ASSESSMENT OF MEDICATION RELATED PROBLEMS AMONG PATIENTS WITH CHRONIC KIDNEY DISEASE IN KENYATTA NATIONAL HOSPITAL

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DECLARATION

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DEDICATION

To my loving husband William and our daughter Letisha. I am because we are.

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ABREVIATIONS AND ACRONYMS

ADR Adverse Drug Reaction

ASHP American Society of Health Systems Pharmacists

BIC Bayesian Information Criterion

BMI Body Mass Index

CI Confidence Interval

CKD Chronic Kidney Disease

CNS Central Nervous System

DI Drug Interaction

DRC Democratic Republic of Congo

DRP Drug Related Problem

DWI Drug Without Indication

eGFR Estimated Glomerular Filtration Rate

ERC Ethics Review Committee

ESRD End Stage Renal Disease

FRD Failure to Receive Drug

GCP Good Clinical Practice

GFR Glomerular Filtration Rate

ICH International Conference on Harmonisations

IDS Improper Drug selection

IWD Indication Without Drug

KDOQI Kidney Disease Outcomes Quality Initiative

KNH Kenyatta National Hospital

MDRD Modification of Diet in Renal Disease

MRPs Medication Related Problems

NCC-MERP National Coordinating Council for Medication Error Reporting and Prevention

OD	Over-dosage
PAS	Problem Assessment and Solutions
PCNE	Pharmaceutical Care Network Europe
PI-DOC	Problem-Intervention Documentation
SHB-SEP	Health Base Foundation Subjective Evaluation Plan
STD	Sub-therapeutic Dosage
UoN	University of Nairobi
USA	United States of America

OPERATIONAL DEFINITION OF TERMS

Chronic kidney disease: A progressive loss of function over several months to years, characterized by gradual replacement of normal kidney architecture with interstitial fibrosis.

Medication related problem- an undesirable patient experience that involves drug therapy and that actually or potentially interferes with a desired patient outcome. Also sometimes referred to as 'drug related problem', 'drug therapy problem', 'medication therapy problem', or 'medicine related problem'

Medication Therapy Management services: A practice focusing on patient-centred process of care. It encompasses the assessment and evaluation of patient's complete medication therapy regimen.

Prevalence: The number of cases of a disease existing in a given population at a specific period of time (period prevalence) or at a particular moment in time (point prevalence).

ABSTRACT

Background: Medication related problems are real or potential medical conditions associated with medication use that could result in undesired health outcomes. Patients with chronic kidney disease are prone to medication related problems due to the complexity of their medication regimens.

Objective: The study aimed at identifying and characterizing medication related problems among patients with chronic kidney disease in Kenyatta National Hospital, Kenya.

Methodology: A cross-sectional study was carried out among conveniently sampled, 60 adult patients with chronic kidney disease stage 3 and 4. Medication related problems were identified and classified according to Hepler and Strand classification (1990). Data were analysed using R statistical programming language. Descriptive summary statistics were presented as means with standard deviation, frequencies and percent proportions. Multivariate logistic regression models were constructed to investigate the associations between the stage of chronic kidney disease and the individual medication related problem while adjusting for possible confounding by other covariates. The odds ratios, the 95% confidence intervals of the odds ratio, and the associated p-values of all the univariate and multivariate models were reported. Variables were considered significant if the odds ratio p-value ≤ 0.05.

Results: There was a female preponderance at 56.7% and the mean age was 54±16.8 years. The mean number of comorbidities and prescribed drugs per participant was 4.9±1.8 and 9.3±3.3 respectively. We identified 271 medication related problems and their mean number per participant was 4.5±1.4. Commonest problems were drug interactions (21.8%), indication without drug (18.1%) and failure to receive drug (15.5%). Compared to patients with chronic kidney disease stage 3, patients with chronic kidney disease stage 4 were 5.9 times more likely to have an improper drug selection problem ($p = 0.01$) and 4.7 times more likely to experience an over-dosage problem ($p = 0.01$). For a unit increase in the number of medications per prescription, the odds of having a drug without indication increased by 1.33 (95% CI, 1.11 to 1.67, $p= 0.01$) and the odds of failure to receive drug increased by 1.27 (95% CI, 1.05 to 1.59, $p = 0.02$). In addition, the odds of having sub-therapeutic dosage increased by 1.27 (95% CI, 1.06 to 1.59, $p = 0.02$) for a unit rise in the number of drugs prescribed.

Conclusion: Prevalence of medication related problems among patients with chronic kidney disease is high. Most occurring problems were drug interactions, indication without drug and failure to receive drug. Several types of problems were significantly associated with number of medications per prescription. To address these problems we advocate for healthcare providers to actively look out for medication related problems among patients with chronic kidney disease who inevitably are prescribed many drugs.

1. CHAPTER ONE: INTRODUCTION

1.1. Background

A medication related problem (MRP) is defined as an unwanted patient experience involving medication therapy and that actually or potentially hampers with desired therapeutic outcomes of the patient (1). According to Hepler and Strand classification (1990), MRPs can be divided into the following eight classes: Sub-therapeutic dosage (STD), improper drug selection (IDS), Drug without indication (DWI), Failure to receive drug (FRD), Indication without drug (IWD), Drug interaction (DI), Over-dosage (OD) and Adverse drug reaction (ADR) (1). Several factors have been associated with the occurrence of MRPs in patients with chronic kidney disease (CKD). These include; high number of comorbid conditions, high number of prescribed medications, old age, advanced stage of CKD and frequent dosage changes (2)(3)(4). Medication related problems contribute a significant challenge to healthcare providers and are associated with morbidity, mortality as well as low quality of life (5).

Patients with CKD often require more than 10 medications to treat various comorbidities associated with CKD (6). These comorbidities include cardiovascular diseases, metabolic abnormalities and endocrine abnormalities (7). Thus, for this group of patients, medication therapy management services are essential for optimum therapeutic outcome and improved quality of life. A core principle of medication therapy management is medication therapy review (8). This is an organized process of collecting specific information from the patient, evaluating medication therapies of the said patient to identify MRPs, and making a strategy to address these MRPs (8).

Pharmacists-led medication reviews and intervention programs are successful at identifying and resolving MRPs in patients with CKD (9). Reduction of MRPs in patients with CKD may improve quality of life and reduce morbidity, mortality and overall healthcare costs (2). Medication related problems are often preventable and pharmaceutical services can significantly reduce the impact and costs of these problems to the healthcare system. Pharmaceutical care services enable pharmacists to identify, prevent or resolve medication related problems thus improve quality of care (10).

1.2. Problem Statement

The significance of CKD not only lies in the burden associated with the disease but also in the burden associated with the use of medications in this disease. Because patients with CKD require complex drug regimens to retard CKD progression and treat associated comorbidities, they are at a higher risk of developing MRPs than the average patient population (5). In general, MRPs in patients with CKD contribute a significant challenge to healthcare providers and have been associated with morbidity, mortality, low quality of life and high healthcare costs (5). Several studies have identified MRPs in patients with CKD especially in United States of America (USA), New Zealand and European countries (2)(11)(12)(13)(14). A few other studies of such nature have been conducted in India, Iraq and Malaysia (15)(16)(17).

Unlike in high income countries, there is a dearth of literature about prevalence of MRPs in CKD in low- and middle-income countries such as those in Sub- Saharan Africa. Furthermore, little is known about the specific predictors of MRPs in patients with CKD residing in Kenya. Because of differences in genetics and in socio-demographic characteristics among patients residing in different regions, findings of studies in other parts of the world may not reflect the true state of MRPs among patients with CKD in Kenya. Additional studies are therefore needed to investigate the prevalence and clinical relevance of MRPs in patients with CKD residing in this region.

1.3. Study Justification

Studies for high resource setting suggest a high prevalence of MRPs among patients with CKD. However, little is known about prevalence of MRPs and patient related risk factors contributing to MRPs among patients with CKD treated at referral hospitals in Sub Saharan Africa. There was need to establish the extent and types of MRPs among patients with CKD, characterize pharmacists' interventions in prevention or resolution of MRPs among patients with CKD as well as identify various patient- related risk factors contributing to MRPs among patients with CKD.

As far as we know, this is the first study on the Kenyan population that has attempted to describe the extent and predictors of MRPs among patients with CKD. The study findings will assist pharmacists to identify patients with CKD at risk of MRPs and institute appropriate intervention strategies. In addition, the study findings will also

assist in policy formulation for management of patients with CKD in addition to stimulating further research in this area.

1.4. Purpose of the Study

The study purposed to provide a better understanding of MRPs among patients with CKD with the overarching goal of improving medication therapy management services for this cohort of patients in a referral facility in Sub Saharan Africa.

Having noted the paucity of data on MRPs among patients with CKD, this research aimed at identifying and characterizing MRPs among patients with CKD in Kenyatta National Hospital (KNH), Kenya

1.5. Research Questions

The research questions for this study were as follows:

1. What is the overall prevalence of MRPs among patients with CKD in KNH?
2. What is the prevalence of different types of MRPs among patients with CKD receiving care at KNH according to Hepler and Strand classification?
3. What patient-related risk factors are associated with different types of MRPs among patients with CKD receiving care at KNH?
4. What pharmacist interventions are employed in preventing and resolving MRPs among patients with CKD in KNH?

1.6. General Objective

The study aimed at identifying and characterizing MRPs among patients with CKD.

1.6.1. Specific Objectives

The specific objectives were as follows:

1. To determine the overall prevalence of MRPs among patients with CKD in KNH
2. To determine the prevalence of different types of MRPs according to Hepler-Strand classification
3. To investigate patient-related risk factors associated with different types of MRPs in patients with CKD receiving care at KNH.

4. To outline pharmacist recommendations/ interventions in preventing or resolving MRPs among patients with CKD.

1.7. Assumptions

This study was based on the following assumptions:

1. That medication related problems are random events that are evenly distributed throughout the study population.
2. That the sample selected was representative of the target population.
3. That the respondents for the interview gave truthful and honest answers.

1.8. Conceptual Framework

The conceptual framework in figure 1 below shows the inter-relationship between MRPs and their causes at different levels. It goes further to indicate the different classes of MRPs according to Hepler and Strand classification (1990) which include: Improper drug selection (IDS), Drug without indication (DWI), Drug Interaction (DI), Indication without drug (IWD), Adverse drug reaction (ADR), Over-dosage (OD), Sub-therapeutic dosage (STD), Failure to receive drug (FRD). The framework also captures pharmacists' plan of action upon identification of a real or potential MRP. The framework with a few modifications is adapted from a 2012 study by Nyakiba *et al* (18).

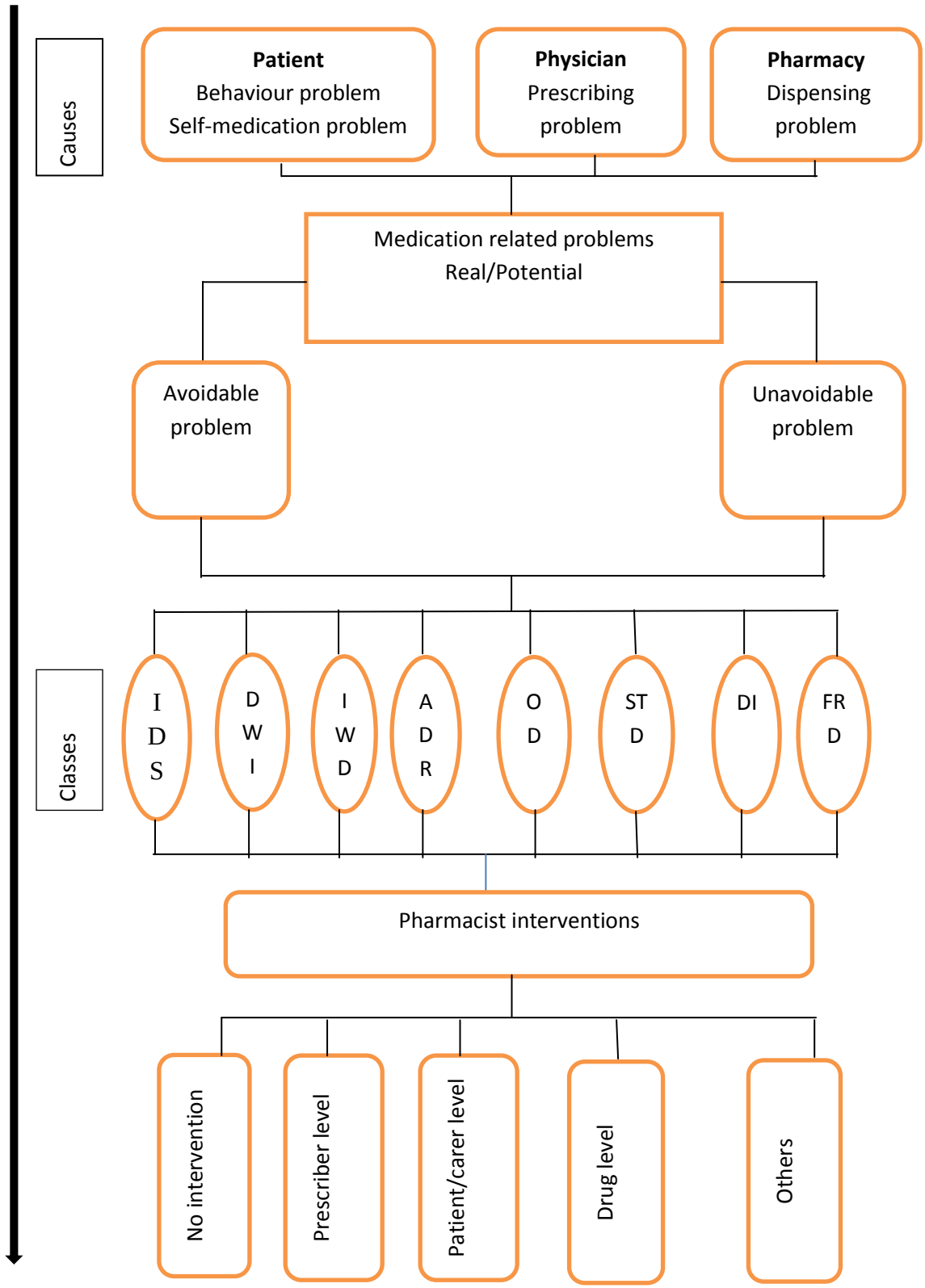

Figure 1: Conceptual Framework

KEY: IDS-Improper drug selection, DWI-Drug without indication, IWD-Indication without drug, ADR-Adverse drug reaction, OD-Over-dosage, STD-Sub-therapeutic dosage, DI-Drug interaction, FRD-Failure to receive drug

2. CHAPTER TWO: LITERATURE REVIEW

2.1. Introduction

This chapter summarizes reviewed literature on CKD burden, pharmaceutical care in patients with CKD, classification of MRPs, prevalence and factors associated with MRPs in patients with CKD and pharmacist interventions on CKD management.

2.2. Chronic Kidney Disease Burden

Chronic kidney disease has been defined as either kidney damage or glomerular filtration rate (GFR) <60 ml/min/1.73m^2 for ≥ 3months (7). It is an irreversible progressive loss of renal function lasting for 3 or more months. Kidney damage has been defined as functional or structural abnormalities of the kidneys initially without reduced GFR, but progressively can lead to reduced GFR (7). CKD is classified into stages (Stage1-5) as shown in the table 1 (7).

Table 1: Stages of chronic kidney disease

Stage	Description	GFR (ml/min/1,73m^2)
1	Kidney damage with normal or increased GFR	>90
2	Kidney damage with mild or decreased GFR	60-89
3	Moderate decrease in GFR	30-59
4	Severe decrease in GFR	15-29
5	Kidney failure	<15 (includes patients on dialysis

KEY: GFR- Glomerular Filtration Rate

Table cited from National Kidney Foundation Kidney Disease Outcomes Quality Initiative (K/DOQI) Clinical Practice Guidelines for Chronic Kidney Disease: Evaluation, Classification and Stratification 2002

Patients with CKD may present with various complications such as anaemia, hypertension, renal bone disease, metabolic disturbances, skin disease, gastrointestinal complications, uremic bleeding, neurologic complications, metabolic and endocrine abnormalities (19).

Non-communicable diseases are on the rise in the 21st century world-wide (20)(21). Chronic kidney disease (CKD) is one of such non-communicable diseases of public health concern (22)(23). About 10% of the world's population has some degree of CKD (24). In Sub Saharan Africa, CKD is estimated to be 3-4 folds more than in

developed countries (25). There is a striking difference in the pattern of CKD in high income and middle and low income countries. In high income countries, CKD presents in older population and is predominantly due to hypertension and diabetes mellitus. In Sub Saharan Africa, CKD is mainly due to glomerular diseases and hypertension and affects younger adults (25). Chronic kidney disease is responsible for increased morbidity, mortality and increased healthcare costs (23)(26). Prevention of progression of renal disease is important in reducing incidence of end stage renal disease (ESRD) as well as complications associated with CKD (27).

