurs at administration at normal dose to humans and is difficult to prevent (Tan et al., 2020). A medication error is defined by the National Coordinating Council for Medication Error Reporting and Prevention (NCC-MERP) as "Any preventable event that may cause inappropriate medication use or patient harm while the medication is in the control of the health provider, patient or consumer. Such events may be related to professional practice, health care products, procedures, and systems, including prescribing, order communication, product labeling, packaging, and nomenclature, compounding, dispensing, distribution, administration, education, monitoring, and use" (NCCMERP,2001). Preventable implies that medication errors can be avoided if they can be clearly identified beforehand. Leape's definition of medication errors as "Any error in the process of prescribing, dispensing or administering medication whether there are adverse consequences or not" Leape (1995) elucidates that medication errors can occur at any stage of the patient treatment. The outcome of many medication errors may have no harm or minimal harm to the patient. However, some medication errors may cause medication related problems (MRPs) and a financial burden to both the patient and a country as a whole.

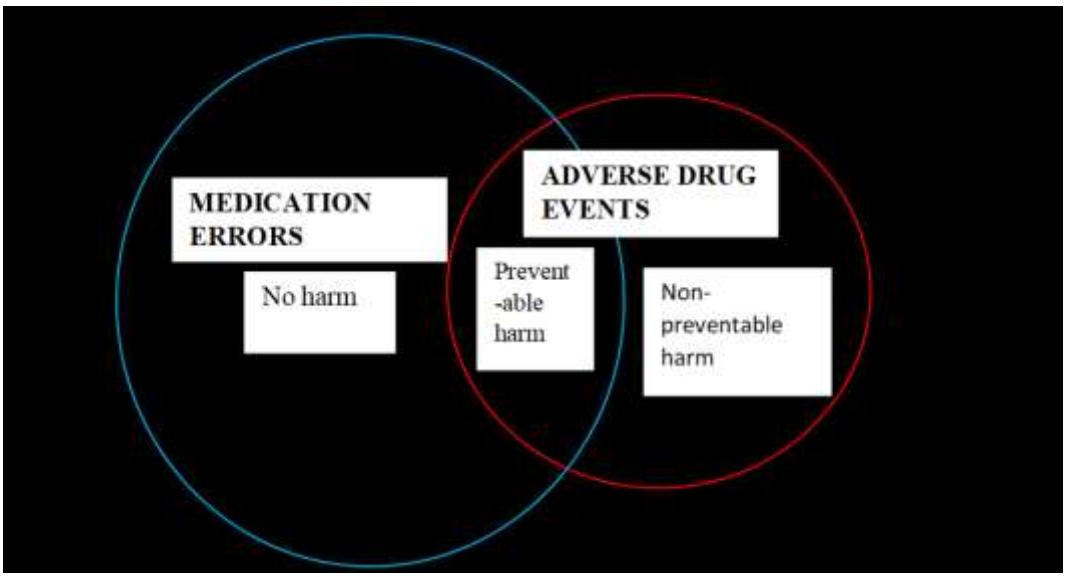


Figure 1.1: Relationship between Medication Errors and Adverse Drug Events

Adapted from Adverse drug events and medication errors: detection and classification methods (Morimoto et al., 2004).

Medication Related Problems (MRPs) are events or circumstances involving drug therapy that actually or potentially interferes with desired health outcomes (PCNE, 2017). The undesired outcome has been further classified to include potential or actual treatment ineffectiveness, treatment adverse events or others related to cost ineffectiveness or unnecessary medication. Factors that may influence medication errors include: polypharmacy, multiple comorbidities, renally eliminated medications, medications with a narrow therapeutic index, patients' characteristics such as literacy and communication skills and health professional's knowledge and experience among others (WHO, 2016). Medication prescribing in CKD patients requires special consideration since the kidney is involved in elimination of a significant number of medications.

Chronic Kidney disease (CKD) is a major global public health problem and a major determinant of poor health outcome namely death from cardiovascular causes or progression to end stage renal disease. A global burden of disease study in 2015

ranked it as the 12th most common cause of death causing 1.1 million deaths worldwide(Hill et al., 2016). There is a striking rise in burden of CKD in low to middle income countries because of rise in obesity and diabetes. CKD alters pharmacokinetic as well as the pharmacodynamics response of various drugs predisposing a patient to diminished medication efficacy and increased medication toxicity. Prevalence of medication errors is high worldwide and is associated with undesirable outcomes particularly in renal disease patients.

Unfortunately, medication errors are prevalent in CKD patients in Kenya with dosing errors as high as 25.26% of all prescribed medicines in Kenyatta National Hospital (KNH) which is a teaching and referral hospital (Macharia, 2016). In a later study at KNH, medication errors were 100% prevalent in the study participants and drug- drug interactions were the most common at 21.8% (Njeri et al., 2018). Pediatrics are also associated with medication errors with dosing errors forming the second highest error at 9% after documentation errors 73% in a study conducted in a county and referral hospital (Khaemba, 2014).

Pharmacists have expertise in medicines hence are equipped with skills to identify medication errors. Pharmaceutical care is a team activity of a pharmacist with other health care professionals offered directly to patients to ensure improved quality use of medicines to achieve desired therapeutic outcomes. One of the clinical pharmacist's role in the team is to identify actual or potential MRPs and come up with ways to resolve them. Hence, pharmaceutical care in CKD patients is important in achieving WHO's third Global Patient Safety Challenge: Medication Without Harm.

1.2 Problem Statement

The problem is that medication errors are adverse drug events that cause negative health outcomes on treatment effectiveness, adverse drug reactions, unnecessary medication and direct cost due to extended hospitalization and broader cost on a country from lost earnings. CKD presents the challenge of a complex health condition since not only do patients present with renal insufficiency at MTRH but it is also commonly associated with various comorbid conditions such as hypertension, diabetes and electrolyte imbalances requiring frequent hospitalization and contact with health care providers and consequently CKD patients are prone to polypharmacy and MRPs. Medication errors in CKD patients may worsen CKD morbidity and increase mortality from cardiovascular diseases and end stage renal disease.

Globally medication errors cost USD 42 billion annually which translates to 0.7% of the global health expenditure that can be saved if medication errors were to be avoided (Aitken et al., 2012). Thus, WHO recognizes the need to reduce medication errors through focus on three priority areas of medication safety that is; high risk situations, polypharmacy and transitions of care. A Cochrane review reported 55.9% of patients were at risk of avoidable medication discrepancies at transitions of care (Redmond et al., 2018). There is need to increase medication safety in medication error prone CKD patients in western Kenya by identifying and resolving potential or actual medication errors that cause MRPs.

1.3 Justification

Studies to assess medication errors in CKD patients in Kenya are scant with one in the largest teaching and referral hospital reporting MRP prevalence of 100% in the study patients. Availability of international, national or hospital guidelines highly influence the prescribing patterns of medications. There are no Kenyan guidelines or MTRH protocols on prescribing in CKD patients hence prescribers refer to international guidelines or clinical knowledge and skills. Kenya does not have a national system for reporting, increasing awareness and prevention of medication errors like that in the United States NCC MERP. From my knowledge, this will be the first study in western Kenya to study prevalence and association of medication errors in CKD patients with the aim to improve their quality of care. This study findings will provide baseline information on the current state of medication errors in CKD patients which will facilitate health care workers to take up the WHO challenge to reduce them by half by the year 2022.

MTRH is in a resource constrained setting in Kenya which has pharmacists providing the invaluable service of medication information and optimization of pharmacotherapy in the wards. This study will increase prescribers and pharmacist's awareness on medication dosing errors and inappropriate medication prescription in CKD patients in order to provide them with safer pharmacological therapy.

1.4 Purpose of Study

The purpose of this study was to identify medication errors related to medication and dose selection in CKD patients in the second largest teaching and referral hospital in Kenya with aim of informing the health care providers on improving medication use and safety in this unique population. The patients in the study were expected to have been prescribed at least one medicine to use. There was a likelihood of multiple medication errors and multiple inappropriate use of the medications. Thus, the term "at least one" was used to aid in framing the research questions and objectives.

1.5 Research Questions

1. What is the prevalence of having at least one medication dosing error in adult CKD patients in MTRH?
2. What is the prevalence of having at least one inappropriate medication use in adult CKD patients in MTRH?
3. What are the factors associated with having at least one medication dosing error in adult CKD patients in MTRH?
4. What are the factors associated with having at least one inappropriate medication use in adult CKD patients in MTRH?

1.6 Objectives

1.6.1 Broad Objective

To determine the prevalence of and factors associated with medication dosing errors and inappropriate medication use in adult CKD patients in MTRH.

1.6.2 Specific Objective

1. To determine the prevalence of having at least one medication dosing error in adult CKD patients in MTRH.
2. To determine the prevalence of having at least one inappropriate medication use in adult CKD patients in MTRH.
3. To assess the factors associated with having at least one medication dosing error in adult CKD patients in MTRH.
4. To assess the factors associated with having at least one inappropriate medication use in adult CKD patients in MTRH.

CHAPTER TWO: LITERATURE REVIEW

2.1 Chronic Kidney Disease Burden

The National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF-KDOQI) 2012 defines Chronic kidney disease (CKD) as "abnormalities of kidney structure or function, present for three or more months, with implications for health" (Inker et al., 2014). CKD can be grouped into five stages based on the estimated Glomerular Filtration Rate (GFR) as illustrated in table 2.1

Table 2.1: Chronic Kidney Disease Stages

STAGE	DESCRIPTION	GFR (ml/min/1.74m^2)
G1	Normal or High	≥ 90
G2	Mild decrease in GFR	60 – 89
G3a	Mild to Moderate decrease in GFR	45 -59
G3b	Moderate to Severe decrease in GFR	30-44
G4	Severe decrease in GFR	16 – 29
G5	Kidney Failure	≤ 15 or on dialysis

Table cited from NKF-KDOQI (Inker et al., 2014).

Chronic kidney disease is an emerging public health problem rated the 12th most common cause of death worldwide causing 1.1 million deaths worldwide according to the 2015 global burden of disease study (Wang et al., 2016). Prevalence of chronic kidney disease is 11-13% with most of the patients developing need for renal replacement therapy and decreased quality of life (Hill et al., 2016). The burden of CKD in the entire Africa continent is 10.1% (Abd ElHafeez et al., 2018) . A systematic review in sub-Saharan Africa which comprises about 85% (974 million) of

Africa's population reports an overall prevalence of CKD of 13.9% and at 4% in Kenya (Stanifer et al., 2014). A three-year prevalence study conducted from 2013 to 2015 from admissions inn a county referral hospital in Kenya reported a progressive increase of CKD prevalence of 0.31% ,0.39% and 0.46% respectively over the three years and an average of 0.41% (41 people per 10,000 population) (Cherono, 2017).

The main risk factors for CKD are diabetes and hypertension (KDIGO, 2012); other risk factors are obesity, heart disease and family history of CKD. Developing countries incidence of CKD is associated with poverty related factors such as poor sanitation which lead to infectious diseases hence glomerulonephritis and interstitial nephritis (Garcia-Garcia & Jha, 2015). Studies have linked apolipoprotein L1 risk variant to increased risk of CKD in African ancestry (Peralta et al., 2016). Food insecurity in low income countries may lead to undernutrition, low birth weight and CKD (Piccoli et al., 2018). In high income countries, food security may lead to overnutrition, obesity, diabetes ,hypertension and CKD (Shariff & Khor, 2005). Recurrent dehydration, heat stress, agrochemicals exposures have a role in development of CKD through tubular atrophy and interstitial fibrosis (Correa-Rotter & García-Trabanino, 2019). Human Immunodeficiency Virus (HIV) infection epidemic in sub-Saharan Africa is also a cause for rising incidence of CKD due to HIV- associated nephropathy (Garcia-Garcia & Jha, 2015). The pooled prevalence of CKD in treatment -naive HIV patients in sub-Saharan Africa is 11.9% (Stanifer et al., 2014). A study in Kibera, Nairobi reported a 17% CKD prevalence in HIV patients (Edwards et al., 2015) whereas an epidemiology study in rural western Kenya reported a 3.7% CKD prevalence in antiretroviral naïve HIV- infected patients (Muiru et al., 2020).

2.2 Medication Use and Dosing Concepts in CKD

Assessment of kidney function is important in determining medication and dose selection in CKD patients. Glomerular Filtration Rate (GFR) is the best overall index of kidney function in healthy and diseased patients however it cannot be measured directly in humans. The most practical method of estimating GFR is by measuring creatinine clearance. Creatinine an endogenous molecule is an appropriate biomarker to estimate renal function since it is produced at a constant rate and excreted by glomerular filtration and tubular secretion Hence, GFR can be assessed by creatinine measurements (measured GFR) from a timed urine collection or serum levels of endogenous filtration markers (estimated Glomerular Filtration (eGFR)) (Levey & Inker, 2016).Timed urine collection measurements are cumbersome and prone to error hence they are no longer recommended routinely to estimate GFR (Stevens et al., 2006).

The Cockcroft- Gault (CG) equation has in the past been the primary method for estimating creatinine clearance (CrCl) in presence of stable renal function (pre dialysis) however it has been shown to be inaccurate in certain populations and the elderly(Flamant et al., 2012). Two newer equations have been studied and validated to estimate glomerular filtration rate (eGFR) one being the 4-variable Modification of Diet in Renal Disease (MDRD) equation and the other Chronic Kidney Disease Epidemiology Collaboration (CKD- EPI) equation. The CKD-EPI has been shown to outperform the MDRD-4 equation in eGFR > 60ml/min/1.73m^2 but both do not appear to be statistically different in use in the elderly. The MDRD-4 equation has been shown to be superior to CG in GFR < 60ml/min/1.73m2 by Poggio et al. (2005) though the recommends use of the CKD-EPI equation for routine evaluation of GFR (Inker et al., 2014). A study in Kenya compared the performance of CG and MDRD

original equation and demonstrated that the MDRD original equation had least bias for African patients (Ndosi E K, 2009). All the three GFR equations use serum creatinine as the biomarker for kidney function. Creatinine levels can be altered by factors affecting its production such as: decreased muscle mass, change in dietary protein and liver disease. Medications such as co-trimoxazole and cimetidine interfere with creatinine tubular secretion while glucocorticoids increase creatinine production hence having a false estimation of renal function (Olyaei & Steffl, 2011). Patient specific factors therefore be should be considered in addition to eGFR when choosing appropriate medication or dose in routine clinical practice.

Two studies, Macharia (2016) and Njeri et al. (2018) have reported the following figures for comorbid conditions in patients with CKD: hypertension between 71.7%-75%, diabetes between 38.3%-40%, anemia between 31.9%-51.7% and Human Immunodeficiency Virus (HIV) infection between 16.7%-20%. Njeri et al. (2018) in-addition reported antihypertensives, anti-infectives, anticoagulants as the most prescribed drugs whereas lipid-lowering agents, hematinics and immunosuppressants were the least prescribed drugs.