2.3. Pharmaceutical Care in Chronic Kidney Disease

Management of patients with CKD usually requires a healthcare team comprising of physicians, nephrologists, nurses, pharmacists and nutritionists. Pharmaceutical care, defined as responsible provision of medication therapy that is patient-oriented, is mainly provided by pharmacists (1). Pharmaceutical care mainly involves identifying and resolving existing problems or preventing potential problems. Providing pharmaceutical care thrives in presence of mutual benefit where the pharmacist is directly responsible for the quality of care of the patient while the patient directly benefits from the pharmacist's competence and commitment (1). Pharmaceutical care is a patient-oriented approach offered as an ongoing process in which the patient is an active participant in the healthcare process (28).

Different researchers have shown that pharmacists have a positive impact in the outcome of patient management especially in patients with CKD. A medication review clinic led by a pharmacist identified MRPs and risk factors associated with these MRPs in patients undergoing haemodialysis (11). Another study showed that pharmacist services in management of renal anaemia had great therapeutic and pharmacoeconomic impact (29). In another study, clinical pharmacists optimized therapies aimed at modifying progression, optimized medication safety as well as management of complications associated with CKD (16). There is also a demonstration of positive impact of pharmacist-led medication dosing services in patients with CKD. There was an increase in usage of certain medications geared towards renal protection and medication dosing adjustment were also made (30). Another study among patients with CKD provide evidence that pharmacists improved hypertension management (31). Pharmaceutical care, geared towards identification and resolution of MRPs, resulted in reduced hospitalization rates,

reduced drug use and reduced costs for haemodialysis patients (32). Another study demonstrated that identification and prevention of DRPs necessitated inclusion of a clinical pharmacist in management of patients with CKD (12). Many other studies have also identified MRPs in patients with CKD through medication chart reviews (2)(33)(34).

2.4. Classification of Medication Related Problems

MRPs are classified with the aim of using such classifications during the process of pharmaceutical care process and research in pharmacy (35). Classification helps identify the most common MRPs and consequently the appropriate action plan especially if preventable MRPs are the most common.

Different classification systems are available and have been used by different researchers. The most commonly used classifications include: Pharmaceutical Care Network Europe (PCNE) system (Version 6.2), National Coordinating Council for Medication Error Reporting and Prevention (NCC-MERP) taxonomy of medication errors, Granada consensus, Westerlund System, ABC of Drug related Problems, Problem Assessment and Solutions (PAS) system, Hepler and Strand classification, American Society of Health Systems Pharmacists (ASHP) classification, Cipolle *et al* classification, Health Base Foundation Subjective Evaluation Plan (SHB-SEP) classification, Krska et al system, Problem Intervention Documentation (PI-Doc), Mackie classification and Hanlon approach (35). Few classifications have been validated.

Hepler and Strand classification system consists of eight categories: improper drug selection (IDS), Sub-therapeutic dosage (STD), Drug without indication (DWI), drug interaction (DI), Indication without drug (IWD), Failure to receive drug (FRD), Over dosage (OD) and Adverse drug reaction (ADR) (36). This is illustrated by the conceptual framework in figure 1. It is based on the definition of DRP as an unwanted patient experience that involves drug therapy and that actually or potentially hampers with a desired patient outcome event or circumstance. This classification system has been used by other researchers (11)(18) (37)(38). Hepler and Strand classification is easier to use in Sub Saharan Africa set up taking into consideration the level of healthcare services currently being offered in these countries.

2.5. Prevalence and Factors Associated with Medication Related Problems in Chronic Kidney Disease

Various studies have identified different MRPs in the CKD populations. Improper drug selection was the commonest (24%) MRP identified in one of the studies (39). Drug interactions was the commonest (28%) MRP in yet another study (33). A different study identified indication without drug therapy as the most common (51%) MRP in the study population (40). This shows that each study population has a different pattern of MRPs in CKD. Most of these studies have included the number of MRPs identified and the most common MRPs in the study population. Others have further identified possible factors associated with MRPs in patients with CKD. According to Hepler and Strand classification, the different classes of MRPs identified include:

2.5.1. Indication Without Drug

Indication without drug (IWD) means the patient is not receiving a drug for a given medical condition despite the need for such a drug (1). Conditions in which the patient is in need of prophylaxis or pre-medication are examples of IWD (36).

One study identified 199 MRPs and the most common (51%) MRP was IWD (40). The study demonstrated MRPs in ESRD patients on admission were frequently related to gaps in medication information transfer between healthcare providers and patients. Another study identified 142 DRPs with increased age and a higher number of medications correlating significantly with the DRPs (13). The study established three-at-risk situations; self-medication habits, unawareness of the beneficial impact of treatment and medical situations at risk (13). In a prospective study, 475 MRPs were identified and the second most common (17.5%) MRP among haemodialysis patients with diabetes mellitus was IWD (3). In this study, as the number of comorbidities increased, the number of MRPs in an individual patient also increased. Indication without drug therapy was at 16.9% of MRPs identified in a pooled analysis of MRPs in ambulatory haemodialysis patients (2). Pharmaceutical care services to patients with CKD in Grenoble university hospital identified 263 MRPs. One of the commonest MRP was IWD at 30% (12). No drug prescribed but clear indication was one of the commonest MRP observed in elderly patients discharged from hospital (41). Several studies reported untreated indication was one of the most common MRP

in admitted patients (18)(42)(43)(44)(45). Hypertension, diabetes mellitus, arthritis, cardiovascular disorders, lipid disorders and renal bone disease were the most common untreated indications.

2.5.2. Sub-therapeutic Dosage

Sub-therapeutic dosage (STD) means the patient is taking too little of the correct drug for a given medical condition (1). Failure to individualise drug dosage for a specific patient taking into consideration all of the specific patient information as well as drug/disease specific information may lead to STD. Receiving inappropriate dosage interval or a regimen not continued long enough can also result to STD (36).

Dialysis presents a challenge to healthcare providers especially on appropriate medication dosing for these patients. This is attributed to multiple comorbidities and changing pharmacokinetics, pharmacodynamics and laboratory parameters for patients on dialysis. A renal drug dosing service for patients with CKD that are hospitalized, can improve dosage adjustments for drugs eliminated primarily via renal system, taking into account the renal function (46).

One study identified 469 MRPs among end stage renal disease (ESRD) patients; the most common (29%) MRP was sub-therapeutic dosage (15). These MRPs were attributed to lack of multidisciplinary services. Another study reported that STD was the second most common (13.6%) MRP (40). The investigators attributed these STD problems to poor information transfer between healthcare providers and the patients.

Another study reported discrepancies between information from electronic records and information on drug history from haemodialysis patients mainly consisted of dosing errors (34.5%) (47). Sub-therapeutic dosage contributed half of these errors. A multi-centre study in French hospitals identified STD as the third most common MRP accounting for 19.2% of MRPs identified (48). The involvement of a clinical pharmacist in the management of patients with CKD identified and prevented MRPs (12). Sub-therapeutic dosage accounted for 25.9% of MRPs in the study population. A prospective observational study identified 354 MRPs in haemodialysis patients and the most common (34%) MRP was medication dosing problems (49).

2.5.3. Drug Without Indication

Drug without indication (DWI) means the patient has no valid medical indication for taking a certain drug (1). This often occurs in self-medication and substance abuse probabilities. There are other several causes for DWI. An instance is when a single condition is treated with multiple drugs despite a single drug being effective (36). Another example is patient being on more than one laxative for treatment of constipation.

Drug without indication was a major MRP among haemodialysis patients, accounting for 30.9% of all MRPs (3). In addition, another prospective study found geriatric patients had more incidences of DWI in comparison to cardiology, rheumatology and respiratory patients ($P<0.01$) (50). Another study identified 10% of MRPs as DWI (45).

2.5.4. Adverse Drug Reaction

Adverse drug reaction (ADR) means that unwanted/unpleasant or harmful drug effects caused a medical condition in a patient (1)(51). An ADR occurs at normal doses used for normal indications. The reasons for a patient experiencing an ADR include: incorrect drug administration, administration of unsafe drug, a drug reaction or even an allergic reaction (36). Examples of ADRs include anaphylaxis with injectable penicillins and Stevens- Johnson syndrome with sulphonamides.

ADR was one of the most common (20.7%) MRP in ambulatory haemodialysis patients (49). Drug record discrepancies placed haemodialysis patients at risk of adverse events in 49.6% of 113 discrepancies (47). The number of drug discrepancies decreased with increase in age. A clinical pharmacist offering renal drug dosing services for patients with CKD may prevent ADRs (46). A study identified 216 potential MRPs among chronic haemodialysis patients (39). The incidence of potential adverse effects averaged 5.5 per patient while medication allergies or intolerances averaged 2.2 per patient. Another prospective interventional study in a tertiary care centre on haemodialysis patients reported 10.25% of MRPs to be ADR (38).

Another study in KNH medical wards identified 338 MRPs of which ADR contributed 10.7% (18). A study in a teaching based hospital identified 147 MRPs; the most common (41.5%) was ADR (52).

2.5.5. Drug Interactions

Drug interaction (DI) means patient has a medical condition due to negative effects of drug-drug/food interactions (1)(51). They can be due to pharmacodynamic or pharmacokinetic interactions in patients receiving various drugs (36). Drug interactions between supplements such as calcium salts and iron products is common seen in dialysis patients (33). The possibility of an ADR due to chemical or physical interaction of food and drug is common (36). An example is milk inhibiting absorption of oral iron compounds. Another example is excessive consumption of Vitamin K-rich foods reducing the efficacy of vitamin K antagonists (51). Enzyme induction or inhibition and protein binding characteristics affect pharmacokinetic and pharmacodynamic profile of various drugs thus DI (36).

Drug interactions are common among patients with CKD due to polypharmacy (17). A study among patients with CKD in a South Indian tertiary care hospital identified 474 DI with incidence rates of 76.09% (17). A prospective study on haemodialysis patients identified 126 MRPs; the most common MRP was drug interactions at 28% (33). Another prospective interventional study in a tertiary care centre on haemodialysis patients identified 39 MRPs; the most common MRP was drug interactions at 25.64% (38). An identification of DI in CKD revealed a prevalence of 74.9% of DI (14). The occurrence of DI increased with addition of a drug to the prescription. Risk factors associated with the DI were body mass index (BMI), age, diabetic and hypertensive nephropathy, hypertension, diabetes and stage of CKD (14)

A study in internal medicine wards, KNH identified 30.5% MRPs as DI (18). A prescription analysis in a university hospital identified 7073 MRPs; one of the commonest being DI at 11.6%) (53). A study on MRPs in a general internal medicine service identified 383 MRPs; most common was DI at 21% (45). A study in a university hospital, Beirut identified the most common MRP as DI at 37% (54).

2.5.6. Improper Drug Selection

Improper drug selection (IDS) means the patient is taking the wrong drug for a given medical condition (1). This can occur where a patient receives drug in presence of contraindications or allergy to that drug. Another incidence of IDS can occur where a patient receives combination therapy yet single therapy is equally effective (36). An example of IDS is not initiating a diuretic in a hypertensive patient.

A study on haemodialysis patients identified 216 potential drug related problems; the most common was improper drug selection at 24% (39). An interventional study found pre-intervention group having 53% of MRPs as IDS (46). Another prospective interventional study in a tertiary care centre on haemodialysis patients identified 7.69% of MRPs as IDS (38).

A multicentre study in French hospitals identified the most common MRP as IDS at 21.3% (48). Improper drug selection accounted for 23% of MRPs identified by clinical pharmacist (54). A prescription analysis identified 12.8% as IDS (53). Improper drug selection was commonly observed in elderly patients discharged from hospital (41). The number of MRPs was associated to the number of drugs prescribed.

2.5.7. Failure to Receive Drug

Failure to receive drug (FRD) means patient is not receiving prescribed medications for a given medical condition (1). Failure to receive drug can also be looked at as patient non-adherence or noncompliance. This could be due to various reasons either within the patient's control or those outside of it. Drug distribution or administration system that fails the patient results in this type of MRP. Formulation problems interfering with ADME profile of the drug also causes this type of MRP (36). An example of non-adherence to medication regimen is a patient failing to bring phosphate binders when they eat out (51). Inability of patient to pay for medication can also lead to FRD. Patients with CKD have many medication-related problems (MRPs) and high rates of medication non-adherence (55). One of the main determinants of preventable medication-related hospital admissions was non-adherence to medication regimen (56)

A study on haemodialysis patients identified 216 potential MRPs; among the commonest was medication noncompliance at 23% (39).The investigator reported an average of 3.4 medication doses per month were missed by 67% of the participants (39). A prospective study on haemodialysis patients in a tertiary care centre found 17.94% of MRPs to be FRD (38). A systematic review identified 51% prevalence of non-adherence to phosphate binders in ESRD patients (57). This prevalence was attributed to patients' related factors such as beliefs about medication and personality characteristics.

Another study found medication non-adherence was common in pre-ESRD patients (58). Potential contributing factors included patients' poor understanding of their regimens, low health literacy and polypharmacy. The study concluded that a multidisciplinary educational program might decrease avoidable morbidity through improving understanding and compliance (58). A study on Irish haemodialysis patients found 62% prevalence of non-adherence to treatment regime (59). Risk reduction of ESRD was related to high adherence to antihypertensive agent(s) (60). A study in KNH medical wards identified non-adherence at 21.9% (18).

2.5.8. Over-dosage

Over-dosage (OD) means patient is taking too much of the correct drug for a given medical condition (1). Failing to adjust the dose of medications eliminated via renal system is a common cause of OD in CKD. Pharmacokinetic monitoring and dose adjustments are important in prevention of OD (36). Dosing adjustments for drugs cleared via renal system should be adjusted according to creatinine clearance and can be calculated using electronic or online calculators(61). Maintenance doses can be adjusted through either the lengthening of dosing intervals or reducing the doses or employing both strategies (61).

A study on dose adjustments in patients with CKD at KNH identified over-dosage as the most common dosing error (62). A study on pharmaceutical care in patients with CKD established over-dosage to constitute 18.3% of the pharmaceutical interventions (12). A prospective observational study on haemodialysis patients identified 354 MRPs of which the most common MRPs was medication dosing problems at 34% (49). Another study in a tertiary care centre on haemodialysis patients identified 39 MRPs; one of the commonest MRP was over-dosage at 23.07% (38).

One of the most common reported MRPs in a study on pharmacy activities in CKD was incorrect dosing (63). Dosing errors accounted for 15.4% of the MRPs identified in a study (3). A pharmacist detected more than 10% of OD in prescription analysis at a university hospital(53). A study in KNH identified 10.1% of MRPs as over-dosage (18). Medication related problems in a general internal medicine service constituted 16% as OD (45). Over-dosage accounted for 28% of MRPs identified by pharmacists in a university hospital (54). Another study also identified one of the commonest MRP to be over-dosage at 22% (64).

2.6. Pharmacist Recommendations/Interventions on Chronic Kidney Disease Management

In the process of medication therapy review, the pharmacist upon identification of MRP should plan a way of resolving or preventing the problem. The resultant decision is discussed with the attending physician and other healthcare team members as a recommendation or intervention protocol. Several studies have reported on various pharmacist recommendations or interventions and sometimes their clinical outcomes/significance.

A study in France where a clinical pharmacist was consulted in outpatient nephrology clinic patient visits, 263 pharmacist interventions were observed (12). The interventions concerned untreated indication (30%), under-dosage (25.9%) and over-dosage (18.3%). The most frequent pharmacist interventions identified in this study were adaptation of doses (42.2%) and addition of drugs (31.9%). Other pharmacist interventions were drug stoppage (17.5%) and drug substitution (4.6%). Another study on medication dosing intervention, led by a pharmacist, made recommendations for medication adjustments for 138 medications (30).

A systematic review on interventions made by pharmacists during management of patients with CKD, 2683 MRPs were identified in slightly over 1000 patients (65). Other results from different studies demonstrated that interventions by pharmacists reduced all-cause hospitalisations, improved management of anaemia, blood pressure, calcium and phosphate parameters and lipid management as well as reducing number of adverse effects (65).

Studies in the CKD population provide more evidence from the wider population of the benefit of including pharmacists in the healthcare team. Such benefits include improved hypertension management in patients with CKD (66). There was intensification of antihypertensive regimens as well as improvement on medication adherence in one of the studies (66). A pharmacist led CKD screening in HIV patients improved CKD screening frequency from 11% to 58% (67).