In the treatment of hypertension in CKD, Angiotensin Converting Enzyme Inhibitors (ACEI) or angiotensin receptor blockers (ARB) alone or in combination are recommended by the 8th Joint National Committee (JNC) as the first line agents since they reduce proteinuria and progression of CKD and provide long term cardiovascular protection (James et al., 2014). Studies have suggested reduction in dose or discontinuation of ACEI or ARB when GFR decreases above 30% from baseline or severe uncontrolled hyperkalemia (Loutradis et al., 2021). Thiazide diuretics are not effective as diuretics and antihypertensives when the GFR <30mls/min/1.73m^2 but thiazide- like diuretics such as metolazone and loop diuretics remain effective

(KDIGO, 2021). Potassium sparing diuretics should be used with caution due to the risk of hyperkalemia in stage 3 or higher CKD stage (Lazich & Bakris, 2014). Beta blockers have different pharmacokinetics with some accumulating in renal disease such as atenolol, bisoprolol and nadolol hence requiring renal dose adjustments while others are metabolized by the liver such as metoprolol, labetalol, propranolol and carvedilol hence dosing adjustment is not required as noted by the KDOQI (Taler et al., 2013). Calcium channel blockers and alpha-blockers do not require dose adjustments in CKD (Munar & Singh, 2007).

CKD is associated with cardiovascular morbidity and mortality. Diabetic nephropathy which is defined by the presence of proteinuria is a common problem in patients who have poor glycemic control. Severe proteinuria leads to progressive decline in GFR which if untreated leads to end stage renal disease. Traditionally, insulin was used for glycemic control and to reverse glomerular hyper filtration, delay albuminuria and slow GFR hence prevent development of diabetic kidney disease. Newer hypoglycemic agents in diabetic nephropathy namely some sodium- glucose cotransporter 2 (SGLT2) inhibitors: empagliflozin, canagliflozin and glucagon like peptide 1 receptor (GLP-1) agonists namely liraglutide are linked with cardiovascular benefit(Cherney et al., 2014; Heerspink et al., 2017; Marso et al., 2016; Neal et al., 2017). SGLT2 inhibitors which were initially developed as hypoglycemic agents since they have direct action on the kidney reducing tubular glucose reabsorption, also have salutary effects by reduction of renal and cardiovascular risk factors such as weight, albuminuria, blood pressure, intraglomerular pressure and reduce glomerular hyperfiltration. Empagliflozin and canagliflozin require renal dose adjustment and are contraindicated if eGFR< 30ml/min/1.73m^2 and eGFR< 45ml/min/1.73m^2 respectively (ADA, 2018).

The United States, American Diabetic Association (ADA) guidelines state that metformin is contraindicated if eGFR <30ml/min/1.73m^2 Tuttle et al. (2014) and the benefits of continuing metformin should be reassessed when GFR < 45ml/min/1.73m^2. Sulphonylureas require dose adjustment in CKD while glyburide is contraindicated. Meglitinides require renal dose adjustment in eGFR < 30ml/min/1.73m^2 while most dipeptidyl peptidase 4 (DPP-4) inhibitors require renal dose adjustments at eGFR < 50ml/min/1.73m^2 except linagliptin. Thiazolidinediones do not require renal dose adjustments as they are 99% metabolized in the liver (American Diabetes, 2018).

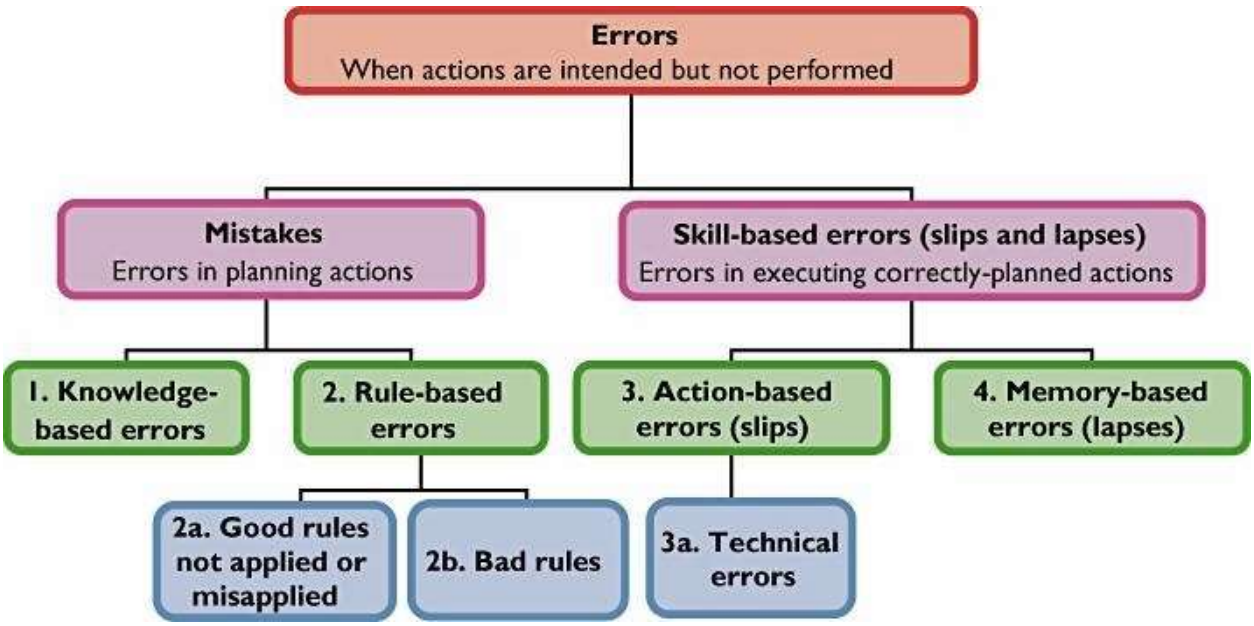
Many antimicrobials are eliminated renally and require dose adjustments. Patterns of antibiotics prescribing in in a tertiary facility in Kenya reported highest prevalence of prescribing in penicillins 46.9% followed by cephalosporins 44.7% and aminoglycosides 26.3% with nitrofurantoin least at 0.6% (Momanyi et al., 2019). Excessive levels of penicillin G, is associated with neurotoxicity reported as seizures or coma hence dose adjustment is required in renal disease (Munar & Singh, 2007). Case reports have identified neurotoxicity with piperacillin in renal disease (Lin et al., 2007). Neurotoxicity has also been reported in the setting of renal impairment in all classes of cephalosporins such as cefazolin, cefuroxime, ceftazidime and cefepime (Grill & Maganti, 2008). Imipenem/cilastatin is associated with increased incidence of seizures in renal dysfunction due to accumulation hence meropenem is the preferred carbapenem in renal disease Lamoth et al. (2009). Tetracyclines have been associated with exacerbation of renal failure in patients with preexisting renal disease by increasing azotemia from amino acid metabolism hence renal dosing is recommended with the exceptions of doxycycline and tigecycline (Shutter; & Akhondi., 2021). Nitrofurantoin can cause peripheral neuritis when its toxic metabolite accumulates in

CKD hence not recommended by manufacturer in creatinine clearance < 60ml/min but recent studies have found it is safe and effective in short term use of acute uncomplicated cystitis eGFR 30-60ml/min/1.73m^2 (Chung & Bouwmeester, 2019; Cunha et al., 2017).

Abnormal lipid metabolism is common in patients with CKD where total and low-density lipoprotein (LDL) are normal but small dense lipoprotein (sdLDL), intermediate density lipoprotein (IDL) and modified LDL which are more atherogenic are increased and contribute to cardiovascular morbidity and mortality (Tsimihodimos et al., 2008). Statins lower death and major cardiovascular events by 20% in non-dialysis CKD patients (Palmer et al., 2014). Kidney Disease Improving Global Outcomes (KDIGO) 2013 guidelines recommend dose reduction of statins if eGFR< 60ml/min/1.73m ^{2} due to reduced renal excretion, increased polypharmacy, and high comorbidity in this population (Wanner & Tonelli, 2014). Both atorvastatin and fluvastatin do not require renal dose adjustment. Caution is advised in use of statins in high doses and when there is a potential for drug-drug interactions in CKD (Kennard & Singer, 2017). In case of drug -drug interactions, statins can be temporarily withheld when co-administered with short duration medications such as antibiotics that may cause increase statins levels or the dose of the statin dose can be reduced or switched to a safer statin in CKD (Wanner & Tonelli, 2014).

2.3 Classification of Medication Errors

Various systems have been used for classification of medication errors to aid in their identification and preventive strategies. A classification system based on psychological approach classifies medication errors into two types; mistakes and skill-based errors. (Aronson, 2009). Mistakes are errors in the planning of an action and may be knowledge based or rule based. Rule based may further be classified as either misapplication of a good rule or application of a bad rule. Skill based errors can be classified into slips and lapses. A slip is an error in performing an action e.g. a transcribing error while a lapse occurs through an erroneous memory. A technical error is a subtype of an action-based error occurs in the event of a failure of a particular skill. The psychological classification theory explains the events rather than merely describing them**.**



Cited from British journal of clinical pharmacology (Aronson, 2009).

Figure 2.1: The Classification of Medical Errors Based On Psychological Approach

The NCC-MERP classification approach classifies errors based on the severity of the outcome. It has four groups and 9 categories of medication errors (A-I) based on: category A-circumstances that may cause error, category (B-D)-errors with no harm, category (E-G)- errors with harm to the patient and category I- errors that cause death (NCC- MERP, 2001).

The Pharmaceutical Care Network Europe (PCNE) version 8.02 classification separates problems from the causes. PCNE defines the problem as "the expected or unexpected event or circumstance that is, or might be wrong, in therapy with drugs". There are 3 primary domains for problems, code (P1-P3). Each potential or real problem has a cause that can be termed as a medication error. The medication errors can be of various types e.g. prescribing errors, drug use errors or administration errors. Several medication errors may cause a problem; there are 8 primary domains for causes, code(C1-C8) as illustrated in table 2 and prescribing errors are illustrated in table 3 (PCNE, 2017). The PCNE classification uses the term "drug" while other classifications may use the term "medicine". A study which used the PCNE version 7 classification system in identifying medication related problems in internal medicine patients in Turkey reported the most common errors to be medication selection errors at 44.78% and dose selection errors at 27.61% (Abunahlah et al., 2018).

Table 2.2: The Pcne V8.02 Classification of Medication Errors

	Code	Primary domains
Problems (also, potential)	**P1**	Treatment effectiveness
	P2	Treatment safety
	P3	Others
Causes (including possible causes for potential problems)	**C1**	**Drug selection**: The cause of the Drug Related Problem (DRP) can be related to the selection of the drug
	C2	**Drug form**: The cause of the DRP is related to the selection of the drug form
	C3	**Dose selection**: The cause of the DRP can be related to the selection of the dosage schedule
	C4	**Treatment duration**: The cause of the DRP is related to the duration of treatment
	C5	**Dispensing:** The cause of the DRP can be related to the logistics of the prescribing and dispensing process
	C6	**Drug use/ process**: The cause of the DRP is related to the way the patient gets the drug administered by a health professional or carer, in spite of proper instructions (on the label)
	C7	**Patient related:** The cause of the DRP can be related to the patient and his behavior (intentional or non-intentional)
	C8	**Others**

Table 2.3: Prescribing Medication Errors Based on PCNE V8.02 System

Primary domain	Code	Cause
1.Drug selection	**C1.1**	Inappropriate drug according to guidelines/formulary
	C1.2	Inappropriate drug (within guidelines but otherwise contra-indicated)
	C1.3	No indication for drug
	C1.4	Inappropriate combination of drugs or drugs and herbal medication
	C1.5	Inappropriate duplication of therapeutic group or active Ingredient
	C1.6	No drug treatment in spite of existing indication
	C1.7	Too many drugs prescribed for indication
2. Drug form	**C2.1**	Inappropriate drug form (for this patient)
3. Dose selection	**C3.1**	Drug dose too low
	C3.2	Drug dose too high
	C3.3	Dosage regimen not frequent enough
	C3.4	Dosage regimen too frequent
	C3.5	Dose timing instructions wrong, unclear or missing
4. Treatment duration	**C4.1**	Duration of treatment too short
	C4.2	Duration of treatment too long

2.4 Factors Associated With Medication Dosing Errors and Inappropriate Medication Use in CKD

Medication dosing errors and inappropriate medication use contribute adversely to therapeutic challenges in inpatients particularly in CKD. Studies are replete with evidence of medication dosing errors from all over the world (Hui et al., 2017; Sah et al., 2014). Few studies to our knowledge have studied the factors associated with these specific MRPs and we found no such study carried out in western Kenya. Knowledge on MRPs predictors would be important in designing and implementing of MRPs eradication strategies.

Medication dosing errors occur in the event of an under dose or overdose of the medication prescribed for a given indication. A study in the United States of America on veteran population showed dosing errors were high in patients older than 85 years, with eGFR < 35ml/min/1.73m^2 (Hanlon et al., 2011). Predictors of inappropriate dosing in an Australian study were advancing age, polypharmacy, comorbid hypertension and diabetes (Khanal et al., 2015). An Iranian study on MRPs in CKD hemodialysis patients reported under dosage among end stage renal disease patients which was attributed to lack of multidisciplinary services by health care team of physicians, nurses, nutritionists and clinical pharmacists who share the goal of preventing chronic disease progression to end stage renal disease and managing CKD associated comorbid conditions (Dlear et al., 2015).

Similar studies done in developing countries for instance an Ethiopian study reported that age over 60 years was associated with medication errors while patients' gender and stage of renal disease are not associated with medication errors in CKD (Getachew, Tadesse, & Shibeshi, 2015). A Pakistani study on patterns and predictors

of medication dosing errors in CKD patients reported that among the 34% drugs that required dosage adjustment only 41.8% were correctly adjusted. Predictors of dosing errors were CKD stage 4 and stage 5, prescribed medicines ≥ 5 and the presence of comorbidity such as hypertension (Saleem & Masood, 2016).