In another study, clinical pharmacists optimized therapies aimed at modifying progression, optimized medication safety as well as management of complications associated with CKD (16). A renal consultation coupled with a clinical pharmacist evaluation detected a higher level of MRPs and reinforced educational messages (13).

It is thus prudent to conclude that pharmacists' interventions in the management of patients with CKD have a positive impact in the general management of these patients.

2.7. Literature Gap

As established from the literature review, it was evident that patients with CKD are at a higher risk of MRPs compared to the general population. This has been attributed to comorbidities, high pill burden and patient related factors such as non-adherence and self-medication habits. There is scarcity of data from African countries including Kenya regarding extent and type of MRPs in patients with CKD. Moreover, patient related risk factors associated with MRPs in patients with CKD in Kenya has not been established. Pharmacist interventions in the identification and resolution of MRPs in patients with CKD in Kenya have also not been established.

The study thus aimed at establishing the extent of MRPs among patients with CKD as well as exploring associations of different covariates with each category of MRP identified. The study findings would provide the much needed data on the extent and types of MRPs among patients with CKD in Sub Saharan Africa. The study would also provide data on possible predictors of these MRPs in patients with CKD treated at a referral hospital in Sub Saharan Africa.

3. CHAPTER THREE: METHODOLOGY

3.1. Introduction

This chapter describes the components of methods that were used to carry out the study. These components include: research design, location of the study, study population, sampling technique, data collection instruments, quality assurance, data collection techniques, data management and analysis techniques as well as logistical and ethical considerations.

3.2. Research Design

To achieve the goals of the study, a cross-sectional survey of adult patients with CKD receiving care at KNH between April and June 2016 was conducted. The cross-sectional study design was chosen for this exploratory study because of its efficiency and cost effectiveness in providing adequate descriptive and analytic snapshots of population phenomena in a given point in time (68).

3.3. Study Site

Kenyatta National Hospital (KNH) is a tertiary care hospital located in Nairobi, Kenya. It is the largest referral hospital in East and Central Africa, and also serves as the teaching hospital for the University of Nairobi, College of Health Sciences and the Kenya Medical Training College. It has a bed capacity of 1800 located in 50 wards and 22 outpatient clinics (69). Most patients with CKD in the country are referred and treated here. Approximately 50 patients with CKD are followed-up at the hospital's ambulatory renal clinic weekly. Majority of patients with CKD admitted into the hospital are admitted to medical wards (7A-7D and 8A-8D) and are cared for by multidisciplinary teams mainly composed of physicians, nurses and pharmacists.

3.4. Study Population

The study population consisted of adult patients diagnosed with CKD stage 3 or 4 and undergoing treatment and follow up at KNH during the study period from April to June 2016.

3.5. Eligibility Criteria

3.5.1. Inclusion Criteria

Patients who met the inclusion criteria were CKD stage 3 or 4 adult patients undergoing treatment at KNH during the study period and who gave voluntary informed consent (self or proxy).

3.5.2. Exclusion Criteria

The eligible participants who declined to sign informed consent, pregnant women, haemodialysis patients and post-renal transplant patients were excluded from study participation.

This study involved only patients with CKD stage 3 or 4 because this group has marked reduction of GFR making dosage modifications mandatory for all drugs eliminated via the renal system. This group is also likely to present with CKD complications and other comorbidities like diabetes mellitus and lipid abnormalities making it a high risk group in experiencing MRPs. They are also not dependent on renal replacement therapy and efforts to retard progression into ESRD are valuable. Patients with CKD stage 1 and stage 2 are likely to be only accidentally diagnosed, not likely to be hospitalised or followed up at the renal clinic and also do not present with complications because of adequate residual renal function. Patients with CKD stage 5 are entirely dependent on renal replacement therapy which is a confounder in identification and prevention or resolution of MRPs in patients with CKD. For these reasons, the eligibility criteria consists of only patients with CKD stage 3 or 4.

3.6. Sample Size

The sample size was based on the estimates of prevalence of MRPs among patients at KNH medical wards of 96.7% and by extension patients with CKD since majority of the admitted CKD cases are treated in these wards (18).

Using Fisher's formula the sample size was calculated as follows (70)

$$N = \frac{z^2_{\alpha/2}\ \mathrm{P(1\text{-}P)}}{\delta^2}$$

Where

N = Minimal sample size required.

P = Estimated prevalence of MRPs in CKD = 96.7% (18).

$z^2_{\alpha/2}$ = Standard normal deviate at 95% confidence interval corresponding to 1.96

δ = Absolute error between the estimated and true population prevalence of CKD of 5%.

The calculated sample size was

$$N = \frac{1.96^2_{\alpha/2}\ 0.967(1\text{-}0.967)}{0.05^2}$$

N = 49 patients.

Adjusted for 20 % incomplete data, the sample size was 60.

At the end of the study 60 participants who met the inclusion criteria were recruited in the study

3.7. Sampling Method and Participant Recruitment

A convenient sampling method was used to consecutively select every accessible patient who met the inclusion criteria from the renal clinic and internal medicine wards. A list of patients admitted who had CKD was obtained from the ward in charge. Files of these patients were perused to identify patients who met the inclusion criteria using screening and eligibility form (Appendix 1). The patients were then approached at an hour when there was not much work and asked to participate using the consent explanation forms (appendix 2A). For patients who were too ill or only spoke mother tongue, the next of kin was identified and approached during visiting hours and proxy consent explained using consent explanation form (appendix 2A). Patients or caregivers consented to participate in the study by signing the consent declaration form (appendix 2B).

Recruitment was also done during clinic visits. The study was fully explained to the patients after they had been seen by the physician. This was done by the study personnel who used a screening and eligibility form (Appendix 1) to recruit eligible patients. An explanation on the procedure, harm, benefits and confidentiality of the study was given to those eligible before administering a consent explanation form

(Appendix 2A). Those who were willing to consent signed a consent declaration form (Appendix 2B).

Chronic kidney disease in this study was defined as GFR <60 ml/min/1.73m^2 for ≥ 3months irrespective of the presence or absence of kidney damage according to KDOQI 2002 guidelines (7).

The stage of kidney disease was categorized using eGFR calculated based on the serum creatinine levels using the MDRD formula (71). This is illustrated below:

eGFR (ml/min/1.73m^2)

$$=175 \times (S_{Cr}^{-1.154}) \times (Age)^{-0.203} \times (0.742\ if\ female) \times (1.21\ if\ black)$$

An electronic calculator based on the above equation was used to estimate GFR and classify the participant to either CKD stage 3 or 4 as shown in Table1

3.8. Data Collection Instruments

A screening eligibility form: This was used to guide selection of patients who met the inclusion criteria (Appendix1).

Informed consent form: This was used to obtain consent from those who met the eligibility criteria. Those unable to understand English version, Kiswahili version was administered instead (Appendix 2B). If there was language barrier proxy consent was obtained from the caregiver.

Data Collection Form: A structured data collection form was used to collect information from patient and from patient file after the patient had signed the consent form. It had three sections. The first section had socio demographics details and medical history from the patient interview. The second section had medical history collecting relevant clinical and laboratory information from the medical record and medication charts review. The third section constituted the evaluation of MRPs including presence, classification and probable causes of the MRP plus documented pharmacist interventions (Apendix3).

3.9. Data Collection

The data collection period was 3 months, that is, between April and June 2016. Each study participant completed an interviewer administered structured questionnaire (see Appendix3) aimed at collecting medical history data from the patient.

The patient treatment charts, prescription records and medical records belonging to each study participant were prospectively reviewed by study investigator after each routine clinical encounter using a structured tool (see appendix3).

Data collection was a two-step process. First step was patient interview and second step was medical records and medication chart reviews. A structured questionnaire was used for data collection. This was administered by the study investigator. The questionnaire had three main sections (Appendix3).

3.9.1. Patient Interview

Once informed consent had been obtained, the study investigator interviewed the admitted patient immediately using a structured questionnaire. If patient was at the renal clinic, the interview was conducted after being seen by the physician. The first section of the questionnaire was used to obtain baseline socio demographic details such as age, sex, marital status, level of education, occupation, level of income and patient status on cigarette smoking and alcohol intake. It also obtained comprehensive medical history including chief complaint, history of present illness, past medical history, medication history and relevant physical examination as well as MRPs reported by the patient and other aspects of patient related risk factors associated with MRPs

3.9.2. Medical Record and Medication Chart Review

A medical record and medication chart review was conducted such that the medical history, physical examination notes and results of laboratory and diagnostic tests, diagnosis and treatment were reviewed. This was done using the second section of the questionnaire. The third section of the questionnaire was used to collect information regarding MRPs, their occurrence, their classification and the probable causes of these MRPs as well as to collect information on documented pharmacist interventions. MEDSCAPE clinical information software was used to provide up to date clinical and medicine information and support decision making on absence or presence of an MRP. Drug interaction analysis was conducted using the MEDSCAPE drug interaction checker (MEDSCAPE®, 2016).

3.10. Variables and Definitions

The study was mainly descriptive with multiple variables. The primary outcome variable was prevalence of MRPs in patients with CKD. A medication related problem (MRP) was defined as an unwanted patient experience that involved medication therapy and that actually or potentially hampered with a desired patient outcome (1). The MRPs were then classified according to Hepler and Strand classification (1990) as shown in the conceptual framework Figure 1. In this study the outcome variables (different categories of MRPs) were defined and evaluated for their presence as follows:

Improper drug selection (IDS)- means patient is taking the wrong drug for a given medical condition (1). In this study it mainly included situations where choice of medications was inappropriate given the comorbidities the patient was suffering from. An example of IDS was where an angiotensin converting enzyme inhibitor (ACEI) or angiotensin II receptor blocker (ARB) was not included in management of hypertension in a patient presenting with proteinuria. Another example of IDS was where a patient had nephrotic syndrome and hypercholesterolemia yet had not been prescribed for a statin. Presence of contraindications was also classified as IDS. An example was the use of metformin when creatinine clearance was below 30ml/min. Management of hypertension without including a diuretic in the regimen was also a common example of IDS.

Failure to receive drug (FRD)- means patient is not receiving prescribed medications for a given medical condition (1). Failure to receive drug was also looked at as patient non-adherence or noncompliance. In this study FRD included situations where patient missed taking their medications due to various reasons. These reasons included cost inhibition, unavailability of the medications, dependence on care taker and side effects limiting adherence to medications.

Over-dosage (OD)- means patient is taking too much of the correct medication for a given medical condition (1). In this study over-dosage was identified where drugs that needed dose adjustment as per creatinine clearance was not done or was done incorrectly leading to possibility of over-dosing. This was common with antiinfectives such as tenofovir, lamivudine, amoxicillin/clavulanate, clarithromycin and levofloxacin. Over-dosage was also considered to be present when too much of a drug

was being used in treatment. An example was the use of high doses of omeprazole in stress ulcer prophylaxis. Over-dosage was also present where the frequency of administration of a drug was higher than recommended.

Sub-therapeutic dosage (STD)- means patient is taking too little of the correct drug for a given medical condition (1). Sub-therapeutic dosage was identified where frequency of dosing was lower than recommended. An example was once daily dosing of carvedilol instead of the recommended twice daily dosing. Another example was in the dosing frequency of erythropoietin stimulating agents where the total weekly doses were below the recommended doses. Sub-therapeutic dosage was also identified where optimal control of symptoms had not been achieved yet the doses of drugs had not been optimized. An example was uncontrolled hyperglycaemia with insulin use.

Indication without drug (IWD)- means patient is not receiving a drug therapy for a given medical condition despite the need for such a drug(1). In this study it included patient diagnoses that were not being addressed. An example was anaemia and bone mineral diseases being present yet no medications to address these conditions. IWD also included conditions that needed prophylaxis yet the patient was not on any prophylactic regimen. Presence of atrial fibrillation with no anticoagulant for prophylaxis against thrombotic episodes was an example of an IDW.

Drug without indication (DWI)- means patient has no valid medical condition for taking a certain drug (1). This definition was applied in this study. An example was the use of antibiotics without evidence of bacterial infection ether clinically or from laboratory work up. Another example was use of iron supplements despite normal haemoglobin levels. The use of different multivitamins and supplements with no clear reason for prescribing them was also a common occurrence contributing to DWI.

Adverse drug reaction/effect (ADR)- means that unwanted/unpleasant or harmful drug effects caused a medical condition in a patient who used the normal dose of the drug for normal medical condition (1)(51). In this study, an ADR included what the patient reported as unwanted effects or side effects associated with taking certain drugs as well as abnormal laboratory findings associated with drug interactions. Examples of ADR included abdominal pain, diarrhoea, nausea vomiting, decreased

libido, confusion, dizziness and coughing. Another example of ADR was hyperkalaemia due to interaction between spironolactone and trimethoprim

Drug interaction (DI)- means patient has a medical condition due to negative effects of drug-drug/food interactions (1)(51). In this study the drug interactions only included drug-drug interactions as evaluated by use of MEDSCAPE®, 2016 drug interaction checker.

For each patient the number of MRPs was computed and to establish possible risk factors for the MRPs, each category of MRP (except drug interactions) was regressed against potential predictor variables shown in table 2.

Table 2: Predictor variables (Covariates)

	Variable	Class
Patient-centred factors	Age	Discrete
	Sex	Binary
	Marital Status	Binary
	Education Level	Binary
	Average monthly Income	Binary
	Occupation	Binary
	Smoking	Binary
	Alcohol Intake	Binary
	CKD stage	Binary
Regimen and comorbidity Factors	Number of medications	Discrete
	Number of comorbidities	Discrete
	Diabetes mellitus	Binary
	Hypertension	Binary
	CCF/HHD	Binary
	HIV	Binary
	Anaemia	Binary
	Chronic glomerulonephritis	Binary
	Nephrotic syndrome	Binary
	Respiratory illness*	Binary
	Other Cardiovascular diseases**	Binary
	Bone mineral disease	Binary
	Electrolyte imbalance***	Binary
	Liver abnormalities	Binary
	Other diseases****	Binary

KEY: *CCF/HHD- Congestive cardiac failure/hypertensive heart disease*
HIV- Human Immunodeficiency Virus
CKD- Chronic kidney disease
**Includes acute and chronic pulmonary disease like pneumonia, tuberculosis, chronic obstructive pulmonary disease, asthma*
*** Includes Myocardial Infarction, Pulmonary Hypertension, Deep Venous Thrombosis, Pulmonary Embolism, Dilated cardiomyopathy, stroke, infective endocarditis and erectile dysfunction*
****Includes hyponatremia, hypokalaemia and hyperkalaemia*
***** Includes Fungal infections, gout/hyperuricemia, uremic encephalopathy, sepsis, peptic ulcer disease, dental caries, osteoarthritis, Benign prostate hyperplasia, lipid abnormalities, constipation, meningitis, chronic obstructive lung disease, Parkinson)*

3.11. Data Management

Data was collected using structured standardized tool and entered into a password protected Microsoft Excel. To ensure confidentiality unique patient identifiers rather than patient names or outpatient numbers were used for forms used to retrieve the data from the files. The patient files were retrieved and the data extracted within the medical wards and renal clinic by the investigator. Any document linking the collected data to the patient files including the raw data was kept under lock and key and was only accessible to the principal investigator or on request by regulatory teams like the Ethics committee and the supervisors.

All collected data was coded, cleaned, processed and stored at the end of each day by the principal investigator. Data entry was done on the day of collection and backed up every three days. This was done in an external hard disk and a flash disk all of which were stored at separate sites. After completion of the project, all collected data was disposed by shredding of used data collection forms and permanently deleting the soft copy in the hard disk as well as formatting the flash disk used for storage.

3.12. Quality Assurance

All data obtained from patient files was double checked by the study investigator during data entry. The standards outlined in the Good Clinical Practice (GCP) and the International Council for Harmonisation (ICH) guidelines were adhered to.

Validity

External validity of the study was established by choosing an appropriate sample size and internal validity was guaranteed by clear definition of variables.

Reliability

Data collection tools were tested for reproducibility of data using the first ten participants in the main study to check for ambiguity but the tool was confirmed effective due to reproducibility of results. Concise descriptions of methodology ensuring reproducibility also guaranteed reliability.

3.13. Statistical Analysis

Data was analysed using R Statistical Programming Language, produced by the R Foundation for Statistical Computing, Vienna, Austria (72). Descriptive summary statistics were presented as means with standard deviation for normally distributed

continuous variables, and medians with interquartile range for non-normally distributed continuous variables. Categorical variables were summarized using frequencies and percent proportions.

Bivariate logistic regression was used to analyse the associations between individual types of MRPs and the covariates identified in the survey data. The primary goal of the analysis was to investigate the associations between CKD Stage and individual type of MRP, and whether these associations are confounded by other covariates (see Table 2). This analysis was achieved in two steps. First, univariate logistic models of CKD Stage and individual MRPs were constructed and their odds ratios, the 95% confidence intervals of the odds ratio, and the associated p-values computed.