Studies in the largest teaching and referral hospital in Kenya KNH, also report prevalence of MRP in CKD patients. One study reported a 100% overall prevalence of MRPs in CKD patients with drug-drug interactions being the commonest at 21.8% and over dosage and sub therapeutic dosage being the least at 7.4 % and 7% respectively. Predictors of MRPs identified in this study were stage of CKD, polypharmacy and presence of comorbidities. Anti-infectives were the most overdosed medicines while hematinics were the most under dosed medicines (Njeri et al., 2018). An earlier study in the same hospital on patterns of antimicrobials and dose adjustment in CKD patients reported only 27.7% adjusted doses out of 59.9% dosing adjustment needs. Meropenem, amoxicillin clavulanic acid, lamivudine and clarithromycin were the main overdosed anti-infectives (Onyango J, 2011). Inappropriate medication use occurs when an unsuitable drug is selected disregarding a patients eGFR, clinical guidelines, concomitant comorbidities or drug- drug interactions. A Brazilian study on drug-drug interactions (DDI) in CKD patients identified 74.9 % potential DDI of all the prescriptions. Of the actual DDI diagnosed 0.4% were contraindicated drugs,16.8% DDI were of serious severity ,76.9% of moderate severity and of 5.9% low severity. Risk factors for DDIs identified in this study were obesity, hypertension, diabetes and advanced stage of CKD(Marquito et al., 2014). A Pakistan study reported potential DDI in nearly 78.5% CKD patients of which 13.4% were contraindicated, 27.8% were major ,41.1% moderate and 60.8%

minor. These potential DDIs were strongly associated with polypharmacy ≥ 5, age < 60years and lengthy hospital stay (Saleem et al, 2017).

Studies in Kenya on CKD patients have reported prevalence of significant drug-drug Interactions (DDI) ranging between 79.13% and 98.3% of the study participants with severe DDI requiring discontinuation of drug ranging between 1.4% and 28.3% (Macharia, 2016; Njeri et al., 2018). The later study reported DDI as the commonest MRP at a prevalence of 21.8% and identified improper drug selection at a prevalence 12.2% which was mainly due to non-inclusion of an ACEI or ARB for management of hypertension accompanied by proteinuria.

2.5 Summary

Medication errors have been reported to be prevalent globally and impact on the quality of care delivered to patients. Chronic kidney disease alters the pharmacokinetics and pharmacodynamics of drugs hence this type of patients is at a high risk of medication and dose selection errors. There is a knowledge gap on the prevalence and factors associated with medication errors in chronic kidney disease patients at MTRH.

CHAPTER THREE: METHODOLOGY

3.1 Research Design

This was a cross-sectional study design since it was cost effective and provided a snapshot on descriptive and analytical information to our research questions. It entailed a questionnaire to the participants and a detailed one-time review of treatment sheets, laboratory data and medical files.

3.2 Study Site

The study was conducted at Moi Teaching and Referral Hospital (MTRH) internal medicine wards and outpatient renal clinic. MTRH is the second largest referral hospital in Kenya located in Eldoret town Uasin Gishu County. MTRH serves residents of western Kenya, parts of Eastern Uganda and Southern Sudan a total population of approximately 24 million (MTRH, 2018). The hospital has a bed capacity of over 900 with about 200 bed capacity in the internal medicine wards. The hospital functions as a level six hospital offering inpatient, outpatient and specialized health services.

3.3 Study Population

The study involved chronic kidney disease stage 3 to 5 patients aged 18 years and above hospitalized and attending outpatient renal clinic in MTRH in March 2019 to August 2019.

3.4 Eligibility Criteria

3.4.1 Inclusion Criteria

i. Patients over 18years with a confirmed diagnosis of CKD from renal ultrasound or ≥ 3 months renal insufficiency.
ii. For those hospitalized, admission should have been at least 24hrs to provide sufficient time for diagnosis and prescription of medication.

iii. Patients who were attending outpatient renal clinic.

iv. Patients who had serum creatinine measurement in their files.

v. Patients whose estimated Glomerular Filtration Rate (eGFR) < 60ml/min/1.73m^2.

vi. Patient who gave informed consent to participate in the study.

3.4.2 Exclusion Criteria

i. Patients who have had a previous renal transplant.

ii. Patients attending renal clinic as first visit since they had no recent serum creatinine measurements and it would have been difficult to establish diagnosis of CKD.

3.5 Participant Recruitment

A review of MTRH hospital records revealed a total of 150 patients with both acute kidney injury and chronic kidney disease had been hospitalized over a period of six months during writing of the proposal. A census was undertaken over six months to recruit all patients who met the eligibility criteria for the study and ensure adequate patient numbers for the study objectives. In total, one hundred and thirty-two patients were recruited on the study.

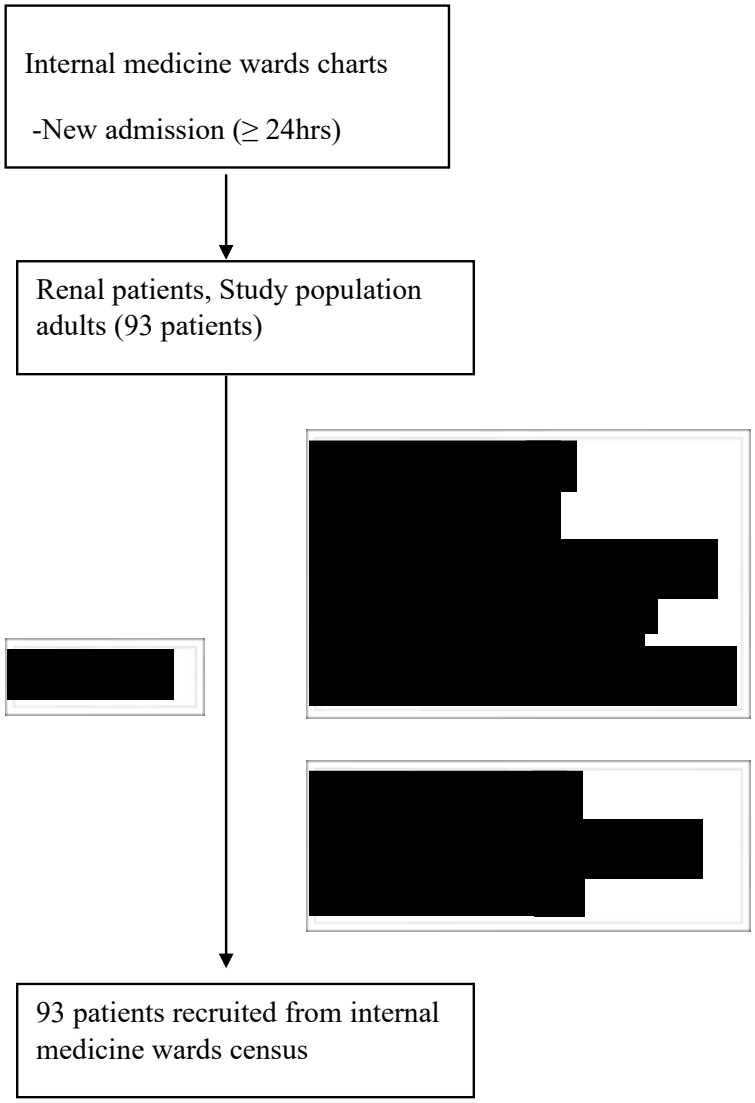


Figure 3.5.1: Participant Recruitment from Internal Medicine Wards Flow Chart

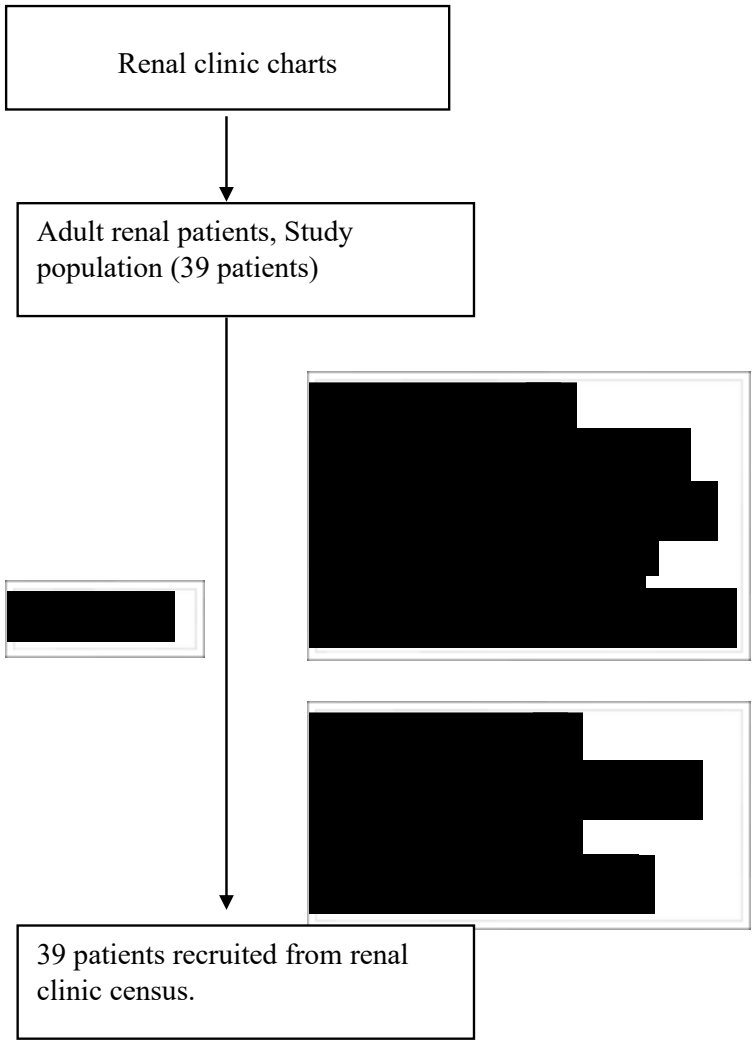


Figure 3.2: Participant Recruitment from Renal Clinic Flow Chart

3.6 Study Procedure

A list of new hospital admissions was obtained from the nurse in charges of the internal medicine male and female wards after the daily ward rounds were over to avoid disrupting the round. The list was used to obtain files from the records officer in the wards and assess patients for potential recruitment to the study. Files of patients attending the outpatient renal clinic on Wednesday (the day when adult renal patients with no renal transplant are scheduled to visit the clinic) were obtained from the records officer and assessed for study eligibility. Patients who met the eligibility criteria were approached after the ward round and renal clinic and requested for informed consent before enrollment to the study. Observation was done for all of the medications prescribed to the study patients in the treatment sheets and medication files. Data was collected at only one instance on day two of admission for hospitalized patients and after the renal clinic visit for outpatient patients. The research investigator administered a structured questionnaire to the enrolled patients to obtain their best past medical history and a structured form was used to review the patient files for relevant clinical data for the study and assess the presence of medication errors. Medication errors were determined based on the eGFR, KDIGO guidelines and UpToDate and Micromedex online references.

The UpToDate system is an evidence-based clinical resource. It includes a collection of medical and patient information, access to Lexi-comp drug monographs and drug-to-drug interactions, and a number of medical calculators. Micromedex is also an evidence-based, multi-database drug search engine that provides summary and in-depth information for drugs, diseases, toxicology, and alternative medicine. It includes clinical tools for drug Interactions, and clinical calculators.

The eGFR was calculated using the CKD- EPI equation on the UpToDate® electronic calculator.

CKD EPI equation for estimated GFR (ml/min/1.73m$^{2)}$

eGFR = 141*min (serum creatinine/kappa,1) ^{alpha} *max (serum creatinine/kappa,1) $^{1.209}$*0.993^{Age}* Sex* Race.

Race = 1.159 if black or 1 if another race.

For female the following values are used; sex =1.018, alpha = -0.329, kappa= 0.7

For male the following values are used; sex= 1, alpha= -0.411, kappa= 0.9

3.7 Study Variables

The PCNE version 8.02 classification system was used to categorize the medication errors under dose and medication selection. In this study, only items coded (C1.1, C1.2, C3.1, C3.2, C3.3 and C3.4) was used to identify the medication errors (PCNE, 2017).

The primary outcome variables for this study were over dosage and under dosage based on amount and frequency of medication. The secondary outcome variables were inappropriate medication based on CKD stage, concomitant comorbidities and drug-drug interactions.

The following predictor variables were studied;

i. Patient demographic characteristics (age and sex)
ii. CKD stage 3, 4 and 5
iii. Patient comorbidities
iv. Number of medications prescribed per patient
v. Classification of the medications prescribed
vi. Cadre of the health care prescriber

3.8 Research Instruments

i. Screening and eligibility form which was used to guide in enrolling eligible patients to the study. (see appendix 1)

ii. Information and consent declaration form which was used to provide description and purpose of the study to potential participants and explain why they were selected to participate. (see appendix 2)

iii. Data collection form comprised an interviewer administered structured questionnaire to obtain the participants best past medical history and a structured medical file review form to obtain all data relevant to the study in a systematic way. (see appendix 3)

3.9 Data Management

Data captured using the questionnaires and those abstracted from the patient files was entered into an electronic database created using Microsoft Access. The data was de-identified of any personal identifying information prior to entry into an electronic database and each participant record was assigned a unique study number which maintained the anonymity of the data collected during the entire study. Upon completion of data entry and data cleaning the data was backed up using external drives that were encrypted and kept in separate locations to cushion against data loss.

Hard copy data collection forms were stored under lock and key accessible only to the principal research investigator. Data collected was shared with the study research supervisors and data analysts upon request during study consultation.

3.10 Data Analysis and Presentation

Data analysis was done using STATA version 13 SE (College Station, Texas 77845 USA) and results were presented using tables and graphs. Descriptive statistics such as percentages, median as well as interquartile range were used to summarize variables. Categorical variables were summarized using frequencies and the corresponding percentages. Continuous variables were assessed for normality assumptions using graphical methods including histograms and quantile probability plots and using Shapiro-Wilks test for normality. The Gaussian (or normality) assumptions were violated for the continuous variables thus they were summarized using median and the corresponding interquartile range (IQR).

Association between medication dosage errors and independent categorical variables was assessed using logistic regression models. The associated odds ratios (OR) and the corresponding 95% confidence intervals (95% CI) were reported. The associated p-values were also reported. The same approach was used to determine the factors associated with inappropriate drug use. The associations were considered present or statistically significant if the 95% CI did not encompass the null value of 1 or if the p-value was < 0.05.

The variables established to be significantly associated with the outcome in the bivariate step were included in the multivariate logistic regression model. Back selection method was used to select the variables to retain in the model where the variables with the largest non-significant p-value > 0.05 were dropped from the model. The prescriber of the drugs was retained in the model despite remaining statistically non-significant in order to remove the variance that could result because of the different professional levels among the prescribers.

3.11 Ethical Consideration

Ethical approval was obtained from the Moi University Institutional Research and Ethics committee prior to commencement of the study. Permission to conduct the study was granted from the MTRH administration as attached on appendix 5. Informed consent was obtained before patients were enrolled into the study from the patients or their care givers. Participants were not exposed to any risks or harm and no extra charges were imposed. Confidentiality of the patients' data was established by giving each patient a unique study number and keeping the hard copy data from the research instruments under lock and key. Soft copy data was kept in a Microsoft excel database and back up information was stored in external hard disks and google drive only accessible to the research investigator.

CHAPTER FOUR: RESULTS

4.1 Demographic and clinical characteristics

One hundred and thirty-two (132) adult CKD patients were recruited for the study during the six-month period and majority were in CKD stage 5 (71.3%). The median age was 53.5 years and males formed slightly higher than half the population (55.3%). Most patients were recruited from the internal medicine wards because the outpatient adult renal clinic day was only once a week and patients were recruited on a cumulative basis. Medication allergies were generally not known as they were reported by only thirteen patients (9.1%). All the patients had at least one comorbidity; the most prevalent comorbid conditions were hypertension 72.7%, electrolyte disturbances 61.3% and anemia 47.7%. Hypocalcemia 37.4%, hyperkalemia 30.8% and hyperphosphatemia 21.7% and hypokalemia 4.5% were the major forms of electrolyte imbalance noted. Other diseases defined as non-CKD associated diseases in the patients include: pneumonia, gastroenteritis, urinary tract infections, hepatitis B, bacteremia, malaria, candidiasis, arthritis, prostrate, bladder and pancreatic cancer, nephrotic nephritis, benign prostrate hyperplasia, liver disease, polycystic kidney disease, gout and hypothyroidism. (table 4.1).

4.2 Medication patterns

The most and least prescribed drugs were antihypertensives and anti-lipidemics in 95(72.0%) and 10 (7.6%) respectively. Ten diabetic patients were not on any glucose lowering medication likely due to reduced elimination of endogenous insulin in severe CKD. Other medications were prescribed to manage mainly electrolyte disturbances, vomiting and constipation (table 4.2.1). The antiretroviral treatment regimen used for HIV patients was abacavir, lamivudine combined either with

dolutegravir or efavirenz. The medications per patient ranged between 2-14 in number. Eighty- four (63.6%) of the patients had more than five medications at the time of the study (table 4.2.2).

4.3 Prevalence of medication dosing errors

Medication dosing errors were assessed by comparing the dose (amount and frequency) prescribed and dosing recommendations based on renal clearance by UpToDate and/or Micromedex. An example of medication dosing assessment of metformin is illustrated in appendix 4. Overdosage of drugs was more common than underdosage. Forty- seven (35.6%) patients had at least one overdosed drug while 36 (27.3%) patients had at least one underdosed drug. One patient had three drugs overdosed. Hematinics and antihypertensive agents were drugs frequently under or overdosed in terms of both amount and frequency of administration. Antidiabetic agents were often under-dosed while anti-infective agents often over-dosed (Table 4.3.1). Overall, over half of the patients (53.0%) had at least either one over-dosed or one under-dosed medication (figure 4.3.1). The number of underdosage or overdosage medication dosing errors per patient are illustrated in figure 4.3.2.

4.4 Prevalence of potential drug-drug interactions (DDIs) and inappropriate drugs

Potential DDIs were assessed by listing all the medications prescribed to the patient on the DDI function of UpToDate and/or Micromedex tool and evaluating the severity for the DDI. Generally, DDIs were termed as either minor, moderate or major based on their severity. Minor DDIs do not require any action, while moderate require monitoring for interactions whilst major DDIs require prescribers to consider therapy modification or discontinue treatment. Moderate DDIs formed majority of the DDIs in

93(70.5%) of the patients. Of the nineteen (14.4%) patients with major DDIs, one (0.8%) patient had DDIs from three drugs (table 4.4.1). Inappropriate drugs were assessed by determining the suitability of the prescribed drug based on the patient's clinical status (eGFR and concomitant comorbidities), KDIGO guidelines and UpToDate and Micromedex online references. Prevalence of inappropriate drugs in this study was 12.1%. Majority of the drugs were inappropriate due to the patients low e GFR. There was also an instance of nifedipine use in concomitant heart failure with reduced ejection fraction. Drugs were inappropriately prescribed in 16 patients and folate was the most (7 patients) inappropriately prescribed drug based on eGFR and concomitant comorbidities (table 4.4.2). The composite outcome of inappropriate use and major drug-drug interaction was derived to quantify the magnitude of inappropriate drug use. The results show that 30 (22.7%) had inappropriate drugs. The cadre of the prescriber from the outpatient clinic was adequate but the records from the inpatient files did not reliably indicate the cadre of the prescribers hence most medication was described to have been prescribed during daily ward rounds headed by a registrar or medical officer intern (table 4.4.3).

4.5 Prevalence of omitted drugs

Omitted drugs were assessed when no drug was prescribed for the CKD patient's clinical status and complications as recommended by KDIGO guidelines. Ninety-five patients had one or more recommended drugs omitted including anti-lipidemic agents and drugs used to manage hyperphosphatemia and hyperkalemia (table 4.5)

4.6 Summary of medication errors and potential unresolved medical problems

Up to 90.2% of the patients had at least one medication error (over dosage, under dosage, inappropriate medication, potential DDIs or omitted drug). None of the patients had all the five types of medication errors. The distribution of number of medication errors in the patients showed that over a quarter of the patients were exposed to either one or three number of medication errors. (figure 4.6).

The medication errors may have caused unresolved treatment outcomes. The unresolved medical problems were determined when the desired treatment targets were not attained possibly due to the medication errors observed in the patients. One quarter (25%) of the patients had high blood pressure, 3.7 % had high blood sugar and another 1.5% were anemic at the point of data collection (table 4.7).

4.8 Factors associated with medication errors

The association between medication errors and independent variables were assessed using logistic regression models. Those variables which were significant on bivariate analysis were introduced to multivariate regression. In bivariate regression analysis of medication dosing errors with independent variables, polypharmacy, presence of anemia, and use of hematinic drugs were associated with a higher probability of ending up with a medication dosing error (table 4.7.1, table 4.7.2, table 4.7.3). The multivariate logistic regression model (table 4.7.4) showed that patients having polypharmacy were 2.93 times more likely associated with medication dosing errors compared to those with no polypharmacy (adjusted odds ratio (AOR): 2.93; 95% confidence interval (CI): 1.28- 6.71). Patients taking hematinic drugs were 2.58 times more likely associated with having medication dosing errors compared to those not taking hematinic drugs (AOR: 2.58; 95% CI: 1.06- 6.28).

In bivariate regression analysis of inappropriate medication with independent variables, CKD stage 5 | 5D, presence of other comorbidities, prescription of analgesics, anti- infectives and calcium supplements were associated with higher probability of inappropriate medication (table 4.7.5, table 4.7.6 and table 4.7.7). In multivariate regression analysis findings indicate presence of other comorbidities were 5.26 times more likely associated with inappropriate medication compared to those without other comorbidities (AOR: 5.26; 95% CI: 1.70-16.29), CKD stage 5 | 5D was 4.93 times more associated with inappropriate medication as compared to those in CKD stage 3-4 (AOR: 4.93; 95% CI: 1.29-18.81). Prescription of hematinic and anti-infective drugs were 3.50 and 2.85 times more likely to be associated with inappropriate medication (AOR: 3.50; 95% CI: 1.28-9.54) and (AOR: 2.85; 95% CI: 1.00-8.12) respectively (table 4.7.8). However, these estimates are highly uncertain as indicated by the wide confidence intervals. Other comorbidities in this study also represented a combination of diseases with low individual prevalence. Hence, they should be interpreted with caution.

Table 4.1: Demographic and Clinical Characteristics Of The Study Patients

Characteristic	Median (IQR)	Prevalence, n (%), N=132
Age (years), Median (IQR)	53.5 (39.0, 65.0)	
Range (Min. - Max.)	18.0 - 92.0	
Gender		
Female		59(44.7)
Male		73 (55.3)
CKD staging		
3A		6 (4.5)
3B		7 (5.3)
3D		1 (0.8)
4		22 (16.7)
4D		2 (1.5)
5		60 (45.5)
5D		34 (25.8)
Site		
Clinic		39 (29.5)
Ward		93 (70.5)
Complications and comorbidities		
Hypertension		96(72.7)
Diabetes		39(29.5)
Anemia		63(47.7)
Electrolyte imbalance		81(61.3)
HIV		15(11.4)
Catheter sepsis		3(2.3)
PUD		8(6.1)
Other diseases		70(53)

IQR–Interquartile Range, D−dialysis, HIV−Human Immunodeficiency Virus, CVD-cardiovascular disease other than hypertension e.g. atrial heart fibrillation, rheumatic heart disease and heart failure, PUD- peptic ulcer disease. Other diseases e.g. pneumonia, gastroenteritis and urinary tract infections.

Table 4.2.1: Classes of Medications Prescribed To the Study Patients

Characteristic	n (%), N=132
Analgesic	33 (25.0)
Antihypertensive	95 (72.0)
Antidiabetic	29 (22.0)
Anti-infective	59 (44.7)
Antilipidemic	10 (7.6)
Antiulcer	42 (31.8)
Anticoagulant	13 (9.8)
Hematinic	41 (31.1)
Calcium supplement	36 (27.3)
Other medications	82(62.2)

Other medications prescribed include insulin plus 50% dextrose, calcium polystyrene acetate, calcium gluconate, sevelamer, aspirin, lactulose, ondansetron, albumin, sildenafil and olanzapine.

Table 4.2.2: Number of Medications Per Study Patient, N=132

Characteristic	n (%) or Median (IQR)
Number of medications, Median (IQR)	6.5 (5.0, 8.0)
Range (Min. - Max.)	2.0 - 14.0
≤ 5	48 (36.4)
> 5	84 (63.6)

IQR - Interquartile range.

Table 4.3.1: Prevalence of Medication Dosing Errors

Characteristic	n (%), N=132
Over dosage of drugs	47 (35.6)
Under dosage of drugs	36 (27.3)
Drugs with over dosage	**n (%), N=47**
Iron sucrose f	8 (17.0)
Ranitidine	5 (10.6)
Lamivudine	4 (8.5)
Iron sucrose	3 (6.4)
Aldactone	1 (2.1)
Amlodipine	1 (2.1)
Amlodipine f	1 (2.1)
Atenolol	1 (2.1)
Atenolol, Methyldopa	1 (2.1)
Atenolol, Iron sucrose	1 (2.1)
Amoxicillin clavulanic acid	1 (2.1)
Ca gluconate	1 (2.1)
Ceftriaxone, Esomeprazole, Iron sucrose	1 (2.1)
Cefuroxime, Ranitidine	1 (2.1)
EPO f	1 (2.1)
Fluconazole	1 (2.1)
Folate	1 (2.1)
Lamivudine, Aldactone	1 (2.1)
Levofloxacin, Iron sucrose	1 (2.1)
Losartan f	1 (2.1)
Methyldopa	1 (2.1)
Metoclopramide	1 (2.1)
Mixtard, Ciprofloxacin	1 (2.1)
Piperacillin	1 (2.1)
Pregabalin f	1 (2.1)
Pyrazinamide, Ethambutol	1 (2.1)
Septrin, Lamivudine	1 (2.1)
Tramadol	1 (2.1)
Iron sucrose, EPO f	1 (2.1)
Iron sucrose, iron sucrose f	1 (2.1)
Iron sucrose, Lamivudine	1 (2.1)
Drugs with under dosage	**n (%), N=36**
Nifedipine	9 (25.0)
Enalapril	5 (13.9)
Carvedilol f	4 (11.1)
Mixtard	3 (8.3)
Labetalol	2 (5.6)
EPO/Nifedipine	2 (5.6)
EPO/Enalapril	1 (2.8)

Amlodipine	1 (2.8)
Enalapril, Nifedipine	1 (2.8)
EPO	1 (2.8)
EPO, Mixtard	1 (2.8)
Hydralazine	1 (2.8)
Labetalol, Enalapril	1 (2.8)
Labetalol	1 (2.8)
Metoprolol	1 (2.8)
Sodium polystyrene sulphonate	1 (2.8)
Iron sucrose	1 (2.8%)

EPO- erythropoietin, f- frequency, medication was prescribed more/less frequently than recommended. *NB-where >1 medication is listed, it means over/under dosage occurred in >1 medication per patient.*

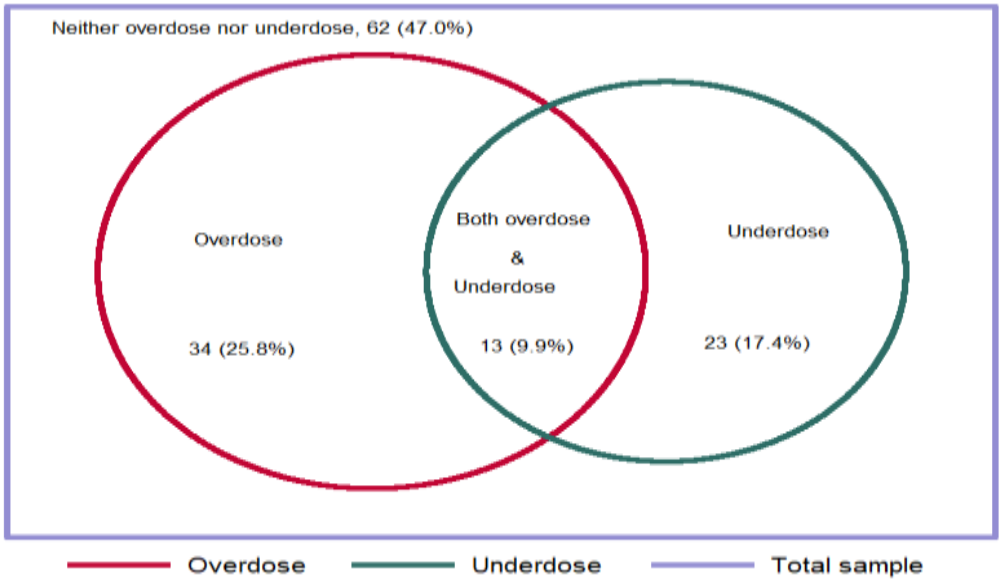


Figure 4.3.1: Proportion of Patients With Overdosage, Underdosage And No Dosage Errors