Second, multivariable logistic regression models were constructed to investigate the associations between CKD stage and individual MRPs while adjusting for possible confounding by other covariates. Due to the relatively large number of covariates and the small sample size in the study, it was necessary to rely on subset selection to estimate the most parsimonious (simplest possible) multivariable models that best explained the associations being investigated. For this task, best subset selection using Bayesian Information Criterion (BIC) was employed to select models with no more than 4 covariates. The odds ratios, the 95% confidence intervals of the odds ratio, and the associated p-values of all the BIC models were computed and reported. Confounding was investigated only in multivariable models having CKD stage as one of the covariates. A covariate was considered to be a confounder if: 1) It was associated with CKD stage, 2) It was associated with the MRP in the model 3) It cannot be an intermediate step between CKD stage and the MRP in the model, and 4) If the coefficient of the CKD stage parameter in multivariable model differed from the CKD parameter in the respective univariate model by more than 10%.

3.14. Ethical Considerations

Approval to carry out the study was obtained from the KNH/ University of Nairobi (UoN) Research and Ethics Review Committee prior to commencement of the study (see appendix 4). The principle of ethical research as outlined in the ‘Nuremberg Code and Declaration of Helsinki (1964)’ was adhered to. The following were considered:

3.14.1. Informed Consent

Informed consent was obtained from patients or proxy consent obtained from caregivers of patients who were too ill or could not communicate in English or Kiswahili. This was done by checking for signed consent declaration forms from participants (Appendix2B).

3.14.2. Risks and Benefits

There was little risk to patients since there were no invasive procedures being done to the patients. Patient confidentiality was maintained. Participants signed a voluntary consent so there was no coercion. Quality of care was not changed. The benefits to the patients were immense because serious MRPs were identified and communicated to the physician resulting in better patient outcomes.

4. CHAPTER FOUR: RESULTS

4.1. Introduction

This chapter depicts the findings of the research. The results have been summarized in form of normal tables, frequency tables and bar graphs. The P values, odds ratio and corresponding confidence intervals have been reported.

4.2. Characteristics of Study Participants

4.2.1. Socio Demographic Characteristics of the Study Participants

The study recruited 60 participants into the study. Socio demographic characteristics of the study participants are summarized as shown in table 3.

Table 3: Socio Demographic characteristics of study participants

Variable	
Age (Years)	54.2±16.8
Mean ± SD	
Gender, n (%)	
Male	26(43.3)
Female	34(56.7)
Marital status, n (%)	
Single	21(35)
Married	39(65)
Employment status, n (%)	
Never	29(48.3)
Ever	31(51.7)
Average monthly income (KES), n (%)	
<10000	36(60)
≥10000	24(40)
Alcohol intake, n (%)	
Never	32(53.3)
Ever	28(46.7)
Smoking cigarette, n (%)	
Never	43(71.7)
Ever	17(28.3)
CKD stage, n (%)	
Stage 3	43(71.7)
Stage 4	17(28.3)
Number of Comorbidities	
Mean ± SD	4.9±1.8
Number of Medications	
Mean ± SD	9.3±3.3
KEY: *SD= Standard deviation, KES= Kenya shillings, CKD= Chronic kidney disease*	

There were more females, 34 (56.7%) than males and the mean age of participants was ranging between 37 and 71 years. Forty-three (71.7%) participants were in stage 3 CKD. Majority, 39 (65%) were married and more than 80% of the participants had

obtained at least primary level of education. More than half of the participants never used alcohol or tobacco for recreation.

4.2.2. Clinical characteristics

Patient comorbidities are summarized in figure 2.

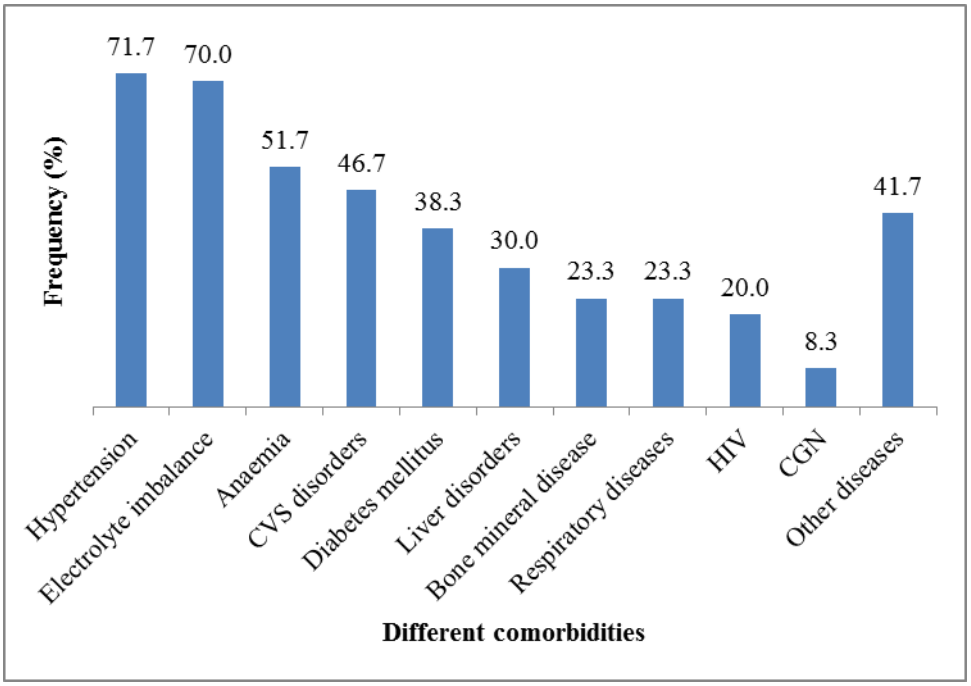

Figure 2: Comorbidities of study participants (N=60)

KEY: *CVS= cardiovascular, HIV= Human immunodeficiency virus, CGN= Chronic glomerulonephritis*

Other diseases includes fungal infections, gout/ hyperuricemia, uremic encephalopathy, sepsis, peptic ulcer disease, dental carries, arthritis, Benign prostate hyperplasia, lipid abnormalities, constipation, meningitis, parkinsonism and nephrotic syndrome

Electrolyte imbalance includes hyponatremia, hypokalaemia and hyperkalaemia

The mean number of comorbidities per participant was ranging between 3 and 7 comorbidities. Majority of the participants, 43 (71.7%) had hypertension as the commonest comorbidity followed by electrolyte imbalances 42 (70%), anaemia 31 (51.7%), cardiovascular disorders 28 (46.7%), diabetes mellitus 23 (38.3%) and liver disorders 18 (30%). Least common comorbidities were retroviral disease 12 (20%) and chronic glomerulonephritis 3 (5%).

The distribution of different comorbidities and association between the two CKD stages is as shown in table 4.

There was statistically significant association between CKD stage and presence of chronic glomerulonephritis (p= 0.020) but there were no statistically significant association between CKD stage and other comorbidities.

Table 4: Distribution of comorbidities across the two CKD stages

Variable		Stage of CKD				P-value
		Stage 3		Stage 4		
		n	**%**	**n**	**%**	
Hypertension	Yes	30	50	13	22	0.755
	No	13	22	4	6	
Diabetes mellitus	Yes	17	28	6	10	0.761
	No	26	43	11	18	
Anaemia	Yes	22	37	9	15	0.901
	No	21	35	8	13	
Respiratory disease	Yes	11	18	3	5	0.737
	No	32	53	14	23	
Electrolyte imbalance	Yes	29	48	13	22	0.550
	No	14	23	4	7	
Cardiovascular disorders	Yes	23	38	5	8	0.150
	No	20	33	12	20	
Liver disorders	Yes	15	25	3	5	0.228
	No	28	47	14	23	
Bone mineral disease	Yes	9	15	5	8	0.511
	No	34	57	12	20	
HIV	Yes	8	13	4	7	0.726
	No	35	58	13	22	
Chronic glomerulonephritis	Yes	0	0	3	5	**0.020**
	No	43	72	14	23	
Other diseases	Yes	17	28	8	13	0.772
	No	26	43	9	15	

KEY: *HIV= Human immunodeficiency virus*
Other diseases includes fungal infections, gout/ hyperuricemia, uremic encephalopathy, sepsis, peptic ulcer disease, dental carries, arthritis, Benign prostate hyperplasia, lipid abnormalities, constipation, meningitis, parkinsonism and nephrotic syndrome
Electrolyte imbalance includes hyponatremia, hypokalaemia and hyperkalaemia

Drugs used by the study participants are as summarized in figure 3 below. The mean number of drugs per participant ranged between 6 and 13 drugs. The most common prescribed drugs among the study participants, in decreasing order, were anti-hypertensive drugs 47 (78.3%), antiinfectives 34 (56.7%), anticoagulants 28 (46.7%) and lipid lowering agents 26 (43.3%). Least prescribed drugs among study participants were haematinics 7 (11.7%) and immunosuppressants 7 (11.7%).

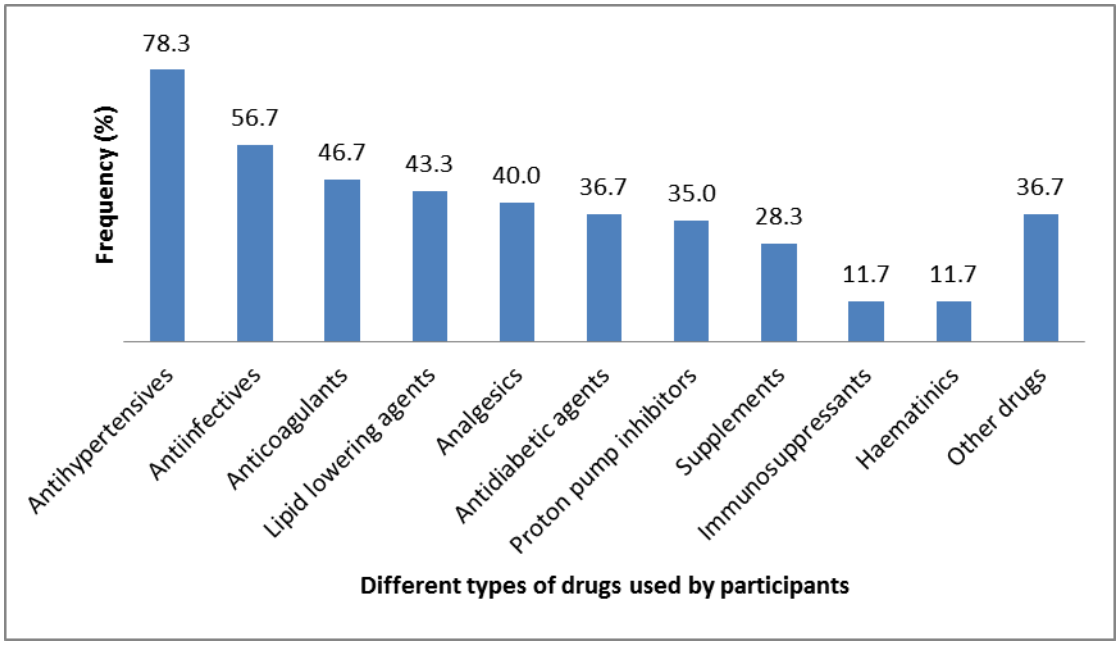

Figure 3: Drugs used by study participants

The distribution of drugs used by study participants and their associations between the two CKD stages is as shown in the table 5.

Table 5: Distribution of drugs used by participants across the two CKD stages

Variable		**Stage of CKD**				**P-value**
		Stage 3		Stage 4		
		n	**%**	**n**	**%**	
Antihypertensives	Yes	33	55	14	23	0.740
	No	10	17	3	5	
Anticoagulants	Yes	20	33	8	13	0.969
	No	23	38	9	15	
Antiinfectives	Yes	23	38	11	18	0.566
	No	20	33	6	10	
Proton pump inhibitors	Yes	14	23	7	12	0.560
	No	29	48	10	17	
Analgesics	Yes	18	30	6	10	0.773
	No	25	42	11	18	
Haematinics	Yes	2	3	5	8	**0.016**
	No	41	68	12	20	
Lipid lowering agents	Yes	18	30	8	13	0.777
	No	25	42	9	15	
Antidiabetic agents	Yes	16	27	6	10	0.890
	No	27	45	11	18	
Immunosuppressants	Yes	5	8	2	3	1.000
	No	38	63	15	25	
Supplements	Yes	14	23	3	5	0.346
	No	29	48	14	23	
Other drugs	Yes	17	28	5	8	0.560
	No	26	43	12	20	

There was a statistically significant association between the CKD stage and use of haematinics (p= 0.016) but there was no statistically significant association between CKD stage and the other types of drugs used by participants.

4.3. Prevalence of Medication Related Problems

Figure 4 below summarizes the different prevalence of medication related problems identified. A total of 271 MRPs were identified among the participants giving an average of 4.5 MRPs per participant with a standard deviation of 1.4. Each of the 60 study participants had at least one of the MRPs resulting in an overall prevalence of 100%. Only one participant had one MRP of a drug interaction. Majority of the participants, 98.3% had drug interactions while 81.7% had an indication without drug. Failure to receive drugs was identified in 70% of the participants while improper drug selection was seen in 55%. Least occurring MRPs among the participants was over-dosage (33.3%) and sub-therapeutic dosage (31.7%).

The identified MRPs were, in decreasing order, drug interactions 59 (21.8%), indication without drug 49 (18.1%), failure to receive drug 42 (15.5%), improper drug selection 33 (12.2%), drug without indication 25 (9.2%), adverse drug reaction/effect 24 (8.9%), over-dosage 20 (7.4%) and sub-therapeutic dosage 19 (7%).

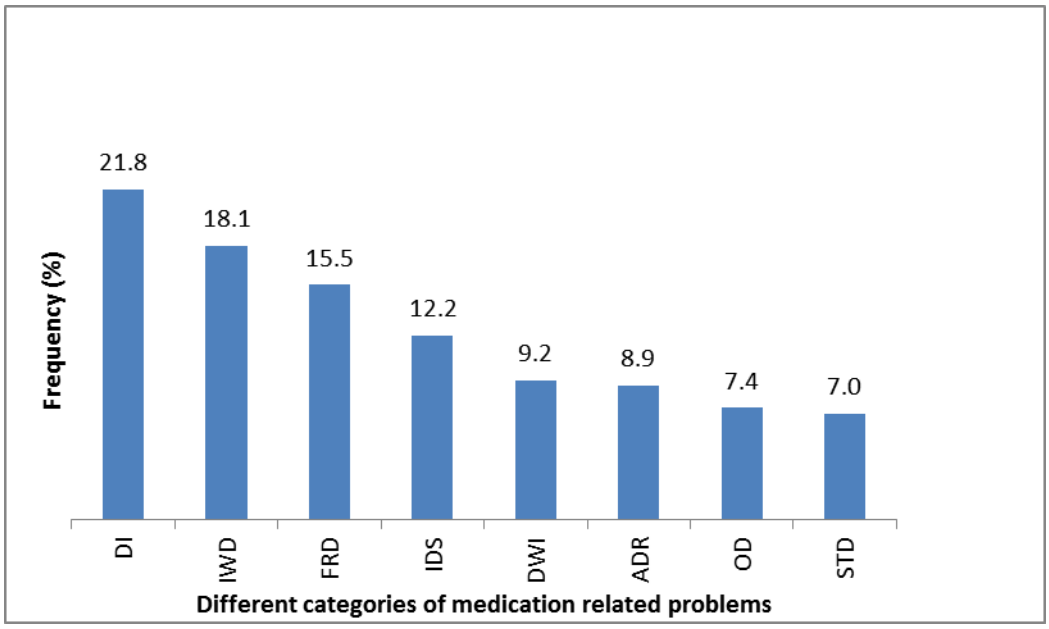

Figure 4: Prevalence of MRPs identified among study participants

KEY:

DI= Dug interaction, IWD= Indication without drug, FRD= Failure to receive drug, IDS= Improper drug selection, DWI= Drug without indication, ADR= Adverse drug reaction, OD= Over-dosage, STD= Sub-therapeutic dosage

Distribution of MRPs across the two CKD stages is as shown in table 6.