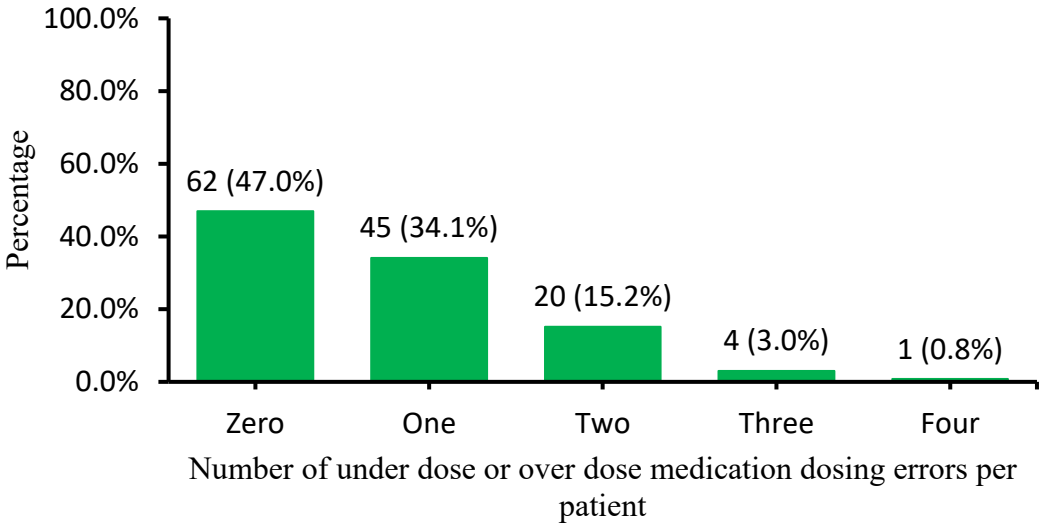


Figure 4.3.2: Distribution of Patients by the Number of Underdoes or Over Dose Medication Errors

Table 4.4.1: Prevalence of Potential Drug-Drug Interactions (DDI)

Characteristic	**n (%), N=132**
Minor DDI	36 (27.3)
Moderate DDI	93 (70.5)
Major DDI	19 (14.4)
Drugs with major DDIs	**n (%), N=19**
Ceftriaxone + calcium gluconate IV	4 (21.1)
Ferrous + calcium carbonate PO	3 (15.8)
Aceclofenac + furosemide	1 (5.3)
Atenolol + Methyldopa	1 (5.3)
Calcium carbonate + Ciprofloxacin PO	1 (5.3)
Carvedilol + methyldopa	1 (5.3)
Ciprofloxacin + sevelamer PO	1 (5.3)
Fluoxetine +clopidogrel +Propranolol	1 (5.3)
KCL + Aldactone	1 (5.3)
Levofloxacin+ calcium carbonate PO	1 (5.3)
Levothyroxine+ calcium carbonate PO	1 (5.3)
Morphine +tramadol	1 (5.3)
Sodium polystyrene sulphonate + calcium carbonate PO	1 (5.3)
Rifampicin +esomeprazole	1 (5.3)

IV- intravenous, PO- per oral, + sign- to denote in addition to

Table 4.4.2: Prevalence of Inappropriate Medication Prescription

Characteristic	**n (%), N=132**
Inappropriate drugs	16(12.1)
Drugs that were inappropriate	**n (%), (N=19)**
Folate	7 (43.8)
Hydrochlorothiazide	2(12.6)
Aceclofenac	1 (6.3)
Aldactone	1 (6.3)
Celecoxib	1 (6.3)
Metformin	1 (6.3)
Metformin, glibencamide	1 (6.3)
Nifedipine	1 (6.3)
Septrin	1 (6.3)

Inappropriate medication above is based on eGFR and concomitant comorbidities.

Table 4.4.3: Distribution of CKD Patients by Prescribers of Medication

Staff prescribing	**n (%), N=132**
DWR	54 (40.9)
Medical Officer (MO)	25 (18.9)
Registrar	19 (14.4)
Consultant	11 (8.3)
Clinical Officer (CO)	10 (7.6)
Medical Officer(MO) – Intern	10 (7.6)
Renal consultation	2 (1.5)
Cardiology consultation	1 (0.8)

DWR – Daily ward round.

Table 4.5: Prevalence of Omitted Drugs in CKD Patients

Omitted drug	n (%), N=95
Antilipidemics	30 (31.6)
Phosphate binder	13 (13.7
Potassium binder	7 (7.4)
Antilipidemics, Phosphate Binder	5 (5.3)
Hematinics	5 (5.3)
Antilipidemics, potassium binder	3 (3.2)
Antilipidemics, potassium binder, phosphate binder	2 (2.1)
Calcium Supplement	2 (2.1)
Calcium supplement, Phosphate Binder	2 (2.1)
Erythropoietin	2 (2.1)
Hematinics, Phosphate binder	2 (2.1)
Hematinics, Antilipidemics	2 (2.1)
Antihypertensive	1 (1.1)
Analgesics	1 (1.1)
Antihypertensive, Calcium supplement, Phosphate Binder	1 (1.1)
Antilipidemics, Antihypertensives	1 (1.1)
Antilipidemics, Phosphate Binder, Calcium supplement	1 (1.1)
Antilipidemics, Hematinics	1 (1.1)
Antilipidemics, Hematinics, Calcium supplement, Phosphate Binder	1 (1.1)
Antilipidemics, Hematinics, Phosphate Binder	1 (1.1)
Antilipidemics, Septrin, Calcium supplement	1 (1.1)
Antilipidemics, Phosphate Binders	1 (1.1)
Potassium binder, antihypertensive	1 (1.1)
Laxative, Antilipidemics	1 (1.1)
Losartan	1 (1.1)
Phosphate binder, Add Antihypertensive	1 (1.1)
Phosphate binder, Antilipidemics, Antidiabetics	1 (1.1)
Phosphate binder, Calcium Supplement, Antilipidemics	1 (1.1)
Phosphate binder, potassium binder	1 (1.1)
Phosphate binder, potassium binder, calcium supplement	1 (1.1)
Phosphate binder, potassium binder	1 (1.1)
Septrin	1 (1.1)

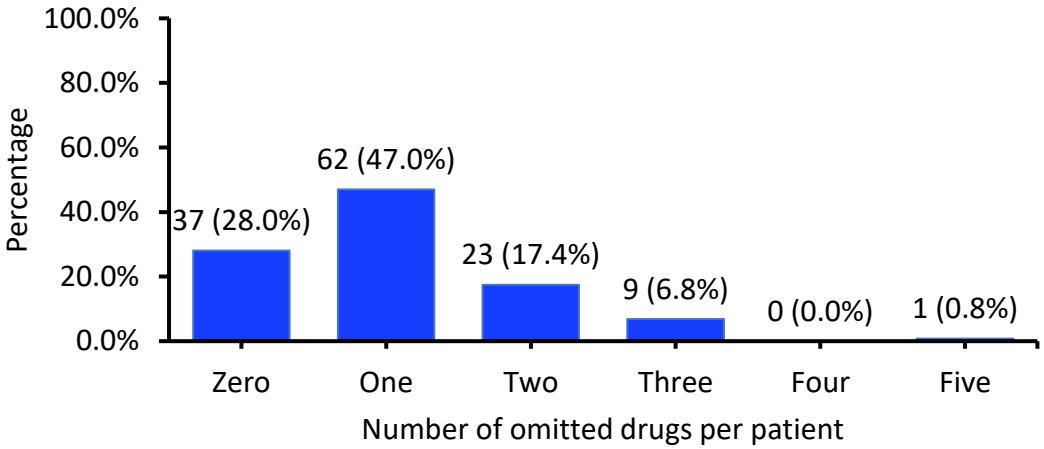
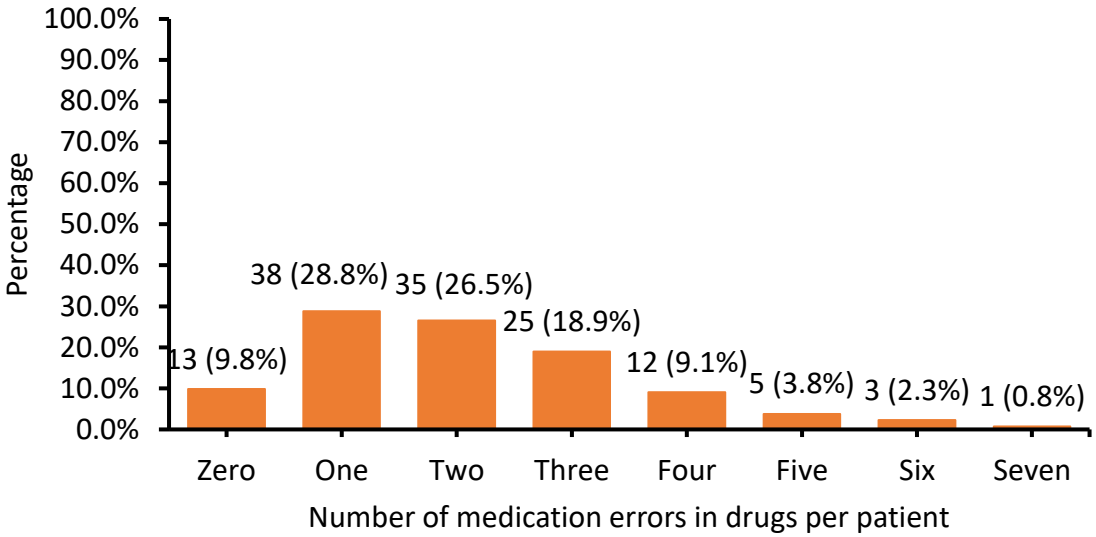


Figure 4.5: Distribution Of The Number Of Drugs Found Omitted For Each Patient



(Medication errors here include- under dose, overdose, potential DDIs, inappropriate and omitted drugs.)

Figure 4.6: Distribution of the Number of Medication Errors per Patient

Table 4.6: Unresolved Medical Problems in CKD Patients

Outcome	n (%), N=132
High blood pressure	30 (22.7%)
Low blood pressure	3 (2.3%)
Anemia	2 (1.5%)
High fasting blood glucose	2 (1.5%)
High random blood glucose and blood pressure	2 (1.5%)
Hyperkalemia	2 (1.5%)
High random blood glucose	1 (0.8%)
Hypokalemia	1 (0.8%)
Hyponatremia, high blood pressure	1 (0.8%)
Pain	1 (0.8%)
No	87 (65.9%)

Table 4.7.1: Bivariate Logistic Regression Models Assessing the Association between Demographic and Clinical Characteristics with Occurrence of At Least One Medication Dosing Error

	Presence of medication dosing errors			
Characteristic	No (N = 62)	Yes (N = 70)	Odds Ratio (95% CI)	P-value
Age (Years)				
< 50	21 (33.9%)	34 (48.6%)	Reference	
≥ 50	41 (66.1%)	36 (51.4%)	0.54 (0.27, 1.10)	0.089
Sex				
Female	27 (43.5%)	32 (45.7%)	Reference	
Male	35 (56.5%)	38 (54.3%)	0.92 (0.46, 1.82)	0.803
Number of medications				
≤ 5	32 (51.6%)	16 (22.9%)	Reference	
> 5	30 (48.4%)	54 (77.1%)	**3.60 (1.70, 7.61)**	**0.001**
Presence of allergies				
No	57 (91.9%)	63 (90%)	Reference	
Yes	5 (8.1%)	7 (10%)	1.27 (0.38, 4.22)	0.700
Site				
Clinic	20 (32.3%)	19 (27.1%)	Reference	
Ward	42 (67.7%)	51 (72.9%)	1.28 (0.60, 2.70)	0.521
CKD Stage 3A | 3B | 3D | 4 | 4D	22 (35.5%)	16 (22.9%)	Reference	
Stage 5 | 5D	40 (64.5%)	54 (77.1%)	1.86 (0.87, 3.98)	0.112

CI – Confidence interval

Table 4.7.2: Bivariate Logistic Regression Models Assessing the Association between Comorbidities and Occurrence of at Least One Medication Dosing Error

Characteristic	Presence of medication dosing errors			P-value
	No (N= 62)	Yes (N = 70)	Odds Ratio (95% CI)	
Hypertension				
No	20 (32.3%)	16 (22.9%)	Reference	
Yes	42 (67.7%)	54 (77.1%)	1.61 (0.74, 3.48)	0.228
Diabetes				
No	43 (69.4%)	50 (71.4%)	Reference	
Yes	19 (30.6%)	20 (28.6%)	0.91 (0.43, 1.91)	0.794
CVD				
No	49 (79%)	54 (77.1%)	Reference	
Yes	13 (21%)	16 (22.9%)	1.12 (0.49, 2.56)	0.794
Anemia				
No	39 (62.9%)	30 (42.9%)	Reference	
Yes	23 (37.1%)	40 (57.1%)	**2.26 (1.12, 4.55)**	**0.022**
HIV				
No	57 (91.9%)	60 (85.7%)	Reference	
Yes	5 (8.1%)	10 (14.3%)	1.90 (0.61, 5.90)	0.267
Electrolyte imbalance				
No	29 (46.8%)	22 (31.4%)	Reference	
Yes	33 (53.2%)	48 (68.6%)	1.92 (0.94, 3.90)	0.072
Catheter sepsis				
No	61 (98.4%)	68 (97.1%)	Reference	
Yes	1 (1.6%)	2 (2.9%)	1.79 (0.16, 20.28)	0.637
Peptic ulcer disease				
No	59 (95.2%)	65 (92.9%)	Reference	
Yes	3 (4.8%)	5 (7.1%)	151 (0.35, 6.61)	0.582
Other comorbidities				
No	31 (50%)	31 (44.3%)	Reference	
Yes	31 (50%)	39 (55.7%)	1.26 (0.63, 2.50)	0.512

CI – Confidence interval

Table 4.7.3: Bivariate Logistic Regression Models Assessing the Association between Medication, Prescriber, Omitted Medication and Occurrence of at Least One Medication Dosing Error

	Presence of medication dosing errors			
Characteristic	**No (N = 62)**	**Yes (N = 70)**	**Odds Ratio (95% CI)**	**P-value**
Analgesics				
No	45 (72.6%)	54 (77.1%)	Reference	
Yes	17 (27.4%)	16 (22.9%)	0.78 (0.36, 1.73)	0.546
Anti-hypertensive				
No	20 (32.3%)	17 (24.3%)	Reference	
Yes	42 (67.7%)	53 (75.7%)	1.48 (0.69, 3.18)	0.310
Anti-diabetic				
No	48 (77.4%)	55 (78.6%)	Reference	
Yes	14 (22.6%)	15 (21.4%)	0.94 (0.41, 2.13)	0.873
Anti-infective				
No	34 (54.8%)	39 (55.7%)	Reference	
Yes	28 (45.2%)	31 (44.3%)	0.97 (0.49, 1.92)	0.920
Anti-lipidemic				
No	59 (95.2%)	63 (90%)	Reference	
Yes	3 (4.8%)	7 (10%)	2.19 (0.54, 8.85)	0.273
Anti-ulcer				
No	40 (64.5%)	50 (71.4%)	Reference	
Yes	22 (35.5%)	20 (28.6%)	0.73 (0.35, 1.52)	0.395
Anti-coagulants				
No	55 (88.7%)	64 (91.4%)	Reference	
Yes	7 (11.3%)	6 (8.6%)	0.74 (0.23, 2.32)	0.602
Hematinic				
No	51 (82.3%)	40 (57.1%)	Reference	
Yes	11 (17.7%)	30 (42.9%)	**3.48 (1.55, 7.78)**	**0.001**
Calcium supplements				
No	47 (75.8%)	49 (70%)	Reference	
Yes	15 (24.2%)	21 (30%)	1.34 (0.62, 2.91)	0.455
Missing drugs				
No	17 (27.4%)	20 (28.6%)	Reference	
Yes	45 (72.6%)	50 (71.4%)	0.94 (0.44, 2.02)	0.883
Prescriber				
MO/MO Intern/CO	26 (41.9%)	19 (27.1%)	Reference	
Registrar	9 (14.5%)	10 (14.3%)	1.52 (0.52, 4.47)	0.446
DWR	22 (35.5%)	32 (45.7%)	1.99 (0.89, 4.44)	0.093
Consultants	5 (8.1%)	9 (12.9%)	2.46 (0.71, 8.54)	0.155

CI – Confidence interval

Table 4.7.4: Multivariate Logistic Regression Model Assessing the Factors Associated With At Least One Medication Dosing Error

Characteristic	Unadjusted Odds Ratio (95% CI)	Adjusted Odds Ratio (95% CI)	Adjusted P-value
Number of medications			
≤ 5	Reference	Reference	
> 5	3.60 (1.70, 7.61)	**2.93 (1.28, 6.71)**	**0.011**
Anemia	2.26 (1.12, 4.55)	1.35 (0.59, 3.07)	0.475
Hematinic	3.48 (1.55, 7.78)	**2.58 (1.06, 6.28)**	**0.037**
Prescriber			
MO/MO Intern/CO	Reference	Reference	
Registrar	1.52 (0.52, 4.47)	0.79 (0.24, 2.61)	0.697
DWR	1.99 (0.89, 4.44)	1.39 (0.56, 3.42)	0.476
Consultant	2.46 (0.71, 8.54)	3.07 (0.81, 11.63)	0.098

CI – Confidence intervals. Adjusted – imply multivariate model, Unadjusted – bivariate model.