Table 6: Distribution of medication related problems across the two CKD stages

Variable		Stage of CKD				P-value
		Stage 3		Stage 4		
		n	**%**	**n**	**%**	
Drug Interaction	Yes	42	70	17	28	1.000
	No	1	2	0	0	
Sub-therapeutic dosage	Yes	11	18	8	13	0.131
	No	32	53	9	15	
Indication without drug	Yes	37	62	12	20	0.265
	No	6	10	5	8	
Over-dosage	Yes	10	17	10	17	**0.014**
	No	33	55	7	12	
Failure to receive drug	Yes	29	48	13	22	0.550
	No	14	23	4	7	
Adverse drug reaction	Yes	17	28	7	12	0.907
	No	26	43	10	17	
Drug without indication	Yes	19	32	6	10	0.575
	No	24	40	11	18	
Improper drug selection	Yes	19	32	14	23	**0.010**
	No	24	40	3	5	

There was a statistically significant relationship between the CKD stage and the possibility of patient being overdosed (p= 0.014) as well as poor drug selection (p= 0.010). There were no statistically significant relationships between CKD stage and presence of other types of MRPs.

Identified causes of the various MRPs in the study are shown in figure 5.

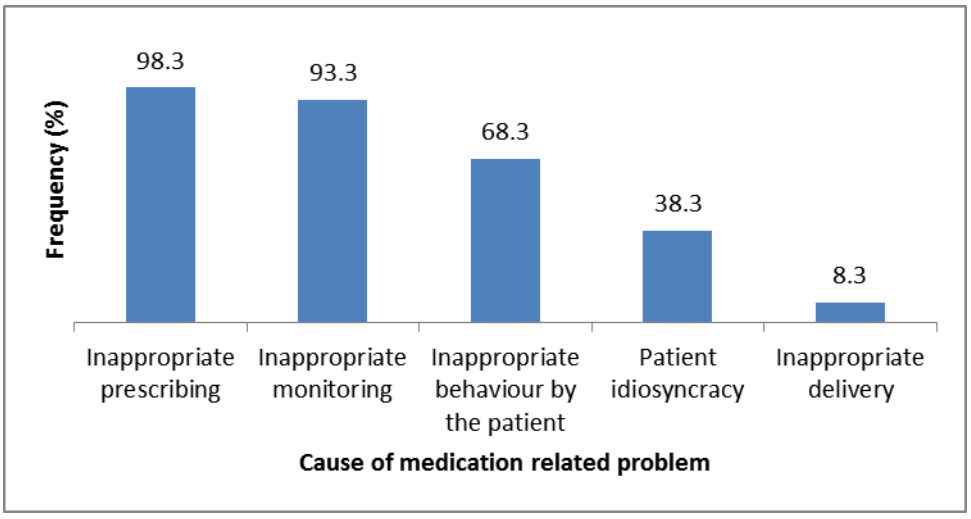

Figure 5: Causes of medication related problems in the study

The most common causes of MRPs in the study were inappropriate prescribing 98.3% followed by inappropriate monitoring, 93.3% and inappropriate behaviour by patient, 68.3%. The least occurring cause of MRPs was inappropriate delivery at 8.3%.

4.4. Association between various covariates with different types of MRPs

The association between the prevalence of MRPs and CKD stage are shown in table 7.

Table 7: Relationship between prevalence of MRPs and the stage of CKD

Variable		Stage of CKD				OR (95%CI)	P-value
		Stage 3		Stage 4			
		n	**%**	**n**	**%**		
Sub-therapeutic dosage	Yes	11	18	8	13	2.59 (0.80 - 8.52)	0.11
	No	32	53	9	15		
Indication without drug	Yes	37	62	12	20	0.39 (0.10 - 1.56)	0.17
	No	6	10	5	8		
Over-dosage	Yes	10	17	10	17	4.71 (1.46 - 16.34)	**0.01**
	No	33	55	7	12		
Failure to receive drug	Yes	29	48	13	22	1.57 (0.46 - 6.36)	0.49
	No	14	23	4	7		
Adverse drug reaction	Yes	17	28	7	12	1.07 (0.33 - 3.35)	0.91
	No	26	43	10	17		
Drug without indication	Yes	19	32	6	10	0.69 (0.20 - 2.16)	0.53
	No	24	40	11	18		
Improper drug selection	Yes	19	32	14	23	5.89 (1.64 - 28.34)	**0.01**
	No	24	40	3	5		

Association of improper drug selection and over-dosage with CKD stage was statistically significant. Patients with CKD stage 4 were 6 times more likely to have improper drug selection (95% CI, 1.64 - 28.34, p= 0.01) and 5 times more likely to experience overdosing problem (95% CI, 1.46 - 16.34, p= 0.01). The associations between CKD stage and adverse drug reaction, drug without indication, noncompliance, indication without drug and sub-therapeutic dose were not statistically significant since the confidence interval of their respective odds ratios spanned 1.

The results of the univariate logistic regression models for different MRP types and other covariates are shown in table 8.

Table 8: U**nivariate logistic regression models for different MRP types and other covariates**

Dependent variable	Predictor variable	OR (95% CI)	p-value
Adverse drug reaction	CVS disease (Yes vs No)	3.51 (1.13 - 11.58)	**0.03**
Improper drug selection	Respiratory Illness (Yes vs No)	0.23 (0.06 - 0.82)	**0.03**
Drug without indication	Number of medications	1.33 (1.11 - 1.67)	**0.01**
Indication without drug	Number of comorbidities	4.59 (2.07 - 15.02)	**0.002**
	Employment Status (Ever vs Never)	0.18 (0.03 - 0.79)	**0.04**
	Monthly Income (>10k vs <10k)	0.18 (0.04 - 0.72)	**0.02**
	Smoking (Ever vs Never)	4.15 (1.06 - 17.05)	**0.04**
Failure to receive drug	Number of comorbidities	1.56 (1.08 - 2.39)	**0.03**
	Number of medications	1.27 (1.05 - 1.59)	**0.02**
Over-dosage	Respiratory Illness (Yes vs No)	3.78 (1.10 - 13.75)	**0.04**
Sub-therapeutic dosage	Number of medications	1.27 (1.06 - 1.59)	**0.02**

Because of the large number of covariates, only associations that were statistically significant are reported. The other associations that were not statistically significant are shown in table 10 (see appendix 5). The number of comorbidities was significantly associated with failure to receive drug (noncompliance) and indication without drugs. For a unit increase in the *number of comorbidities*, the odds of failure to receive drug (noncompliance) increased by 1.56 (95% CI, 1.08 - 2.39, p= 0.03), and the odds of having an indication without a drug increased by 4.59 (95% CI, 2.07 - 15.02, p= 0.002). The number of medications was associated with the presence of drug without indication, failure to receive drug (noncompliance) and sub-therapeutic dosage. For a unit increase in the *number of medications*, the odds of having a drug without indication increased by 1.33 (95% CI, 1.11 - 1.67, p= 0.01), the odds of noncompliance increased by 1.27 (95% CI, 1.05 - 1.59, p= 0.02), and the odds of having sub-therapeutic dosage increased by 1.27 (95% CI, 1.06 - 1.59, p= 0.02). Except for indication without drug, socio-economic factors did not appear to have statistically significant association with MRPs. The odds ratio for having an indication without drug comparing those who have ever been employed to those who have never been employed was 0.18 (95% CI, 0.03 - 0.79, p= 0.04). Similarly the odds of having an indication without drug were 0.18 (95% CI, 0.04 - 0.72, p= 0.02) among those

whose monthly income was more than KES 10000 compared to those whose monthly income was below KES 10,000. On the other hand, the odds of having an indication without drug were 4.15 (95% CI, 1.06 - 17.05, p= 0.04) times higher among those who have ever smoked compared to those who have never smoked.

The best subset multivariable models selected by Bayesian Information Criterion (BIC) for each of the MRPs are shown in Table 9.

Table 9: Multivariate analysis on independent predictors of MRPs in the study population

Dependent variable	Predictor variable	OR (95% CI)	p-value
Adverse drug reaction	Age (Numeric)	0.96 (0.93 - 1.00)	**0.047**
	CVS disease (Yes vs No)	4.18 (1.27 - 15.17)	**0.022**
Improper dug selection	CKD stage (Stage 4 vs Stage 3)	6.09 (1.60 - 31.49)	**0.015**
	Respiratory Illness (Yes vs No)	0.22 (0.05 - 0.86)	**0.038**
Drug without indication	Alcohol use (Ever vs Never)	0.19 (0.04 - 0.71)	**0.020**
	Number of medications (Numeric)	1.50 (1.19 - 2.01)	**0.002**
Failure to receive drug	Number of medications (Numeric)	1.27 (1.05 - 1.59)	**0.025**
Over-dosage	CKD stage (Stage 4 vs Stage 3)	6.69 (1.85 - 27.69)	**0.005**
	Respiratory Illness (Yes vs No)	5.75 (1.47 - 25.60)	**0.015**
Sub-therapeutic dosage	Number of comorbidities (Numeric)	0.56 (0.31 - 0.91)	**0.031**
	Number of medications (Numeric)	1.82 (1.32 - 2.86)	**0.002**
	Sex (Male vs Female)	7.30 (1.60 - 44.42)	**0.017**

CKD Stage was only selected in the *improper drug selection* and in the *overdose* multivariable models. The odds of having an improper drug selection among CKD stage 4 is 6.09 (95% CI, 1.60 – 31.49, p= 0.015) times of the odds of having an improper drug selection among CKD stage 3 patients, adjusting for the presence of a respiratory illness. Similarly, the odds of overdosing among CKD stage 4 patients was 6.69 (95% CI, 1.85 - 27.69, p= 0.005) times the odds of overdosing among CKD stage 3 patients, adjusting for the presence of a respiratory illness. However, because the association between respiratory illness and CKD stage (p= 0.51) was not statistically significant, respiratory illness did not satisfy all the criteria for confounding in both models. It was therefore reasonable to report the crude odds ratios in univariate models previously described.

The *adverse drug reaction* multivariable model had the covariates Age and CVS disease. Based on the 10% rule, age was a potential confounder of the association

between CVS disease and adverse drug reaction. However, age was not considered a true confounder in this model since it was neither significantly associated with CVS disease (p= 0.68) and nor was it associated with adverse drug reactions (p= 0.07). The simpler model was therefore reported. Similarly, in the *drug without indication* model, alcohol use did not appear to confound the relationship between the number of medications and the presence of a drug without indication. The best subset model for *failure to receive drug* (*noncompliance)* consisted of the number of medications as the only predictor variable. Based on this model, for a unit increase in the number of medications, the odds of failure to receive drug (noncompliance) increased by 1.27 (95% CI, 1.05 - 1.59, p= 0.025). The *sub-therapeutic dosage* model had 3 covariates – the number of medications, the number of comorbidities and sex. However, the number of comorbidities and sex did not satisfy the criteria for confounding the association between number of medications and sub-therapeutic dosage.

5. CHAPTER FIVE: DISCUSSION, CONCLUSION AND RECOMMENDATIONS

5.1. Introduction

This chapter discusses the research findings within the perspective of previous research literature. Conclusion and recommendations have been highlighted based on the research findings.

5.2. Discussion

This study showed a female predominance which tallies with a closely related study done in the same setting (18). However, the findings were in contrast to expectations as well as to various studies done in other settings (13)(49). Reasons for this difference were not clear and were beyond the scope of this study. The mean age (SD) of participants was 54.2 (16.8) years. This finding was consistent with a closely related study done in the same setting (73). Conversely, other studies reported a mean age greater than 60 years (12)(13)(49). Reasons for this difference could be explained by the fact that CKD in developed countries is common among older population while in Sub Saharan Africa it affects younger adults (25). Majority of participants had obtained at least primary level of education. This was similar to other studies done in the same setting (18)(73). This is expected since the study area was urban.

We found a high prevalence of MRPs in the studied population. Each study participant had at least one type of MRP and the mean number of MRPs per participant ranging between 3 and 6. Studies from other settings report similar findings, with MRPs experienced by 93% to 99% of studied patients and ranged between 2 and 6 MRPs per patient on average (12)(13)(16)(18). This shows that CKD population is a group with high burden of MRPs both in developed and developing countries. This has been attributed to multiple medications and complex medication regimens used to treat comorbidities or retard disease progression among patients with CKD (5).

Our study identified *drug interactions* as the commonest MRP accounting for 21.8% of the observed MRPs. 59 (98.3%) of the 60 participants had at least one drug interaction, with 17 participants (28.3%) having severe drug interactions that required therapy discontinuation or the use of alternative treatment. The serious drug interactions identified in our study primarily involved ceftriaxone + enoxaparin, clarithromycin + enoxaparin, clarithromycin + atorvastatin, sulfamethoxazole +

enoxaparin drug pairs. In contrast to our findings, other studies have identified drug interactions ranging between 75% and 76% among studied participants with severe interactions accounting for 17 to 20% of the identified drug interactions in these studies (14)(17). However, other studies suggest that indication without therapy and dosing problems are the commonest MRPs (13)(12)(16)(63). The reasons for the heterogeneity of these observations are not clear. It is plausible that CKD populations from different settings experience MRPs to different extents because of differences in genetics, socio-demographics, behavioural characteristics, and healthcare practices.

The second most common MRP in our study was *indication without drug therapy* or what is also termed as untreated indication contributing 18.1% of all MRPs identified. The findings of our study can be explained by the high burden of comorbidities in these patients. The main conditions that had not been addressed were anaemia, electrolyte imbalance (specifically hyponatremia) and bone mineral disease. Reasons for not treating these conditions were beyond the scope of the study and further studies are warranted. In contrast to our findings, untreated indications accounted for a larger proportion (30% to 32%) of the MRPs in studies conducted in France (12)(13). The differences between our findings and those of the studies done in France could be explained by differences in the lengths of the study periods (3 months vs 6 to 15 months).

Univariate analysis showed there was statistically significant association of *indication without drug* with socio-demographic factors which included having ever been employed (p= 0.04), high monthly income (p-value= 0.02) and cigarette smoking (p= 0.04). Reasons why cigarette smoking, having ever been employed and earning higher monthly income was significantly associated with *indication without drug* were beyond the scope of this study.

Additionally, there was statistically significant association of *indication without drug* with high number of comorbidities (p-value= 0.002). Possible explanation is that patients with CKD may be having other comorbidities not picked up by prescribers during assessment and investigation thus not being addressed. Possible reasons for prescribers not picking up some of the comorbidities among patients with CKD may be due to inadequate assessment time as the prescribers may be rushing to clear the queue or ward round resulting in inadequate information transfer between the patient

and the prescriber. Indeed, a study in a teaching hospital in Toronto concluded that MRPs in end stage renal disease patients were frequently related to gaps in medication information transfer between healthcare providers and patients upon admission (40). However, on multivariate analysis, *indication without drug* problem had no significant associations with either socio-demographic or clinical factors.

Failure to receive drug mainly arising from patients non-adherence was the third major MRP identified in this study accounting for 15.5% of all MRPs identified. In comparison, another study identified non-adherence at 17.4% among patients with CKD at baseline study (4). These findings can be attributed to failure of the patients to understand their disease process and the benefits of adhering to medications as prescribed. Indeed, a study in France established an obvious lack of knowledge concerning CKD and its treatment objectives which led to a potential for non-adherence (13). Another study also attributed non-adherence to poor patients' understanding of their regimens, low health literacy and polypharmacy (58). The high number of drugs per participant as well as well as comorbidities could also contribute to the high prevalence of non-adherence. The drugs missed ranged across the board including antihypertensives, immunosuppressants, antidiabetics and others such as calcium supplements and lipid lowering agents. Main reasons for failure to receive drugs in this study were cost inhibition 27 (45%), resolution of symptoms 18 (30%), forgetting to take drugs as prescribed 18 (30%) and unavailability of drugs 5 (8.3%).

Association between *failure to receive drug* with high number of medications and number of comorbidities was statistically significant following univariate analysis. However, on multivariate analysis, the only statistically significant association was with the number of medications ($p= 0.025$). This could be explained by the fact that patients with CKD have high number of drugs per prescription thus higher chances of non-adherence either due to cost inhibition, side effects or forgetting to take some of the drugs. In comparison a study in Brunei observed that one of the main contributing factors to non-adherence was polypharmacy (58). In contrast to expectations, there was no statistically significant association of noncompliance with age in this study. However, a study in Brazil identified a significant relationship between non-adherence and older age(4)

The frequency of improper drug selection in our study was 12.2%. This tallies with a closely related study done in France which reported 12.8 % (53). The main occurrence of *improper drug selection* in our study resulted from non-inclusion of an ACEI or ARB in the management of hypertension accompanied by proteinuria. Another example of inappropriate choice was non-inclusion of a diuretic in the management of hypertension in some of the participants. Use of non-steroidal anti-inflammatory drugs (NSAIDs) in patients with CKD for purposes of analgesia was also a common contributor of poor drug selection. Conversely, another study reported slightly lower prevalence (7.6%) of IDS in the CKD population(38). Possible explanation for this difference in prevalence is that, the study by Joel *et al* was on patients undergoing haemodialysis; accordingly, prescribers in their choice of medications, might have taken haemodialysis into consideration when prescribing resulting in lower burden of IDS in this study than in our study.

Univariate and multivariate analysis showed statistically significant associations of *improper drug selection* with CKD stage 4 (p= 0.01) and presence of respiratory illness (p= 0.03). This could be explained by the fact that those with CKD stage 4 have more deteriorated kidney function than those with CKD stage 3 posing a challenge in drug selection in management of various comorbidities associated with CKD. This challenge may come about when prescribing because some of the drugs available for use might be contraindicated for use in CKD stage 4, for example metformin, yet alternatives might be more expensive for the patient, for example pioglitazone. Choice of drugs used in most respiratory illnesses especially antiinfectives also contributed to poor drug selection and this could be the reason for the significant association of improper drug selection with respiratory illness. Nonetheless, further research is needed to attest this finding.

The prevalence of drug without indication in our study was 9.2%. In comparison, a study in a university hospital identified 7.2% of MRPs to be drug without indication (12). The drugs commonly prescribed without clear indication included proton pump inhibitors, anticoagulants, antiinfectives and various supplements. In contrast, another study reported a lower prevalence (2.56%) of drug without indication (38). This difference in prevalence could be explained by the fact that there was evident inappropriate monitoring of disease process in our study, probably due to less intense

follow up of CKD stage 3 and 4 patients compared to follow up of patients undergoing haemodialysis.

Multivariate analysis showed a statistically significant association of *drug without indication* with high number of medications (p= 0.002) and alcohol consumption (p= 0.02). In comparison, a study in France also observed significant correlation between MRPs and a higher number of medications (13). This could be explained by the fact that polypharmacy is common among CKD population but sometimes the drugs prescribed are not necessary thus contributing to drug without indication. It was observed that alcohol consumers were prescribed such other agents as vitamin B complex without a clear indication. Probably the prescribers presumed that alcoholics required these owing to depletion of body vitamins by alcohol. However, we did not explore reasons for this trend because it was beyond the scope of the present study.

Adverse drug reaction was another MRP identified in the study accounting for 8.9% of all MRPs identified. Similarly, two other studies also identified adverse drug reactions accounting for 8-10% of all MRPs (12)(38). Majority of these drug reactions were self -reported by participants although some of them were also documented in the patient's medical records. The ADRs mainly involved gastrointestinal system effects such as abdominal pain, dyspepsia, diarrhoea, constipation, bloating, nausea and vomiting. Conversely, more than two-fold prevalence of ADR (22%) was identified in another study in Brunei (58). The difference in this prevalence could be explained by the fact that the study by Liew *et al* was carried out over a six month period thus could identify more ADRs over time compared to our study whose study period was three months.

Univariate analysis showed there was a statistically significant association of *adverse drug reactions* with presence of cardiovascular disease (p= 0.022). On multivariate analysis, there was an additional statistically significant association of *adverse drug reactions* with older age (p= 0.047). In comparison a study in France observed significant correlation between increased age and number of drugs (p= 0.0027) which was in turn significantly associated with MRPs (p= 0.049) (13). Possible explanation is the fact that geriatrics are more likely to present with cardiovascular diseases and such diseases alter pharmacokinetic and pharmacodynamics properties of different drugs they are likely to be using thus contributing to adverse drug reactions/effects.

Over-dosage (OD) accounted for 7.4% of all MRPs identified in our study. Similarly a closely related study in KNH identified 10.1% of MRPs to be over-dosage (18). Indeed another study on dose adjustments in patients with CKD at KNH identified over-dosage as the most common dossing error (62). The main drugs that were not renal dosed leading to over-dosages were antiinfectives such as amoxicillin/clavulanate, clarithromycin, lamivudine and meropenem. Other drugs frequently overdosed especially in prophylactic use were omeprazole and enoxaparin. Inappropriate disease monitoring could be the reason for the occurrence of OD due to the failure of adjusting renal dosed drugs as per the renal function. In contrast, another study identified near double the prevalence of over-dosage in haemodialysis patients (49). The difference in this prevalence could be explained by the fact that the study by Manley *et al* involved haemodialysis patients. Appropriate dosing in haemodialysis patients is challenged by pharmacokinetic and pharmacodynamics changes due to dialysis treatments thus likely to have more burden of over-dosage.

Following univariate and multivariate analysis, there was a statistically significant association of *over-dosage* with CKD stage4 (p= 0.01) and presence of respiratory illness (p= 0.04). In comparison, a previous study by Onyango *et al* in KNH targeting patients with CKD, observed that severity of renal disease was the most important risk factor for inappropriate dosage adjustment (62). This could be explained by the fact that those with CKD stage 4 have more deteriorated kidney function than those with CKD stage 3 posing a problem in drug dosing in management of various comorbidities. Drugs used in respiratory illnesses such as antiinfectives may require dosage adjustments as per the renal functions and these may have been overlooked by prescribers resulting in over-dosage problem. However, further research is warranted.

Least occurring MRP identified in our study was sub-therapeutic dosage accounting for 7% of all MRPs identified. In comparison, another study identified STD accounting for 7.69% of all MRPs identified (38). Sub-therapeutic dosage was common with haematinics including erythropoietin stimulating agents and antiinfectives such as ceftazidime and clindamycin. Conversely, another study identified STD accounting for 29% of all identified MRPs (15). This difference could be explained by the fact that the study in Iraq had a study period of five months and also involved ESRD patients and thus may have presented with a higher burden of MRPs including STD.

Univariate analysis showed a statistically significant association of *sub-therapeutic dosage* with high number of medications (p= 0.02). Multivariate analysis showed additional statistically significant associations of *sub-therapeutic dosage* with high number of comorbidities (p= 0.031) and being male (p= 0.017). In comparison a study by Manley et al observed statistically significant correlations between the number of MRPs and high number of comorbid conditions (p< 0.001) (3). Possible explanation could be that CKD population have high burden of comorbidities thus polypharmacy is inevitable and prescribers may opt to giver lower doses due to use of many drugs in a patient with deteriorated kidney function thus giving rise to sub-therapeutic dosage problem. Interestingly, there was a statistically significant association of sub-therapeutic dosage with being male. Reasons for this observation were not clear and may need further investigations.

Despite each participant having at least one type of MRP among patients with CKD in KNH, there was no single documented pharmacist intervention or recommendation geared towards preventing or resolving identified MRPs. However, possible interventions/recommendations a pharmacist would have been expected to have offered included advising on appropriate drug selection, monitoring of drug effects and disease process, adherence counselling to medications and renal dosing services or dose adjustments as per renal function. A study in France that included a clinical pharmacist consultation in outpatient nephrology clinic reported the most frequent pharmacist interventions as adaptation of doses, addition of drugs, drug stoppage and drug substitution (13). In another study, clinical pharmacists optimized progression modifying therapies, optimized medications safety as well as management of complications associated with CKD (16). These studies clearly show benefits of involvement of clinical pharmacists in management of patients with CKD.

5.3. Study Strengths and Weaknesses

As far as we know, this was the first study that attempted to assess the extent, types of MRPs and predictors of these MRPs among CKD adult patients in a teaching and referral hospital in Sub Saharan Africa. The study also identified socio demographic and clinical factors associated with specific types of MRPs. Interestingly, there was statistically significant association of indication without drug/untreated indication (IWD) with cigarette smoking, having ever been employed and earning approximately >$1200 per year. In addition, there was statistically significant association of sub-

therapeutic dosage with being male and a statistically significant association of drug without indication with alcohol use. Statistically significant association of improper drug selection and over-dosage with presence of respiratory illness was also another unique finding in this study.

However, the study was inherently prone to selection and information bias due to its cross-sectional design. Some patients especially those over 65 years found it difficult to recall all aspects regarding their illness and medications they were using hence this could have led to distortion of information. There was also no guarantee in terms of how honestly the patients reported non-prescribed drugs and other information.

Most patients with CKD on care and follow up in KNH had not been staged. The investigator used most current laboratory investigations to calculate estimated GFR using MDRD equation and subsequently stage the participant to either CKD stage 3 or 4. This may have introduced some aspect of selection bias.

The sample size calculation was based on a closely related study done in KNH assuming similar proportions of MRPs among patients with CKD and those in internal medicine wards in KNH. This resulted in a small sample size limiting investigations on associations between various predictors and MRP categories. The small sample size and convenient sampling prevent extrapolation of study results to the general population of patients with CKD.

The determination of presence or absence of an MRP was also not validated by a second person and this may have introduced an observer bias. Despite the aforementioned limitations, this study forms a baseline for further research among patients with CKD.

5.4. Conclusion

In our study, a total number of 271 MRPs were identified. The mean number of MRPs per participant was 4.5 with a standard deviation of 1.4. The overall prevalence of MRPs was 100%. Commonest occurring MRPs identified were drug interactions (21.8%), indication without drug (18.1%) and failure to receive drug (15.5%).

Socio-demographic factors significantly associated with indication without drug were cigarette smoking, having ever been employed and earning a higher income. Sub-therapeutic dosage was significantly associated with being male while drug without

indication was significantly associated with alcohol use. Adverse drug reaction was significantly associated with older age.

Drug without indication, failure to receive drug and sub-therapeutic dosage were all significantly associated with high number of medications per prescription. Over-dosage and improper drug selection were both significantly associated with CKD stage 4 and presence of respiratory illness. Indication without drug and sub-therapeutic dosage were both significantly associated with high number of comorbidities while adverse drug reaction was the only one significantly associated with presence of other cardiovascular diseases.

There was no single documented pharmacist intervention despite there being many areas a pharmacist could have intervened. However, data from literature supports benefits of including pharmacists in the healthcare team managing patients with CKD (65).

5.5. Recommendations

5.5.1. Recommendations for Policy and Practice

1. Due to high prevalence of MRPs we recommend implementation of strategies for the early identification, prevention and resolution of MRPs among patients with CKD to guarantee optimal patient outcomes. One of these strategies should include formation of multidisciplinary healthcare team including pharmacists to manage patients with CKD as such a team would be vigilant regarding such problems.
2. Healthcare professionals should be trained on MRPs and encouraged to have a high index of suspicion especially among patients with CKD and to actively seek out these problems to enable early detection, prevention and management of these problems.

5.5.2. Recommendations for Research

1. Further prospective studies are warranted to establish etiological relationships between different MRPs and associated factors.

2. Upon inclusion of pharmacists in the management of patients with CKD, further studies should be performed to assess the impact of such an inclusion.

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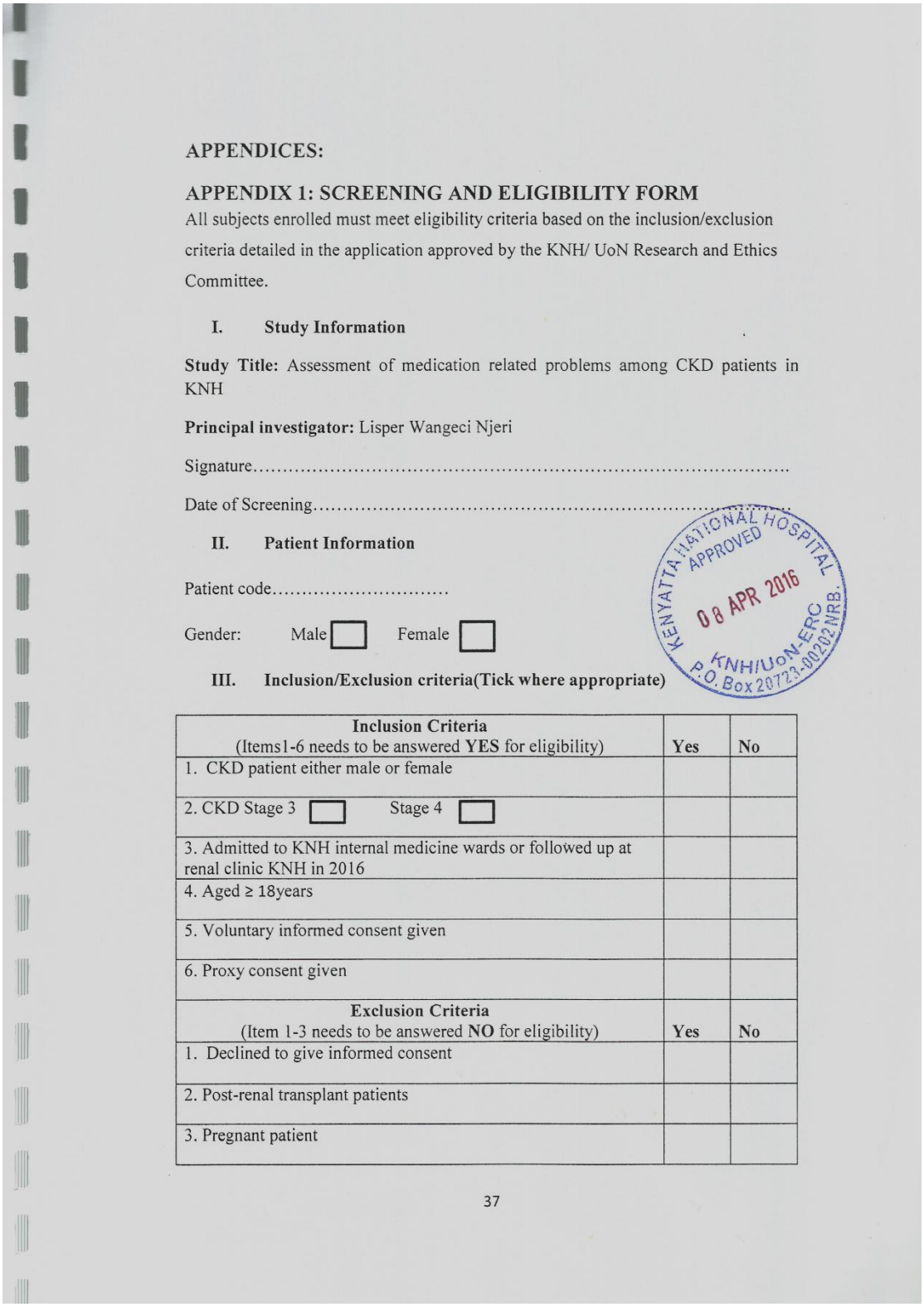
APPENDICES:

APPENDIX 1: SCREENING AND ELIGIBILITY FORM



APPENDICES:

APPENDIX 1: SCREENING AND ELIGIBILITY FORM

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

I. **Study Information**

Study Title: Assessment of medication related problems among CKD patients in KNH

Principal investigator: Lisper Wangeci Njeri

Signature.....

Date of Screening.....

KENYATTA NATIONAL HOSPITAL APPROVED 08 APR 2016 KNH/UoN-ERC P.O. Box 20723-00202 NRB.

II. **Patient Information**

Patient code.....

Gender: Male ☐ Female ☐

III. **Inclusion/Exclusion criteria(Tick where appropriate)**

Inclusion Criteria (Items1-6 needs to be answered **YES** for eligibility)	**Yes**	**No**
1. CKD patient either male or female		
2. CKD Stage 3 ☐ Stage 4 ☐		
3. Admitted to KNH internal medicine wards or followed up at renal clinic KNH in 2016		
4. Aged ≥ 18years		
5. Voluntary informed consent given		
6. Proxy consent given		
Exclusion Criteria (Item 1-3 needs to be answered **NO** for eligibility)	**Yes**	**No**
1. Declined to give informed consent		
2. Post-renal transplant patients		
3. Pregnant patient		

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APPENDIX 2A: CONSENT EXPLANATION FORM

APPENDIX 2A: CONSENT EXPLANATION FORM
PATIENT ☐

CAREGIVER ☐ **RELATION TO PATIENT**.....

Study Title: Assessment of medication related problems among chronic kidney disease patients in Kenyatta National Hospital

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

Principal Investigator: Dr. Lisper Wangeci Njeri, postgraduate student (Clinical pharmacy) P.o. Box 46996-00100, Nairobi.

Supervisors: Dr. Sylvia Opanga, Lecturer, Department of Pharmaceutics and Pharmacy Practice, University of Nairobi

Dr. Alfred Birichi, Clinical Pharmacist, Pharmacy department, Kenyatta National Hospital

I am Dr. Lisper Njeri conducting the above study to partly fulfil requirements for a Master Degree in Clinical Pharmacy of the University of Nairobi.

Ethical Approval:

Kenyatta National Hospital/University of Nairobi Ethical and Research Committee

What is the purpose of the study?

The study you are being requested to participate in aims at assessing the extent of medication related problems among chronic kidney disease patients being treated in Kenyatta National Hospital. It further intends to determine any association between medication related problems and patient related risk factors.