Table 4.7.5: Bivariate Logistic Regression Models Assessing the Association Between Demographic And Clinical Characteristics With Inappropriate Medication Use

	Presence of inappropriate drug use			
Characteristic	No (N = 102)	Yes (N = 30)	Odds Ratio (95% CI)	P-value
Age (Years)				
< 50	42 (41.2%)	13 (43.3%)	Reference	
≥ 50	60 (58.8%)	17 (56.7%)	0.92 (0.40, 2.08)	0.833
Sex				
Female	46 (45.1%)	13 (43.3%)	Reference	
Male	56 (54.9%)	17 (56.7%)	1.07 (0.47, 2.44)	0.864
Number of medications				
≤ 5	48 (47.1%)	0 (0%)	Reference	
> 5	54 (52.9%)	30 (100%)	-	-
Presence of allergies				
No	92 (90.2%)	28 (93.3%)	Reference	
Yes	10 (9.8%)	2 (6.7%)	0.66 (0.14, 3.18)	0.602
Site				
Clinic	30 (29.4%)	9 (30%)	Reference	
Ward	72 (70.6%)	21 (70%)	0.97 (0.40, 2.37)	0.951
CKD				
Stage 3A | 3B | 3D | 4 | 4D	34 (33.3%)	4 (13.3%)	Reference	
Stage 5 | 5D	68 (66.7%)	26 (86.7%)	**3.25 (1.05, 10.06)**	**0.041**

CI – Confidence intervals. The odds ratio quantifying the association of number of medications with inappropriate drug use were not calculated due to zero cell count.

Table 4.7.6: Bivariate Logistic Regression Models Assessing The Association Between The Presence Of Comorbidities And Inappropriate Medication Use

	Presence of inappropriate drug use			
Characteristic	**No (N = 102)**	**Yes (N = 30)**	**Odds Ratio (95% CI)**	**P-value**
Hypertension				
No	26 (25.5%)	10 (33.3%)	Reference	
Yes	76 (74.5%)	20 (66.7%)	0.68 (0.28, 1.65)	0.398
Diabetes				
No	71 (69.6%)	22 (73.3%)	Reference	
Yes	31 (30.4%)	8 (26.7%)	0.83 (0.33, 2.07)	0.694
CVD				
No	80 (78.4%)	23 (76.7%)	Reference	
Yes	22 (21.6%)	7 (23.3%)	1.11 (0.42, 2.92)	0.837
Anemia				
No	57 (55.9%)	12 (40%)	Reference	
Yes	45 (44.1%)	18 (60%)	1.90 (0.83, 4.35)	0.129
HIV				
No	93 (91.2%)	24 (80%)	Reference	
Yes	9 (8.8%)	6 (20%)	2.58 (0.84, 7.97)	0.099
Electrolyte imbalance				
No	43 (42.2%)	8 (26.7%)	Reference	
Yes	59 (57.8%)	22 (73.3%)	2.00 (0.82, 4.93)	0.130
Catheter sepsis				
No	99 (97.1%)	30 (100%)		
Yes	3 (2.9%)	0 (0%)	-	-
PUD				
No	95 (93.1%)	29 (96.7%)	Reference	
Yes	7 (6.9%)	1 (3.3%)	0.47 (0.06, 3.96)	0.487
Other comorbidities				
No	56 (54.9%)	6 (20%)	Reference	
Yes[h]	46 (45.1%)	24 (80%)	**4.87 (1.84, 12.92)**	**0.001**

Confidence intervals, [h] the confidence interval is so wide due to the small cell count. Hence interpret the estimate with caution. The odds ratio quantifying the association of catheter sepsis with inappropriate drug use was not calculated due to zero cell counts.

Table 4.7.7: Bivariate Logistic Regression Models Assessing The Association Between Medications And Inappropriate Drug

	Presence of inappropriate drug use			
Characteristic	**No (N = 102)**	**Yes (N = 30)**	**Odds Ratio (95% CI)**	**P-value**
Analgesics				
No	81 (79.4%)	18 (60%)	Reference	
Yes[h]	21 (20.6%)	12 (40%)	**2.57 (1.07, 6.16)**	**0.034**
Anti-hypertensive				
No	29 (28.4%)	8 (26.7%)	Reference	
Yes	73 (71.6%)	22 (73.3%)	1.09 (0.31, 2.35)	0.850
Anti-diabetic				
No	79 (77.5%)	24 (80%)	Reference	
Yes	23 (22.5%)	6 (20%)	0.86 (0.31, 2.35)	0.767
Anti-infective				
No	62 (60.8%)	11 (36.7%)	Reference	
Yes	40 (39.2%)	19 (63.3%)	**2.68 (1.15, 6.22)**	**0.022**
Anti-lipidemic				
No	94 (92.2%)	28 (93.3%)	Reference	
Yes	8 (7.8%)	2 (6.7%)	0.84 (0.17, 4.18)	0.831
Anti-ulcer				
No	68 (66.7%)	22 (73.3%)	Reference	
Yes	34 (33.3%)	8 (26.7%)	0.73 (0.29, 1.80)	0.492
Anti-coagulants				
No	92 (90.2%)	27 (90%)	Reference	
Yes	10 (9.8%)	3 (10%)	1.02 (0.26, 3.98)	0.975
Hematinic				
No	76 (74.5%)	15 (50%)	Reference	
Yes	26 (25.5%)	15 (50%)	**2.92 (1.26, 6.79)**	**0.013**
Calcium supplements				
No	80 (78.4%)	16 (53.3%)	Reference	
Yes	22 (21.6%)	14 (46.7%)	**3.18 (1.35, 7.51)**	**0.008**
Missing drugs				
No	29 (28.4%)	8 (26.7%)	Reference	
Yes	73 (71.6%)	22 (73.3%)	1.09 (0.44, 2.73)	0.850
Prescriber				
MO/MO Intern/CO	35 (34.3%)	10 (33.3%)	Reference	
Registrar	12 (11.8%)	7 (23.3%)	2.04 (0.64, 6.56)	0.231
DWR	44 (43.1%)	10 (33.3%)	0.80 (0.30, 2.12)	0.648
Consultants	11 (10.8%)	3 (10%)	0.95 (0.22, 4.10)	0.950

CI – Confidence intervals, [h] the confidence interval is so wide due to the small cell count. Hence interpret the estimate with caution.

Table 4.7.8: Multivariate Logistic Regression Model Assessing the Factors Associated With Inappropriate Drug Use

Characteristic	Unadjusted Odds Ratio (95% CI)	Adjusted Odds Ratio (95% CI)	Adjusted P-value
Other comorbidities			
No	Reference	Reference	
Yes	4.87 (1.84, 12.92)	**5.26 (1.70, 16.29)** [h]	**0.004**
CKD			
Stage 3A | 3B | 3D | 4 | 4D	Reference	Reference	
Stage 5 | 5D	3.25 (1.05, 10.06)	**4.93 (1.29, 18.81)** [h]	**0.020**
Anti-infective			
No	Reference	Reference	
Yes	2.68 (1.15, 6.22)	**2.85 (1.00, 8.12)** [h]	**0.050**
Hematinic			
No	Reference	Reference	
Yes	2.92 (1.26, 6.79)	**3.50 (1.28, 9.54)** [h]	**0.014**
Prescriber			
MO/MO Intern/CO	Reference	Reference	
Registrar	2.04 (0.64, 6.56)	0.30 (0.07, 1.39)	0.124
DWR	0.80 (0.30, 2.12)	**0.15 (0.04, 0.59)**	**0.007**
Consultants	0.95 (0.22, 4.10)	0.68 (0.12, 3.86)	0.667

CI – Confidence intervals, adjusted – imply multivariate model, unadjusted – bivariate model [h] the confidence interval is wide thus interpretation of the estimate should be done with caution.

CHAPTER FIVE: DISCUSSION, CONCLUSION AND RECOMMENDATIONS

5.1 Discussion

This study aimed to determine the prevalence and factors associated with medication dosing errors and inappropriate medication use. The age and CKD severity in this study were comparable to another study in Kenya by Njeri et al. (2018) that reported a mean age of 54.2 years, and CKD stage 4 majority. This study had slight male predominance while the latter study had a female predominance. A study in Ethiopia on drug dose adjustment in renal impairment reported a median age of 42 years, a male predominance and a majority of patients in CKD stage 3 (Getachew et al., 2015). The age prevalence was in par with Africa's prevalence which reported prevalence of CKD stage 3-5 to be higher in older age (median ≥ 43.5years) (Kaze et al., 2018). Possible explanation for high CKD stage 5 patients is that the most patients in earlier stages of CKD are usually asymptomatic and hence they do not seek health services until the late stages of the disease. Also, MTRH is the main referral hospital in western Kenya it is expected that those with severe illness would end up getting care at MTRH.

Over dosage errors were the most frequent medication error occurring in 34.6% of the patients. Similar findings were reported in Kenya and Ethiopia where overdose prevalence was 33% and 31% respectively (Getachew et al., 2015; Njeri et al., 2018). Over dosed medications involved hematinics, antihypertensives and anti-infectives which was comparable to anti-infectives reported in the Kenyan study (Njeri et al., 2018). Prevalence in other developing countries ranged from 20% to 62.8% in India and Saudi Arabia respectively .Prevalence in other developing countries ranged from 20% to 62.8% in India and Saudi Arabia respectively (Saad et al., 2019; Sah et al.,

2014).The differences may be due to study methodology (two sites vs one site), data collection at patient admission or discharge and study period range (3months – 13 months).

Intravenous iron sucrose accounted for the highest over dose occurring in 34 .0% of all over dosages. It was mainly dosed as 200mg every day or alternate day dosing as opposed to 200mg every 72hrs over two weeks for non-dialysis patients or 100mg on consecutive dialysis sessions. Higher frequency prescription may have been due to urgent need to build up the patient's iron stores before hospital discharge of the patient or knowledge gap on dosing recommendation based on the safety of the drug. Intravenous iron short term side effects such as anaphylaxis and long-term side effects iron overload can advance the CKD–associated oxidative stress, inflammation, and cardiovascular disease; increase the risk of infections; worsen the severity of type 2 diabetes; and exacerbate neurologic and cognitive dysfunction (Vaziri, 2016).

Over dose of anti-infectives accounted for 29.7% of over dosages, with lamivudine the most frequent drug. Similar occurrence of over dose of lamivudine was reported in Kenya possibly due to its common use in HIV patients in the region (Njeri et al., 2018). Over dosage occurred due to Lamivudine tablet formulation whose lowest strength is 150mg whereas manufacturers renal adjustment of lamivudine may require dose as low as 25-50mg to be taken once a day. Half a tablet(75mg) was prescribed when renal dose adjustment was warranted since that was the lowest dose that could be provided (FDA, 2017). Manufacturers renal dose adjustments were based on pharmacokinetic models that showed that lamivudine levels increased with decreasing renal function since 70% of the drug is eliminated renally (Johnson et al., 1999). Clinical experience has shown that lamivudine is generally well tolerated however it

has rare adverse effects of lactic acidosis and hepatomegaly. Lactic acidosis has not been documented to occur with lamivudine increasing levels but may occur in females or obese patients (FDA, 2017). Hence, a cross-sectional design study recommended rounding the lamivudine dose to the lowest available strength irrespective of eGFR to avoid the inconveniences of liquid formulation(Fischetti et al., 2018).

Antihypertensives over dosage accounted for 21.2% of over dosages with the common drugs being atenolol, amlodipine, aldactone, methyldopa and losartan. Non-assessment of whether or not a beta blocker is eliminated through the kidney may have resulted in overdose as some drugs like atenolol and bisoprolol are hydrophilic and hence required dose adjustment. Moreover, hypertension therapeutic targets of patients are difficult to attain in CKD even in maximum doses of more than three classes of drugs hence contributing to scheduling overdose of amlodipine, methyldopa and losartan which are commonly used in these patients. Aldactone has been recommended for use for CKD resistant hypertension and albuminuria but its overdose can exacerbate hyperkalemia in CKD.

Other drugs overdosed were ranitidine which is a histamine 2 receptor antagonist (H2RA) overdose. H2RA drugs are eliminated by the renal route hence require dose adjustment in renal insufficiency. Lack of calculation of eGFR may have resulted in the overdose. Also, systematic reviews studies have attributed proton pump inhibitors to nephritis, acute kidney injury, CKD and end stage renal disease (Qiu et al., 2018). Hence, prescribers preferred H2RAs over proton pump inhibitors to manage the CKD patients.

Under dosage errors were the second most frequent medication errors occurring in 27.3% of the patients. They occurred with antihypertensives, biphasic insulin and hematinics; this is comparable with a study in Kenya which had under dosage prevalence of 31.7%, involved anti- infectives and hematinics (Njeri et al., 2018). Studies have acknowledged there is a challenge in managing CKD associated hypertension since there are several pathogenic mechanisms involved in the disease. Under dosage errors of antihypertensives may lead to cardiovascular disease, worsening of CKD and death(Hamrahian & Falkner, 2017). Under dosage errors in biphasic insulin- mixtard may have resulted in high glucose levels in 3% of the patients studied due to lack of titration of insulin doses accordingly. Erythropoietin was under dosed in patients who may have weighed over 80kg as doses given were standardized to 4000 units per dose in adults. Routine weight assessment in hospitalized CKD patients is necessary to ensure optimization of pharmacotherapy.