Why have I been invited to participate?

You have been approached for consideration as a participant because you are an adult patient with stage3/stage 4 chronic kidney disease and you are being treated at KNH.

What is expected of me as a participant?

Should you agree to participate in the study, you will be asked to be interviewed using a structured questionnaire to collect socio-demographic data and medical history. This will take less than an hour of your time.

Who will have access to the collected data?

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All data collected from you will be coded and entered in a password protected computer without access to the public in order to protect your identity. Only the research investigator will have access to the personal information. However, ethics review committee members may access information if need be to inspect research records. At the end of the study, there will be no way to link your name with the collected data. Any published work, arising from the study, will not bear your name or any other direct identifier

Must I participate?

Your participation is completely voluntary. If you decide to participate you are free to withdraw or refuse to answer any questions at any time without jeopardy to your treatment in KNH. You will not be required to give any reason for such withdrawal or refusal.

Are there any benefits of participating?

Immediate benefits to you as a participant is that if any serious MRP is identified, it will be communicated to your physician for review and/or intervention. The information gathered will also give insight into the types of MRPs among CKD patients. Any observed gaps will inform future treatment services to improve quality of CKD management in KNH.

What are the risks associated with my participation?

No risk or harm is anticipated in this study. However, it is possible that you might not be comfortable answering some of the questions in the study tools. All information obtained will be treated in confidence.

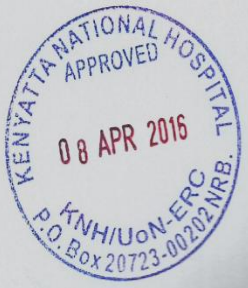
What will happen to the study findings?

Study findings will form part of the Master degree in Clinical pharmacy project dissertation. This will further be published in a peer reviewed journal. The findings will also be shared with the University of Nairobi College of Health Sciences administration, KNH administration and in presentations at scientific conferences.

What do I do in case of a problem?

You are free to raise any concerns about your rights as a participant in this study to me or KNH-UoN ethics and research committee who have approved this study.

.....



If patient only understands Kiswahili use the section below

MGONJWA ☐

MLEZI ☐ UHUSIANO NA MGONJWA.....

Kuhusu Utafiti huu: Tathmini ya matatizo yanayoweza tokea ambapo dawa hutumiwa miongoni mwa wagonjwa walio na Ugonjwa wa figo katika hospitali kuu ya Kenyatta

Taasisi: Idara ya Pharmaceutics and Pharmacy Practice, Shule ya Pharmacy, Chuo kikuu cha Nairobi, S.L.P. 30197-00400, Nairobi

Mtafiti mkuu: Dkt. Lisper Wangeci Njeri, Mwanafunzi uzamili (utabibu dawa), S.L.P. 46996-00100, Nairobi

Wasimamimizi: Dkt. Sylvia Opanga, Idara ya Pharmaceutics and Pharmacy Practice, Chuo kikuu cha Nairobi

Dkt. Alfred Birichi, Idara ya Pharmacy, hospitali kuu ya Kenyatta

Mimi ni dkt. Lisper Njeri nafanya utafiti huu kutimiza sehemu ya mahitaji ya bwana shahada katika utabibu dawa, Chuo kikuu cha Nairobi.

Idhini ya kimaadili:

Kamati ya kimaadili na utafiti ya Hospitali kuu ya Kenyatta/ Chuo kikuu cha Nairobi.

Nini madhumuni ya utafiti?

Utafiti huu una lengo la kutathmini kiwango cha matatizo yanayohusiana na dawa miongoni mwa wagonjwa walio na ugonjwa wa figo wanaotibiwa katika hospitali kuu ya Kenyatta. Pia utafiti huu unalenga kuamua kama kuna uhusiano kati ya matatizo haya na hatari zinazotokana na mambo ya mgonjwa mwenyewe.

Mbona mimi nimealikwa kushiriki?

Umealikwa kuwa mshiriki kwa sababu wewe ni mtu mzima uliye na ugonjwa wa figo na unatibiwa katika hospitali kuu ya Kenyatta.

Nini kinachotarajiwa mimi kama mshiriki?

Ukikubali kuwa mshiriki utahojiwa kwa kutumia muundo wa dodoso kukusanya nakala za kijamii na historia ya matibabu yako. Hii itachukua muda ndogo kuliko lisaa limoja lako.

Nani watakuwa na fursa ya nakala zilizokusanywa?

Nakala yoyote inayotokana na huu uchunguzi itahifadhiwa kwa siri na itatumika tu

kwa utafiti huu. Baada ya kumaliza utafiti huu hakuna njia ya kuunganisha jina lako na kiungo chochote cha utafiti huu. Kazi itakayochapishwa kutoka utafiti huu pia haitakuwa na kitambulisho chochote chako.

Lazima nishiriki?

Kushiriki kwako ni hiari yako. Ukikubali kushiriki bado uko huru kuondoka ama kukataa kujibu swali lolote wakati wowote ule bila kuweka matibabu yako hapa Kenyatta hatarini yoyote. Sio lazima upeane sababu ya kuondoka ama kukataa kushiriki katika utafiti huu.

Kuna faida ya kushiriki?

Faida ya haraka kwako kama mshiriki ni kuwa kama shida kubwa inayohusiana na dawa imetabulika, muuguzi wako atafahamishwa kwa haraka ili aweze kurekebisha . Pia utafiti huu utaweza kusaidia hospitali kujua ni shida zipi zinazohusu madawa zinozoadhiri wagonjwa walio na ugonjwa wa figo. Kama kuna mapengo yatakayotambulika pia yataweza kufahamisha jinsi ya kuboresha matibabu kwa wagonjwa hawa.

Nini hatari za kushiriki?

Hakuna hatari inayotarajiwa katika utafiti huu. Kuna uwezekano kuwa utakosa starehe ya kujibu maswali zingine utakozoulizwa. Taarifa yote itakayochukuliwa katika utafititi huu itakuwa ya siri.

Nini kitafanyika na matokeo ya utafiti?

Matokeo ya utafiti itakuwa sehemu moja ya mradi wa bwana shahada ya utabibu dawa. Matokeo pia yatachapishwa katika jarida la mapitio ya rika. Matokeo yatapewa wasimamizi wa hospitali kuu ya Kenyatta, wasimamizi wa chuo cha Nairobi cha sayansi ya afya na pia kuwasilishwa katika mikutano ya kisayansi.

Nifanye nini kama kuna shida?

Uko huru kuongeza wasiwasi wowote kuhusu haki zako kama mshiriki katika utafiti huu kwangu ama kamati ya kimaadili na utafiti ya KNH-UoN ambayo imepitisha utafiti huu.

APPENDIX 2B: CONSENT DECLARATION FORM

APPENDIX 2B: CONSENT DECLARION FORM
Informed consent

PATIENT ☐

CARE GIVER ☐ **RELATION TO PATIENT**.....

I, the undersigned, willingly agree to participate in this study. I have read and understood the nature of the study, my responsibilities as a study participant, the inconveniences associated with voluntary participation in the study and that all my questions and concerns relating to the study have been answered satisfactorily. I understand that I may choose to leave the study at any time and will not be prejudiced or penalized in any way. I understand that the information gathered will be used for the purposes of this study only and maximum confidentiality will be maintained.

I will receive a copy of this signed consent document to take away and keep

Respondent Name.....
Signature.....

Date.....

Witness (colleague)

Sign.....Date.....

Investigators statement

I, the undersigned, have explained the information in this document to this participant and encouraged them to ask questions which I took time to answer. I am satisfied that the participant adequately understands all aspects of the research as discussed in the consent process information document above.

.....

Name and Signature of person obtaining consent

In case of any concern you may contact the following Principal investigator on Email: lisperwangeci@gmail.com/ Tel: 0723980219 or KNH-UoN Ethics and Research Committee Secretary: Prof. Mark Chindia Tel +254 207 726300 ext. 44355, Email: uonknh.erc@uonbi.ac.ke

.....

If patient only understands Swahili use the section below

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Ridhaa

MGONJWA ☐

MLEZI ☐ **UHUSIANO NA MGONJWA**.....

Mimi, mtiaji sahihi, kwa hiari yangu nimekubali kushiriki katika utafiti huu. Nimesoma na kuelewa asili ya utafiti, majukumu yangu kama mshiriki, usumbufu unouhusiana na hiari yangu ya kushiriki katika utafiti huu na maswali pamoja na wasiwasi kuhusu utafiti huu yamejibiwa kwa kuridhisha. Nimeelewa kuwa naweza acha kushiriki katika utafiti huu wakati wowote bila kuweka matibabu yangu hatarini yoyote. Nimeelewa kuwa taarifa yoyote kutokana na utafiti huu itatumika kwa utafiti huu pekee na usiri utahakikishwa wakati wote.

Nitapata nakala yangu ya ridhaa iliyowekwa sahiihi nichukue niweke.

Jina la anayejibu.....
Sahihi.....

Tarehe.....

Shahidi (Mwenzangu)

Sahihi.....Tarehe.....

Kauli ya mtafiti

Mimi, mtiaji sahihi, nimeelezea taarifa iliyomo katika hati hii kwa mshiriki na nikamuhimiza kuuliza maswali yenye nimemjibu. Nimeridhika kuwa mshiriki anaelewa vizuri vipengele vinavyohusiana na utafiti kama ilivyoelezewa katika mchakato wa ridhaa uliyo hapo juu.

.....

Jina na Sahihi ya mwenye kuchukua ridhaa

Kwa maelezo zaidi wasiliana na Mtafiti mkuu kwa barua pepe: lisperwangeci@gmail.com/ simu ya rununu: 0723980219 ama KNH-UoN Kamati ya Maadili na Utafiti katibu: Profesa. Mark Chindia nambari ya simu +254 207 726300 ext. 44355, Barua pepe: uonknh.erc@uonbi.ac.ke

KENYATTA NATIONAL HOSPITAL
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08 APR 2016
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P.O. Box 20723-00202 NRB

APPENDIX 3: QUESTIONNAIRE

APPENDIX 3: QUESTIONNAIRE
SECTION A: PATIENT SURVEY

Code Number of the participant: .....

I. BIO DATA

What is the patient's bio data? Please fill in these details in the spaces provided

1. **Date of Birth:** Day.....Month.....Year.....,.

2. **Sex:** Male ☐ Female ☐

3. **Marital status**:

Single ☐ Separated ☐ Married ☐ Divorced ☐ Widowed ☐

II. CHIEF COMPLAINT

2. What is the patient's chief complaint? Briefly state it in the space below.

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III. HISTORY OF PRESENT ILLNESS

3. What is the patient's history of present illness? Briefly state it in the space below.

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V. PAST MEDICAL HISTORY

4. What is the patient's past medical history? Briefly state it in the space below.

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V. MEDICATION HISTORY

5. What is the patient's medication history? Please conduct a comprehensive medication history and fill in the table below.

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Medicine/Dose	Indication	Duration (start.stop dates)	Comments (outcome, allergy, adverse effects)
Allergies:			
Current medication history: prescription and non-prescription medicines			
Past medication history (up to 1 month ago): prescription and non-prescription medicines			
Home remedies / Herbal preparations/ Dietary supplements/Recreational drugs			

VI. FAMILY HISTORY

6. What is the patient's relevant family history? Briefly state it in the space below.

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VII. SOCIAL HISTORY

7. What is the patient's social history? Please fill in the details in the spaces below.

Occupation	Unemployed ☐ Self employed ☐ Employed ☐ Retired ☐
Income per month (Ksh)	< 10,000 ☐ 10,000-30,000 ☐ > 30,000 ☐
Educational status	None ☐ Primary ☐ Secondary ☐ Tertiary ☐

Religion	Protestant ☐ Catholic ☐ Muslim ☐ Traditional ☐ None ☐
Alcohol intake	Yes ☐ No ☐
Smoking	Yes ☐ No ☐
Daily diet composition	

VIII. REVIEW OF SYSTEMS

8. Please conduct a comprehensive review of systems. Are there any significant findings on the review of systems in relation to pharmacotherapy?

YES ☐ NO ☐

If yes, briefly clarify it in the space below.

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IX. MRPs REPORTED BY THE PATIENT

9. Does the patient wish he/she knew more about his/her medicines? YES ☐ NO ☐

If yes, briefly state their concerns in the space below.

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.....
.....

10. Does the patient have trouble using his/her medicines? YES ☐ NO ☐

If yes, briefly state their concerns in the space below.

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11. Does the patient have trouble understanding or remembering how to take his/her medicine? YES ☐ NO ☐

If yes, please list the problems they encounter in the space below.

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.....

12. Do any patient's medications make him/her feel unwell? YES ☐ NO ☐

If yes, please indicate how they feel when they take medicines in the space below.

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13. When patient feels like symptoms are under control, does he/she sometimes stop taking his/her medicine? YES ☐ NO ☐

If yes, please indicate which symptoms, when they cease, lead them to stop taking medicine in the space below.

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

14. Does the patient feel like he/she is taking too many drugs? YES ☐ NO ☐

If yes, please indicate their major concerns in the space below.

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.....

15. Does the patient feel like the medicine he/she is taking is making him/her feel better? YES ☐ NO ☐

If no, please indicate what they feel and which medicine makes them feel that way in the space below.

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.....

16. Does the cost of patient's medicine make it hard for him/her to take it as prescribed? YES ☐ NO ☐

If yes please state which medicines they have missed because they find them expensive in the space below.

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17. Whenever the patient has any problem with his/her medication, do they mention it to any healthcare practitioner? YES ☐ NO ☐

If yes, briefly state whom they contact and what is done about it in the space below.

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SECTION B: MEDICAL RECORD AND MEDICATION CHART REVIEW

I: CHIEF COMPLAINT

1. Are there any inconsistencies between the chief complaint by the patient and that in the medical record? YES ☐ NO ☐

If yes, briefly clarify it in the space below.

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.....

If yes, what is the chief complaint after agreement with clinician?

.....

II. HISTORY OF PRESENT ILLNESS

2. Are there any inconsistencies between the history of present illness by the patient and that in the medical record? YES ☐ NO ☐

If yes, briefly clarify it in the space below.

.....
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.....

If yes, what is the history of present illness after agreement with clinician?

.....

III. PAST MEDICAL HISTORY

3. Are there any inconsistencies between the past medical history by the patient and that in the medical record? YES ☐ NO ☐

If yes, briefly clarify it in the space below.

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

If yes, what is the past medical history after agreement with clinician?

.....
...

IV. MEDICATION HISTORY

4. Are there any inconsistencies between the medication history by the patient and that in the medical record? YES ☐ NO ☐

If yes, briefly clarify it in the table below.

Medicine/Dose	Indication	Duration (start.stop dates)	Comments (outcome, allergy, adverse effects)
Allergies:			
Current medication history: prescription and non-prescription medicines			
Past medication history (up to 1 month ago): prescription and non-prescription medicines			
Home remedies / Herbal preparations/ Dietary supplements/Recreational drugs			

V. FAMILY HISTORY

5. Are there any inconsistencies between the family history by the patient and that in the medical record? YES ☐ NO ☐

If yes, briefly clarify it in the space below.

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

If yes, what is the family history after agreement with clinician?

.....

VI. SOCIAL HISTORY

6. Are there any inconsistencies between the social history by the patient and that in the medical record? YES ☐ NO ☐

If yes, briefly clarify it in the space below.

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

If yes, what is the social history after agreement with clinician?

.....

VII. REVIEW OF SYSTEMS

7. Are there any inconsistencies between the review of systems by the patient and that in the medical record in relation to pharmacotherapy?

YES ☐ NO ☐

If yes, briefly clarify it in the space below.

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

If yes, what are the significant findings in the review of systems after agreement with clinician?

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

X. INVESTIGATIONS

9. Have any investigations been carried out? Please fill in the results in the table below.

Test/Investigation	Date carried out	Value	Comment (normal or abnormal)
Vitals			
Heart rate			
Blood pressure			
Respiratory rate			
Body temperature			
Full haemogram			
RBC			
Hb			
MCV			
WBC			
Neutrophils			
Lymphocytes			
Monocytes			
Eosinophils			

Coaugulation			
Prothrombin time			
APTT			
INR			
UECs			
Na+			
K+			
Mg^{2+}			
Cl-			
Urea			
Cr			
Clcr			
Ca^{2+}			
PO^{-}_4			
LFTs			
ALT			
AST			
GGT			
ALP			
Alb			
Tbili			
Ibili			
Dbili			
BGA			
pH			
PO_2			
PCO_2			
HCO_3^-			
Blood glucose			
RBS			
FBS			
HbA1c			
Others			
LP			
CXR			
ECHO			
ECG			
Urinalysis			
AFB			
MPS			
HIV			
HBV			
HCV			
Biopsy			

X. DIAGNOSIS

10. What is the current working diagnosis or confirmed diagnosis? Briefly state it in the space below.

Diagnosis	Comment
.....	.....
.....	.....
.....	.....