Polypharmacy was significantly associated with medication dosing errors which is similar to studies conducted in Kenya, Ethiopia, Pakistan and France (Belaiche et al., 2012; Garedow et al., 2019; Njeri et al., 2018; Saleem & Masood, 2016). Possible reason for association is that CKD is a complex disease which may require more than one medication. Polypharmacy is an increasing phenomenon in CKD due to its associated comorbidities and complications. There is emphasis to describe polypharmacy not in terms of number of medications but to shift from inappropriate polypharmacy to appropriate polypharmacy. Appropriate polypharmacy is present when all the medications prescribed are optimal whereas inappropriate polypharmacy occurs one or more medications prescribed are not beneficial (Stewart et al., 2017). Risk of medication errors due to polypharmacy can be minimized by polypharmacy management which has been defined by the Stimulating Innovation Management of

Polypharmacy and Adherence in The Elderly (SIMPATHY) consortium as “A whole systems approach which optimizes the care of multimorbid patients through maximizing benefit while reducing the risks of inappropriate polypharmacy”(Mair, 2017). Another factor that was significantly associated with medication dosing errors in this study was hematinics prescription to the CKD study patients. Possible reason is due to high prevalence of anemia 47.7% in the CKD study patients managed using iron supplementation and erythropoietin.

Potential major DDIs were the third common medication error (14.4%) observed in the patients which in contrast is lower to that of a study in Kenya (28.3%) and Nigeria (24.9%) (Njeri et al., 2018) (Busari et al., 2019). Prevalence variation may have been due to use of different use of different tools to assess the severity DDIs in the three studies. The mechanisms of potential DDIs identified in this study are illustrated below: Physicochemical interactions - precipitate formation due to intravenous formulations of ceftriaxone and calcium gluconate which can lodge in the kidneys and lungs when the drugs are administered concomitantly (Roche, 2015). Calcium gluconate is usually prescribed when the patient has hyperkalemia for stabilization of the myocardium while ceftriaxone is a commonly used antibiotic. Instructions should be given to flush the line if the two drugs are given sequentially.

Pharmacokinetic interactions affecting absorption. Oral formulations of calcium salts and sevelamer decrease absorption of other oral formulation of drugs like iron, quinolones, sodium polystyrene sulphonate, levothyroxine when administered concomitantly (UpToDATE®, 2021) . Scheduling instructions should be written when both types of drugs are prescribed. Pharmacokinetic interactions affecting metabolism examples: Fluoxetine and propranolol DDI may cause inhibition of

metabolism of CYP2D6 substrate and cause propranolol toxicity (Shin et al., 2020). Clopidogrel and fluoxetine DDI may decrease concentration of active metabolite of clopidogrel and antiplatelet activity (Bykov et al., 2017). Rifampicin and esomeprazole DDI may decrease serum concentration of esomeprazole due to induction of CP2C19 (Park et al., 2017).

Pharmacodynamic interactions affecting desired response of the drug examples; aceclofenac and furosemide DDI in which aceclofenac may decrease efficacy of furosemide while in turn furosemide increase in nephrotoxic effect of aceclofenac (Dreischulte et al., 2015). Morphine and tramadol DDI may enhance central nervous system depressant and serotonergic effects especially at higher drug doses (Molina et al., 2018). Methyldopa and carvedilol DDI in which methyldopa may enhance carvedilol atrioventricular and sinus node blocking effect and rebound antihypertensive effect (Bailey & Neale, 1976). Aldactone and potassium chloride DDI may enhance hyperkalemia in CKD patients and hence the prescriber should beware to avoid such occurrences (KDIGO, 2012). Nevertheless, in this study the patient in whom the DDI occurred needed potassium supplementation due to hypokalemia associated with furosemide use in heart failure.

DDIs may at times be considered beneficial to the patient depending on the clinical context hence the drugs may not be excluded rather the patient will require close monitoring to avoid undesirable effects. Monitoring in our developing world may be limited by patient's financial constraints, unavailability of laboratory or imaging tests or even prescriber recalling or not to order to tests when required. Hence, this study suggests taking into consideration the above factors when beneficial DDIs are encountered in clinical practice.

The least frequent medication error in our study was inappropriate drugs occurring at a prevalence of 12.1% which was comparable to 12% observed in another Kenyan study with NSAIDS among the inappropriate drugs as well (Njeri et al., 2018). Adjunctive therapies such as nutritional supplements e.g. folate are not recommended by KDIGO 2012 guidelines for treatment for anemia in non-dialysis CKD due to low quality evidence from studies (Drüeke & Parfrey, 2012; NICE, 2015). Folate supplementation may be appropriate in CKD dialysis patients since it is dialysable to prevent inadequate levels which may result in hyperhomocysteinemia related complications e.g. atherosclerosis. A study reported that low folate levels were associated with a higher risk of all-cause mortality (Soohoo et al., 2016). Unnecessary prescription of folate in non -dialysis CKD patients may contribute to polypharmacy which may lead to undesirable treatment outcomes.

Other inappropriate drugs in this study due to severe renal disease in the study patients were, NSAIDS, metformin, glibencamide, hydrochlorothiazide and cotrimoxazole. The prescribers may not have been forewarned not to dispense some drugs like metformin and hydrochlorothiazide when eGFR reduced <30ml/min due to failing to calculate eGFR. It is possible that prescribers were aware of the nephrotoxic effects of the drugs but dispensed anyway after weighing the benefit to risk ratio and having no other alternate drug available for conditions like gout and diabetes in which NSAIDS and glibencamide were prescribed respectively. When the NSAID is prescribed, the gout patient should be monitored closely and drug discontinued if worsening renal function tests. Alternatives such as glucocorticoids can be used for a short duration to manage the gout flares in CKD as they are suggested to be the safest option for the kidney in the American journal of kidney disease (Vargas-Santos & Neogi, 2017). KDIGO 2012 guidelines suggests calcium channel blockers as valuable

for management of hypertension in CKD but a prescriber should assess each patient case individually and consider his/her comorbidities while selecting the most appropriate drug (James et al., 2014). Hence, nifedipine should not have been prescribed in a patient with heart failure with reduced ejection fraction as it can cause hemodynamic deterioration.

More severe CKD was significantly associated with inappropriate medication (potential major DDI and inappropriate medication) which is similar to the Kenyan study (Njeri et al., 2018). Possible explanation is that patients in CKD stage 5 and 5D formed the majority of the patient population 71.3%, were more likely to have several comorbidities and complications, needed polypharmacy and hence the inappropriate medication. Other studies in Nigeria and Pakistan on DDIs in CKD report polypharmacy and hypertension association with inappropriate medication (Adibe et al., 2017), (Saleem et al., 2017).

Anti-infectives and hematinics were significantly associated with inappropriate medication. This is comparable to a study in Kenya which suggested anti-infectives may have led to association of respiratory illness with improper drug use (Njeri et al., 2018). Inappropriate anti-infectives and hematinics prescription was due to the major DDIs such as combination of oral formulations of calcium salts or sevelamer and fluoroquinolones such as levofloxacin may result in decreased absorption of the levofloxacin. Intravenous ceftriaxone a commonly used antibiotic at MTRH might have had physicochemical interactions with intravenous calcium salts when given concomitantly. Inappropriate hematinics prescription was due to unnecessary indication of folate in non- dialysis patients in this study.

Other comorbidities though statistically significant with inappropriate medication were not considered to be clinically useful in this study as they involved a summation of diseases which formed a small prevalence on their own and not commonly associated with CKD. Contrary to previous studies, age and patient comorbidity with hypertension did not have a significant association with the medication errors in this study (Saleem et al., 2017) (Adibe et al., 2017). Also, contribution of the cadre of health care prescribers to medication errors was not effectively assessed due to the study design and available records. Medication errors may be attributable to lack of knowledge, sub-standard performance and lack or failure of the system to prevent the errors (Brunetti & Suh, 2012). A study in India attributed medication dispensing errors to poor knowledge and inexperienced pharmacy staff (Ibrahim et al., 2020). Though most medication errors are due to human error, health care professionals may not intentionally commit the errors as the errors may due to inadequate systems such as unavailability of recommended medication recognized in this study and not necessarily lack of knowledge on the inappropriateness of the medication selected. Strategies to prevent such errors should be aimed at enhancing knowledge of staff and medication availability in CKD patients.

This study had incidental findings where medications were not prescribed to the CKD patients as recommended by KDIGO guidelines. As high as 40.1% of the CKD patients had no anti-lipidemics prescribed to them when clinically indicated; drugs used to manage electrolyte imbalances and hematinic such as erythropoietin were also omitted. The omission may have been due to failing to refer to patient's electrolyte values or forgetting to prescribe the drug when the laboratory results were availed. There may have also been a knowledge gap on at what level the deranged electrolyte needed to be managed. This enriched our knowledge that untreated indications are

prevalent and may adversely affect the quality of care in CKD patients and can form basis for future research as they also contribute to medication errors.

5.2 Strength and Limitations

The cross-sectional design of this study had the advantage of gathering information about medication errors at a specified time, and this information can be used for hypothesis formulation in future research.

Limitations of the study; One is that it relied mainly on data from medical charts, hence was affected by incomplete records. This was minimized by examining all medical charts; medical files and prescriptions as well as administering a questionnaire to each of the study participants to ensure complete records as possible. Second, there was subjectivity in assessing the medication errors as only one person was involved but this was minimized by using evidence-based guidelines as sources for reference. Third, the study design involved assessment of the medication errors at a single point in time, there might be interventions that were done to correct the errors after the data has been collected or new errors that arose after the data was collected which may not have been captured. Though unresolved medication problems were observed, a prospective study may draw more valid associations between medication errors and CKD therapeutic outcomes. Fourth, the study was observational in nature, the medication errors were not discussed with the prescribers and hence no immediate interventions were made. Finally, most dosing recommendations use the cock-croft gault equation to assess the renal insufficiency but our study used CKD-EPI since weight of most patients was not available.

5.3 Conclusion

This study showed there was a high prevalence of medication errors in CKD patients which may impact on their quality of health care. Prevalence of medication errors in descending order were; Over dosage (34.6%), under dosage (27.3%), major potential DDIs (14.4%) and inappropriate drugs (12.1%). Prescription of hematinics was associated with both medication dosing errors and inappropriate medication. Polypharmacy prescription was associated with medication dosing errors while severity of CKD and prescription of anti-infectives were associated with inappropriate medication. Further larger prospective studies are needed so as to draw more valid conclusions on factors associated with medication errors in CKD patients.

5.4 Recommendations

This study has established there is urgent need to improve medication safety and efficacy in all CKD patients at MTRH. The following measures may prevent and reduce medication errors;

1. Use of caution when prescribing to CKD patients who might either have CKD stage 5 or polypharmacy or on hematinics or anti-infectives since this study suggests they are significantly associated with medication errors.
2. Calculation of a patient's current eGFR when prescribing medication to guide in selecting appropriate medication and dosage in CKD patients. This can be done by involvement of clinical pharmacists in management of CKD patients since they are experts in pharmacotherapy and are able to identify, resolve and warn other health prescribers to avoid potential medication errors.

3. Highlight the importance of using prescribing and decision support tools such as:
    i. UpToDate which describes if a medication is safe to use at a particular eGFR, renal dosing adjustments needed and categorizes various drug-drug interactions so that the prescriber can offer safe and effective pharmacotherapy to CKD patients. During data collection for this study, MTRH did not have access to UpToDate but institutional rights were acquired in august 2020 after this study was conducted. A second study can be done to determine the impact of use of UpToDate on medication errors after prescribers have used it.
    ii. Formulation of hospital protocols for medication use in CKD patients which include the types of medication to use in CKD, renal dosing adjustments and medications that should be avoided. An example of a CKD protocol is attached in appendix 4. The protocol should be updated frequently to reflect new evidence from guidelines and the prescribers should receive regular trainings on the protocol.
4. Adoption of digital technology in prescribing such as computerized prescriber order entry (CPOE) and clinical decision support systems (CDSS) to help prescribers choose evidence-based decisions and to reduce medication errors by providing alerts to prescribers including pharmacists in case of a potential medication errors hence giving personnel opportunity to review and rectify the selected medication and dosage and hence optimize quality of care to CKD patients.

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APPENDICES

Appendix 1: Study Eligibility Screening Form

Study information: Prevalence and factors of Medication dosing errors and inappropriate use in adult Chronic Kidney Disease patients at Moi Teaching and Referral Hospital.

Patient information

Patient identification code: _____Gender: Male____ Female ____

Study site: outpatient clinic/internal medicine wards _____

Inclusion criteria (**four** responses must be ticked to be included in the study)	**YES**
Is the CKD patient over 18years of age?	
Does the patient have a creatinine measurement in their file?	
Is the estimated Glomerular Filtration Rate < 60ml/min/1.73m^2	
Exclusion criteria (Any one ticked response excludes one from the study)	**YES**
Has the CKD patient declined to give consent to participate in the study?	
Is this a first visit to the outpatient renal clinic?	
Is the CKD patient a kidney post-transplant patient?	

Appendix 2A: English, information and consent declaration form.

Part I: Study information

Study Title: Prevalence and factors associated with medication errors in adult chronic kidney disease patients at Moi Teaching and Referral Hospital.

Investigator: Dr. Rhoda Marion M. Gatutha, a post graduate Masters of Pharmacy in clinical Pharmacy student

Institutional affiliation: Department of Pharmacology and Toxicology, School of Medicine, College of Health sciences, Moi University

Supervisors:

Dr. Zipporah Kamuren, Lecturer, Department of Pharmacology and Toxicology, Moi University

Dr. Cheptinga Kipkurui Philip, Head of Department of Renal Service, Moi Teaching and Referral Hospital

Sonak Pastakia, PharmD, visiting lecturer from Purdue University, United States of America.

Ethical Approval: Moi University and Moi Teaching and Referral Hospital (MTRH)

Purpose of the Study: To find out the type of drugs prescribed in adult chronic kidney disease patients in MTRH renal clinic and identify any medication and dose selection errors that could lead to undesired health outcome. It also intends to identify the factors that lead to the identified medication related problems.

Why You have been selected to Participate in the Study: You are a Chronic Kidney Disease stage 3, stage 4 and 5 attending MTRH renal clinic and taking various medication. The study is aims to critically review each of your medication

Participant role in the study: If you participate in the study you will be requested to be interviewed using a questionnaire to gather your socio-demographics information and medical history. Your prescription and files will also be reviewed to collect data on the treatment you are receiving at MTRH**.**

Confidentiality: All the Information you provide will be confidential and will be used for the purpose of research. The research Investigator will enter all your information in a computer database which will have limited access. The ethics and review committee may inspect the records but all the information will be coded so that no one will be able to link the information with you.