XI. MEDICATION RECONCILIATION

11. Please conduct medication reconciliation from the patient interview and medical record review. Please list all the medication (prescription and non-prescription) the patient is currently on including regimen details in the table below.

NO	Start Date	Stop Date	MEDICATION NAME	FORMULATION AND STRENGTH	DOSE	FREQ	ROUTE	INDICATION	COMMENT
			STAT/PRN MEDICATION						
1.									
2.									
3.									
			REGULAR MEDICATION						
1.									
2.									
3.									
4.									
5.									
6.									
7.									
8.									
9.									
10.									
			IV FLUIDS						

1.									
2.									
	Home remedies / Herbal preparations/ Dietary supplements/Recreational drugs								
1.									
2.									
3.									

SECTION C: EVALUATION OF MRPs

I. PREVALENCE OF MRPs

1. Did the patient have any MRPs? YES ☐ NO ☐

If yes, please elaborate by filling the sections below. If no, the following sections do not apply.

II. CLASSIFICATION

2. Please classify the MRP (s) in the categories provided below. Please justify by providing a comment. Also state the medicine involved and the therapeutic category to which it belongs.

Classification	Comment	Medicine involved	Therapeutic Category
☐ Improper drug selection			
☐ Failure to receive drug(Noncompliance)			
☐ Over-dosage			
☐ Sub-therapeutic dosage			
☐ Indication without drug			
☐ Drug without indication			
☐ Drug interactions			
☐ Adverse drug reaction			

III. SEVERITY

3. Is the severity of the MRP mild, moderate, severe or fatal? Please justify by providing a comment.

Severity	Comment
☐ Mild	
☐ Moderate	
☐ Severe	
☐ Fatal	

IV. CAUSES

4. Which of the following is the cause of the MRP? Please clarify?

Cause	Comment
☐ Inappropriate prescribing	
☐ Inappropriate delivery	
☐ Patient idiosyncracy	
☐ Inappropriate behaviour by the patient	
☐ Inappropriate monitoring	

V. PHARMACIST INTERVENTIONS

5. Is there pharmacist intervention on prevention or resolution of the MRP? Please clarify?

Intervention	Comment
☐ Yes	
☐ No	

APPENDIX 4: ETHICAL APPROVAL LETTER

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

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

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

Ref: KNH-ERC/A/121

8th April, 2016

KENYATTA NATIONAL HOSPITAL APPROVED 08 APR 2016 KNH/UoN-ERC P.O. Box 20723-00202 NAIROBI

Lisper Wangeci Njeri
Reg. No. U56/75157/2014
Dept. of Pharmaceutics and Pharmacy Practice
School of Pharmacy
College of Health Sciences
University of Nairobi

Dear Lisper,

Revised Research Proposal: Assessment of Medication Related Problems among Chronic Kidney Disease Patients in Kenyatta National Hospital (P76/02/2016)

This is to inform you that the KNH- UoN Ethics & Research Committee (KNH-UoN ERC) has reviewed and approved your above proposal. The approval period is from 8th April 2016 – 7th April 2017.

This approval is subject to compliance with the following requirements:

a) Only approved documents (informed consents, study instruments, advertising materials etc) will be used.
b) All changes (amendments, deviations, violations etc) are submitted for review and approval by KNH-UoN ERC before implementation.
c) Death and life threatening problems and serious adverse events (SAEs) or unexpected adverse events whether related or unrelated to the study must be reported to the KNH-UoN ERC within 72 hours of notification.
d) Any changes, anticipated or otherwise that may increase the risks or affect safety or welfare of study participants and others or affect the integrity of the research must be reported to KNH- UoN ERC within 72 hours.
e) Submission of a request for renewal of approval at least 60 days prior to expiry of the approval period. (*Attach a comprehensive progress report to support the renewal*).
f) Clearance for export of biological specimens must be obtained from KNH- UoN ERC for each batch of shipment.
g) Submission of an *executive summary* report within 90 days upon completion of the study.
This information will form part of the data base that will be consulted in future when processing related research studies so as to minimize chances of study duplication and/ or plagiarism.

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

Yours sincerely,

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

c.c. The Principal, College of Health Sciences, UoN
The Deputy Director, CS, KNH
The Assistant Director, Health Information, KNH
The Dean, School of Pharmacy, UoN
The Chair, Dept. of Pharmaceutics and Pharmacy Practice, UoN
Supervisors: Dr. Sylvia Opanga, Dr. Alfred Birichi Rugendo

APPENDIX 5: STATISTICALLY NON-SIGNIFICANT UNIVARIATE LOGISTIC REGRESSION MODELS FOR DIFFERENT MRP TYPES AND OTHER COVARIATES

Table 10: Statistically non-significant univariate logistic regression models for different MRP types and other covariates

MRP (Outcome)	Predictor	OR (95% CI)	P-value
Adverse drug reaction	Age	0.97 (0.94 - 1.00)	0.07
	Alcohol (Ever vs Never)	1.06 (0.37 - 3.01)	0.92
	Education (Tertiary vs Non-tertiary)	1.06 (0.36 - 3.09)	0.91
	Employment Status (Ever vs Never)	1.18 (0.42 - 3.37)	0.75
	Marital Status (Married vs Not married)	1.13 (0.38 - 3.44)	0.83
	Monthly Income (>10k vs <10k)	1.12 (0.39 - 3.22)	0.83
	Number of comorbidities	1.03 (0.76 - 1.39)	0.83
	Number of medications	0.99 (0.84 - 1.16)	0.94
	Sex (Male vs Female)	0.50 (0.17 - 1.43)	0.20
	Smoking status (Ever vs Never)	1.90 (0.59 - 6.84)	0.30
	Diabetes mellitus (Yes vs No)	0.51 (0.16 - 1.51)	0.24
	Respiratory illness* (Yes vs No)	1.71 (0.50 - 5.82)	0.39
	HIV (Positive vs Negative)	1.67 (0.46 - 6.11)	0.43
	Liver abnormalities (Yes vs No)	0.67 (0.20 - 2.07)	0.49
	CCF/HHD (Yes vs No)	0.76 (0.22 - 2.38)	0.64
	Bone mineral disease (Yes vs No)	0.79 (0.21 - 2.67)	0.71
	Anaemia (Yes vs No)	0.89 (0.32 - 2.53)	0.83
	Hypertension (Yes vs No)	0.93 (0.30 - 3.02)	0.91
	Electrolyte imbalance*** (Yes vs No)	1.07 (0.35 - 3.42)	0.91
Improper drug selection	Age	1.00 (0.97 - 1.03)	0.95
	Alcohol (Ever vs Never)	0.85 (0.30 -2.36)	0.76
	Education (Tertiary vs Non-Tertiary)	1.75 (0.60 - 5.30)	0.31
	Employment Status (Ever vs Never)	1.70 (0.61 - 4.82)	0.31
	Marital Status (Married vs Not married)	1.18 (0.40 - 3.44)	0.76
	Monthly Income (>10k vs <10k)	0.95 (0.33 - 2.69)	0.92
	Number of comorbidities	0.92 (0.68 - 1.24)	0.58
	Number of medications	1.10 (0.94 - 1.31)	0.24
	Sex (Male vs Female)	0.92 (0.33 - 2.59)	0.88
	Smoking status (Ever vs Never)	1.56 (0.50 - 4.93)	0.44
	Diabetes mellitus (Yes vs No)	1.10 (0.39 - 3.20)	0.85
	HIV (Positive vs Negative)	0.33 (0.08 - 1.19)	0.10
	Liver abnormalities (Yes vs No)	0.54 (0.17 - 1.65)	0.28
	CCF/HHD (Yes vs No)	1.24 (0.40 - 4.00)	0.71
	Bone mineral disease (Yes vs No)	2.50 (0.72 - 10.18)	0.17
	Anaemia (Yes vs No)	0.99 (0.35 - 2.74)	0.98
	Hypertension (Yes vs No)	2.18 (0.70 - 7.11)	0.18
	Electrolyte imbalance*** (Yes vs No)	0.97 (0.31 - 2.94)	0.95
	Cardiovascular disease** (Yes vs No)	0.54 (0.17 -1.65)	0.28

Drug without indication	Age	1.02 (0.99 - 1.05)	0.25
	Alcohol (Ever vs Never)	0.52 (0.18 - 1.47)	0.22
	Education (Tertiary vs Non-Tertiary)	0.71 (0.23 - 2.05)	0.53
	Employment Status (Ever vs Never)	1.02 (0.36 - 2.88)	0.97
	Marital Status (Married vs Not married)	0.38 (0.12 - 1.10)	0.08
	Monthly Income (>10 vs <10k)	0.75 (0.26 - 2.14)	0.59
	Number of comorbidities	1.16 (0.86 - 1.58)	0.33
	Sex (Male vs Female)	0.79 (0.27 - 2.23)	0.66
	Smoking status (Ever vs Never)	1.03 (0.33 - 3.32)	0.96
	Diabetes mellitus (Yes vs No)	1.51 (0.52 - 4.37)	0.45
	Respiratory illness* (Yes vs No)	1.07 (0.31 - 3.57)	0.92
	HIV (Positive vs Negative)	1.00 (0.26 - 3.59)	1.00
	Liver abnormalities (Yes vs No)	1.62 (0.53 - 5.03)	0.39
	CCF/HHD (Yes vs No)	0.69 (0.20 - 2.16)	0.53
	Bone mineral disease (Yes vs No)	2.27 (0.68 - 8.00)	0.19
	Anaemia (Yes vs No)	1.78 (0.63 - 5.15)	0.28
	Hypertension (Yes vs No)	0.53 (0.17 - 1.64)	0.27
	Electrolyte imbalance*** (Yes vs No)	0.44 (0.14 - 1.36)	0.16
	Cardiovascular disease** (Yes vs No)	1.18 (0.38 - 3.60)	0.78
Indication without drug	Age	0.98 (0.94 - 1.02)	0.27
	Alcohol (Ever vs Never)	2.33 (0.62 - 9.90)	0.22
	Education (Tertiary vs Non-Tertiary)	0.64 (0.17 - 2.50)	0.51
	Marital Status (Married vs Not married)	1.08 (0.25 - 4.10)	0.92
	Number of medications	1.17 (0.95 - 1.50)	0.17
	Sex (Male vs Female)	0.57 (0.15 - 2.16)	0.41
	Diabetes mellitus (Yes vs No)	1.11 (0.29 - 4.70)	0.88
	Respiratory illness* (Yes vs No)	36346763.60(0.0-NA)	0.99
	HIV (Positive vs Negative)	1.15 (0.25 - 8.35)	0.87
	Liver abnormalities (Yes vs No)	111549230(0.0-NA)	0.99
	CCF/HHD (Yes vs No)	1.07 (0.26 - 5.40)	0.93
	Bone mineral disease (Yes vs No)	36346763.43(0.0-NA)	0.99
	Anaemia (Yes vs No)	3.56 (0.91 - 17.76)	0.08
	Hypertension (Yes vs No)	0.21 (0.01 - 1.22)	0.15
	Electrolyte imbalance*** (Yes vs No)	2.31 (0.58 - 9.00)	0.22
	Cardiovascular disease* (Yes vs No)	1.18 (0.29 - 5.94)	0.83
Failure to receive drug	Age	1.00 (0.96 - 1.03)	0.77
	Education (Tertiary vs Non- Tertiary)	0.87 (0.28 - 2.81)	0.82
	Employment Status (Ever vs Never)	0.58 (0.18 - 1.76)	0.34
	Marital Status (Married vs Not married)	0.42 (0.11 - 1.41)	0.18
	Monthly Income (>10k vs <10k)	0.56 (0.18 - 1.71)	0.30
	Sex (Male vs Female)	0.35 (0.11 - 1.08)	0.07
	Smoking status (Ever vs Never)	2.04 (0.61 - 6.70)	0.24
	Diabetes mellitus (Yes vs No)	2.89 (0.87 - 11.54)	0.10
	Respiratory illness* (Yes vs No)	1.77 (0.47 - 8.70)	0.43

	HIV (Positive vs Negative)	1.36 (0.35 - 6.80)	0.67
	Liver abnormalities (Yes vs No)	0.80 (0.25 - 2.74)	0.71
	CCF/HHD (Yes vs No)	0.49 (0.15 - 1.64)	0.24
	Bone mineral disease (Yes vs No)	3.20 (0.75 - 22.21)	0.16
	Anaemia (Yes vs No)	2.94 (0.95 - 9.91)	0.07
	Hypertension (Yes vs No)	1.41 (0.41 - 4.62)	0.57
	Electrolyte imbalance*** (Yes vs No)	1.25 (0.37 - 4.05)	0.71
	Cardiovascular disease** (Yes vs No)	1.17 (0.35 - 4.24)	0.81
Overdose	Age	1.01 (0.97 - 1.04)	0.69
	Alcohol (Ever vs Never)	0.60 (0.20 - 1.78)	0.36
	Education (Tertiary vs Non-Tertiary)	0.90 (0.28 - 2.72)	0.85
	Employment Status (Ever vs Never)	1.22 (0.42 - 3.65)	0.72
	Marital Status (Married vs Not married)	1.00 (0.33 - 3.19)	1.00
	Monthly Income (>10K vs < 10K)	1.00 (0.33 - 2.98)	1.00
	Number of comorbidities	1.13 (0.83 - 1.55)	0.43
	Number of medications	1.09 (0.92 - 1.30)	0.31
	Sex (Male vs Female)	1.50 (0.51 - 4.48)	0.46
	Smoking status (Ever vs Never)	0.62 (0.19 - 2.03)	0.42
	Diabetes mellitus (Yes vs No)	0.58 (0.17 - 1.77)	0.35
	Liver abnormalities (Yes vs No)	2.00 (0.63 - 6.36)	0.24
	CCF/HHD (Yes vs No)	0.78 (0.21 - 2.54)	0.69
	Bone mineral disease (Yes vs No)	0.75 (0.18 - 2.65)	0.67
	Anaemia (Yes vs No)	1.66 (0.56 - 5.07)	0.36
	Hypertension (Yes vs No)	0.44 (0.13 - 1.40)	0.16
	Electrolyte imbalance*** (Yes vs No)	0.70 (0.22 - 2.29)	0.55
	Cardiovascular disease** (Yes vs No)	1.00 (0.30 - 3.17)	1.00
Sub-therapeutic dosage	Age	1.00 (0.97 - 1.04)	0.83
	Alcohol (Ever vs Never)	0.52 (0.17 - 1.54)	0.24
	Education (Tertiary vs Non-Tertiary)	1.94 (0.63 -6.00)	0.24
	Employment Status (Ever vs Never)	1.44 (0.48 - 4.44)	0.51
	Marital Status (Married vs Not married)	1.25 (0.40 - 4.19)	0.71
	Monthly Income (>10 vs <10k)	1.56 (0.51 - 4.75)	0.43
	Number of comorbidities	0.85 (0.60 - 1.17)	0.33
	Sex (Male vs Female)	2.38 (0.79 - 7.46)	0.13
	Smoking status (Ever vs Never)	0.39 (0.12 -1.26)	0.11
	Diabetes mellitus (Yes vs No)	2.39 (0.79 - 7.47)	0.13
	Respiratory illness* (Yes vs No)	0.83 (0.20 - 2.94)	0.78
	HIV (Positive vs Negative)	0.67 (0.13 - 2.60)	0.58
	Liver abnormalities (Yes vs No)	0.32 (0.07 - 1.18)	0.11
	CCF/HHD (Yes vs No)	0.36 (0.08 - 1.32)	0.15
	Bone mineral disease (Yes vs No)	1.27 (0.34 - 4.40)	0.71
	Anaemia (Yes vs No)	1.44 (0.48 - 4.44)	0.51
	Hypertension (Yes vs No)	1.16 (0.35 - 4.22)	0.81
	Electrolyte imbalance*** (Yes vs No)	0.63 (0.20 - 2.06)	0.43

Cardiovascular disease** (Yes vs No)	1.12 (0.33 - 3.57)	0.86

KEY: *CCF/HHD- Congestive cardiac failure/hypertensive heart disease*
HIV- Human Immunodeficiency Virus
**Includes acute and chronic pulmonary disease like pneumonia, tuberculosis, chronic obstructive pulmonary disease, asthma*
*** Includes Myocardial Infarction, Pulmonary Hypertension, Deep Venous Thrombosis, Pulmonary Embolism, Dilated cardiomyopathy, stroke, infective endocarditis and erectile dysfunction*
****Includes hyponatremia, hypokalaemia and hyperkalaemia*