Voluntary Participation: If you do not wish to participate at any point during the interview or after the interview, you can withdraw at any time without giving your reasons without jeopardy to your treatment at MTRH**.**

Benefits for Participation: The information gathered will be important in improving medication quality of care of all CKD patients being managed at MTRH**.** No financial compensation will be given

Risks or discomforts of Participation: There are no risks or harm anticipated to the participants in this study. No extra charges will be charged by MTRH for participation.

Invitation to participate in the study: I am inviting you to take part in the study. Your participation will only be through your consent. You are also invited to make clarifications on anything that is not clear regarding this study.

Contact person in case of questions: Principal investigator on email mutundu11@gmail.com, telephone number +254725907450

Part II: Consent declaration

I…… I willingly agree to participate in the research conducted by Dr. Rhoda Marion Gatutha, whose purpose has been explained to me. After explanation regarding the aim of the study, I understand that my participation is on my free will. The study results may be beneficial to my kin, other patients, and health care professionals through better understanding of medication errors in adult chronic kidney disease patients.

……. Signature/thumb print

Date …… dd/mm/yy

Appendix 2B: Kiswahili, Information and Consent Declaration Form

Sehemu ya kwanza: Maelezo kuhusu utafiti

Jina la utafiti: Tathmini ya namna na uhusiano wa makosa ya madawa yanayotumika katika wagonjwa wa figo katika hospitali kuu ya Moi.

Mtafiti: Dkt. Rhoda Marion Gatutha, mwanafunzi uzamili (utabibu dawa) katika Chuo Kikuu cha Moi, Kenya.

Uhusiano wa kitaasisi: Idara ya Pharmacology na Toxicology, Shule ya Medicine, Chuo Kikuu cha Moi, Kenya

Wasimamizi: Dkt. Zipporah Kamuren, Mhadhiri, Idara ya Pharmacology na Toxicology, Chuo Kikuu cha Moi

Dkt. Cheptinga Kipkurui Philip, daktari mkuu katika idara ya matibabu ya magonjwa ya figo katika hospitali kuu ya Moi.

Sonak Pastakia, PharmD, Mhadhiri mgeni kutoka Chuo Kikuu cha Purdue, Marekani.

Idhini ya kimaadili: Kamati ya kimaadili ya Chuo Kikuu cha Moi na hospitali ya Moi.

Madhumuni ya Utafiti: Utafiti huu utatahmini namna na uhusiano wa makosa ya madawa yanayotumika kwa watu wazima wenye ungonjwa wa figo katika hospitali ya Moi ili kushawiri wafanyikazi wa huduma ya afya kuhusu kuboresha utumizi wa madawa katika ugonjwa sugu wa figo**.**

Sababu ya kuchaguliwa: Umechaguliwa kushiriki kwa sababu wewe una ugonjwa wa sugu wa figo, unatibiwa kwa madawa, na umelazwa katika hospitali ya Moi.

Kinachohitajika kwa mshiriki katika utafiti: Ukikubali kushiriki katika utafiti huu, utahojiwa kutumia muundo wa dodoso ili kukusanya nakala ya historia ya kijamii, magonjwa yote ulionayo na matibababu ya madawa unayopata. Recordi za matibabu

unayopata katika hospitali ya Moi pia zitachunguzwa ili kupata nakala ya hali ya ugonjwa wako na madawa unayopata.

Usiri: Nakala zote zitazokusanywa katika utafiti huu zitatumika kwa utafiti pekee. Jina lako halitatumika katika utafiti na recordi zitahifadhiwa katika tarakilishi kwa jinsi ya siri kwa mtafiti mkuu pekee. Kamati kuu ya utafiti na wasimazi pia watakuwa na idhini ya kuchunguza recordi za utafiti.

Kujitolea kushiriki: Kushiriki ni kwa hiari yako. Unaweza kataa kushiriki wakati wowote na haitadhuru matibabu utakayopata ukiwa katika hospitali ya Moi.

Faida: Faida kuu ya kushiriki kwa huu utafiti utatumika kuboresha utumizi wa madawa katika watu wazima wenye ugonjwa wa figo katika hospitali ya Moi. Hakuna faida ya pesa katika utafiti huu.

Hatari: Hakuna hatari ya kushiriki katika utafiti huu**.**

Ombi kushiriki: Nakualika ushiriki katika utafiti huu. Ushiriki wako utakuwa tu kupitia idhini yako. Unaweza kuuliza ufafanuzi wowote juu ya jambo ambalo linatatiza katika utafiti huu.

Mawasiliano: Kwa maswali yeyote kuhusu tutafiti huu wasiliana na mtafiti kwa barua pepe mutundu11@gmail.com, nambari ya simu +254725907450.

Sehemu ya Pili: Cheti cha idhini ya mgonjwa

Mimi……kw

a mapenzi yangu napeana idhini ya kushiriki katika utafiti utakaofanywa na Dkt. Rhodamarion Gatutha, ambao madhumuni yake nimeelezwa naye. Baada ya maelezo kuhusu lengo la utafiti, nimeelewa kwamba kushiriki kwangu ni kwa mapenzi yangu. Matokeo ya utafiti huu inaweza kuwa na manufaa kwa jamaa zangu na wagonjwa wengine. Pia wataalamu wa huduma za afya wataelewa vizuri utumizi sahihi wa madawa kwa wagonjwa walio na ugonjwa sugu wa figo.

…….

Sahihi / alama ya kidole

Tarehe …… siku/mwezi/mwaka

Appendix 3: Data Collection Form

Study title: Prevalence and factors associated with medication errors in adult chronic kidney disease patients at Moi Teaching and Referral Hospital

Part I: Questionnaire

1.To investigate the patient demographic characteristics associated with medication errors under study. Obtain the following information from the study participant.

Serial no.	Description	Responses
1.	Age in years	
2.	Gender	
3.	Date when diagnosis of CKD was made (month/year)	
4.	Other comorbidities	
5.	Medication allergies	

2. Obtain the Best Possible Medical History (BPMH) by asking the following questions

i. What is the chief complaint (what problem brought them to the hospital)?

ii. What is the history of the presenting illness?

iii. What is the patient's past medical history?

11. What is their medication history? Does the Patient have any medication or herbal preparations they have been taking at home? If he or she responds Yes. List all the medications and herbal preparations in the table below.

Serial no.	Medication	Dose	Frequency	Duration	Indication

Part 2: Medical file Review form

Patient clinical details

a) eGFR: _____ CKD stage: _____

b) Established comorbidities:

_____

1. To determine the prevalence of medication dosing errors, list the patient's medication as prescribed and carry out an analysis of the dose given using Micromedex® and UpToDate®

Medication	Dose	Frequency	Indication	Prescriber cadre	(overdosage/ underdosage)

2. To determine the prevalence of medication selection errors proceed to step (2a) and (2b)

2a. Identify likely whether the medication is inappropriate by reviewing the patient's eGFR and laboratory information collected, established guidelines, Micromedex ® and UpToDate®

Medication	Indication	Prescriber cadre	Day of the week	Contraindicated

2b. Identify and classify severity of any potential drug- drug Interactions from the patient's medications using Micromedex ® and /or UpToDate®

Medication combination	Day of the week	Prescriber cadre	Minor DI	Moderate DI	Severe DI

3. Clinical and laboratory investigations details that are relevant to the participant CKD, comorbidities and routine medication monitoring.

3.1 Vitals

vitals	Date	Value	Comment (normal/abnormal)
Blood Pressure			
Heart rate			
Temp			
SPO2			

3.2 Urea Electrolytes, Creatinine

	Date	Value	Comment (normal/abnormal)
Urea			
sodium			
potassium			
Magnesium			
Chloride			
Calcium			
Phosphate			
Creatinine			
eGFR/ CrCl			CKD STAGE

3.3 Full hemogram

	Date	Value	Comment (normal/abnormal)
RBC			
WBC			
Neutrophils			
Hg			
Platelets			

3.4 Blood Glucose

Date	Date	Value	Comment(normal/abnormal)
RBS			
FBS			

Appendix 4: medication dosing in CKD.

4A) METFORMIN DOSING IN RENAL IMPAIRMENT RECOMMENDATIONS FROM UPTODATE.

Metformin.

eGFR ≥60 mL/minute/1.73 m2: No dosage adjustment necessary. Monitor renal function at least annually.

eGFR >45 to <60 mL/minute/1.73 m2: No dosage adjustment necessary; a maximum dose of 1.5 g/day in 2 divided doses (eg, 500 mg in the morning, 1 g in the evening) has been suggested.

eGFR 30 to 45 mL/minute/1.73 m2:

Initiation of therapy: Use generally not recommended. However, initial therapy with 500 mg once daily with the evening meal titrated to 500 mg twice daily, if tolerated, with close monitoring of kidney function has been recommended by some experts.

Continuation of existing therapy: May continue at a reduced dose up to a maximum of 500 mg twice daily with close monitoring of kidney function.

eGFR <30 mL/minute/1.73 m2: Use is contraindicated.

Cited from UpToDate (Mueller et al., 2020)

4B) AN EXCERPT FROM UNIVERSITY OF MICHIGAN CKD MANAGEMENT GUIDELINE.

Generic (Brand) Name	Dosage Range for Normal Kidney Function	Dose Adjustments Based on GFR (mL/min/1.73 m^2) (Percentage of Usual Dosage)			Cost 30 days Generic Brand	Comments
		30-59	10-29	< 10		
Thiazide Diuretics						
Hydrochlorothiazide	12.5 - 50 mg q24h	-	-	Avoid	$6 n/a	Consider avoiding thiazide diuretics if GFR < 30 mL/ min/1.73 m^2; potassium-sparing diuretics and aldosterone blockers can increase risk of hyperkalemia in CKD patients
Metolazone (Zaroxolyn)	2.5 - 20 mg q24h	-	-	-	$35-44 $98-101	
Chlorothiazide (Diuril)	0.5 - 1 g (divided q12-24h)	-	-	Avoid	$35-67 n/a	
Chlorthalidone	15 - 50 mg q24h	-	-	Avoid	$28	
Potassium-sparing Diuretics						
Amiloride (Midamor)	5 mg q24h	50-100%	50%	Avoid	$22 $35	
Other Diuretics						
Furosemide (Lasix)	20 - 600 mg q24h	-	-	-	$5 $25-36	
Torsemide (Demadex)	5 - 200 mg q24h	-	-	-	$10-26 $17-164	
Beta Blockers						

Atenolol (Tenormin)	50 - 100 mg q24h	50-100%	50%	Max dose 25mg q24h	$7 $412	Atenolol is generally not recommended for BP control in CKD patients Atenolol, and nadolol are eliminated renally; others are metabolized hepatically and do not need any dose adjustments due to CKD (e.g., metoprolol, propranolol, labetalol)

ADAPTED FROM UNIVERSITY OF MICHIGAN HEALTH SYSTEM CKD GUIDELINE, JULY 2019(LUKELA ET AL., 2019).

Appendix 5: Ethical Approval from Institutional Research and Ethics Committee (IREC) and Moi Teaching and Referral Hospital.

MU/MTRH-INSTITUTIONAL RESEARCH AND ETHICS COMMITTEE (IREC)

MOI TEACHING AND REFERRAL HOSPITAL
P.O. BOX 3
ELDORET
Tel: 33471/2/3

MOI UNIVERSITY
COLLEGE OF HEALTH SCIENCES
P.O. BOX 4606
ELDORET

Reference: IREC/2018/198
Approval Number: 0003268

14th March, 2019

Dr. Rhodamarion Mutundu Gatutha,
Moi University,
School of Medicine,
P.O. Box 4606-30100,
ELDORET-KENYA.

Dear Dr. Gatutha,

RE: FORMAL APPROVAL

The MU/MTRH- Institutional Research and Ethics Committee has reviewed your research proposal titled: -

"Prevalence and Factors Associated with Medication Errors in Chronic Kidney Disease Patients at Moi Teaching and Referral Hospital".

Your proposal has been granted a Formal Approval Number: ***FAN: IREC 3268*** on 14th March, 2019. You are therefore permitted to begin your investigations.

Note that this approval is for 1 year; hence will expire on 13th March, 2020. If it is necessary to continue with this research beyond the expiry date, a request for continuation should be made in writing to IREC Secretariat two months prior to the expiry date. You will be required to submit progress report(s) on application for continuation, at the end of the study and any other times as may be recommended by the Committee.

Furthermore, you must notify the Committee of any proposal change (s) or amendment (s), serious or unexpected outcomes related to the conduct of the study, or study termination for any reason. You will also be required to seek further clearance from any other regulatory body/authority that may be appropriate and applicable to the conduct of this study.

Sincerely,

DR. S. NYABERA
DEPUTY-CHAIRMAN
INSTITUTIONAL RESEARCH AND ETHICS COMMITTEE

INSTITUTIONAL RESEARCH & ETHICS COMMITTEE
14 MAR 2019
APPROVED
P.O. Box 4606-30100 ELDORET

cc CEO - MTRH Dean - SOP Dean - SOM
Principal - CHS Dean - SON Dean - SOD

An ISO 9001:2015 Certified Hospital

MOI TEACHING AND REFERRAL HOSPITAL

Telephone :(+254)053-2033471/2/3/4
Mobile: 722-201277/0722-209795/0734-600461/0734-683361
Fax: 053-2061749
Email: ceo@mtrh.go.ke/directorsofficemtrh@gmail.com

Nandi Road
P.O. Box 3 – 30100
ELDORET, KENYA

Ref: ELD/MTRH/R&P/10/2/V.2/2010

18th March, 2019

Dr. Rhodamarion Mutundu Gatutha,
Moi University,
School of Medicine,
P.O. Box 4606-30100,
ELDORET-KENYA.

APPROVAL TO CONDUCT RESEARCH AT MTRH

Upon obtaining approval from the Institutional Research and Ethics Committee (IREC) to conduct your research proposal titled:-

"Prevalence and Factors Associated with Medication Errors in Chronic Kidney Disease Patients at Moi Teaching and Referral Hospital".

You are hereby permitted to commence your investigation at Moi Teaching and Referral Hospital.

MOI TEACHING AND REFERRAL HOSPITAL
CEO
APPROVED
18 MAR 2019

DR. WILSON K. ARUASA, *MBS*
CHIEF EXECUTIVE OFFICER
MOI TEACHING AND REFERRAL HOSPITAL

P. O. Box 3 - 30100, ELDORET

cc - Senior Director, (CS)
- Director of Nursing Services (DNS)
- HOD, HRISM