UNIVERSITY OF NAIROBI

ASSESSMENT OF RATIONAL UTILIZATION OF DRUGS IN ADULT PATIENTS WITH CHRONIC RENAL FAILURE AT KENYATTA NATIONAL HOSPITAL

KARANI PHILIP MACHARIA

U56/76059/2014

A Dissertation submitted in partial fulfillment of the requirements for the award of the degree of Master of Pharmacy in Clinical pharmacy in the school of Pharmacy of the University of Nairobi.

November, 2016

DECLARATION

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

1. Signature _____ Date _____

   Dr. Peter Ndirangu Karimi

   Department of pharmaceutics and pharmacy practice

   University of Nairobi

2. Signature_____ Date_____

   Dr. David Gitonga Nyamu

   Department of pharmaceutics and pharmacy practice

   University of Nairobi

DEDICATION

I dedicate this research to my beloved mother Monica Karani and to the memory of my late father, Francis Karani. You have successfully made me the person I am. You will never be forgotten.

ACKNOWLEDGEMENT

I am highly grateful to God for His blessing that continue to flow into my life, and because of Him, I was able to pursue this work.

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ABBREVIATIONS AND ACRONYMS

ACEI	Angiotensin Converting Enzyme inhibitors
ADME	Absorption, Distribution, Metabolism, and Excretion
ADEs	Adverse Drug Effects
ADRS	Adverse Drug Reactions
AKI	Acute Kidney Disease
ARBs	Angiotensin Receptor Blockers
CKD	Chronic Kidney Disease
CVD	Cardiovascular Disease
eGFR	Estimated Glomerular Filtration Rate
ERC	Ethics and Research Committee
ESRD	End Stage Renal Disease
HIV	Human Immunodeficiency Virus
K/DOQI	Kidney Disease Outcome Quality Initiative
KNH	Kenyatta National Hospital
KRA	Kenya Renal association
MDRD	Modification of Diet in Renal Disease
RRT	Renal Replacement therapies
SD	Standard Deviation
RHE	Recombinant Human Erythropoetins
NRTI	Nucleoside Reverse Transcriptase inhibitors
NNRTI	Non-nucleoside Reverse Transcriptase inhibitors

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OPERATIONAL DEFINITION OF TERMS

Comorbidities: diseases/conditions that occur together in one person at the same

Chronic kidney disease: Chronic Kidney Disease is a progressive disease that persists at least three months with destruction of renal mass and function with irreversible sclerosis and nephron loss

Morbidity: a diseased state, disability, or poor health

Mortality: a measure of the number of deaths in a given population

Polypharmacy: Is the concurrent use of multiple medications associated with the prescription and use of too many or unnecessary medicines. However, multiple medications are often necessary and can constitute best care for patients.

Prevalence: It is a proportion showing 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: Pharmacokinetics and pharmacodynamics of systemically administered drugs profoundly change when the renal function is compromised. This necessitates appropriate choice of drugs and dosing in such patients to avoid errors that can result to toxicity or under dosing. There is paucity of published data on the extent of rational use of drugs in compromised renal function in Kenyatta National Hospital.

Objective: To assess the rational utilization of drugs in adult patients with chronic renal failure at Kenyatta National Hospital.

Methodology

Design: A cross section design

Sample size: A sample of 72 adult patients with chronic renal failure was selected. The participants were either admitted in medical wards or those attending renal unit at Kenyatta National Hospital.

Sampling technique: Simple random sampling was used where a coin was tossed. The patients who scored the tail were recruited as study participants.

Data collection: Ethical approval was sought from Kenyatta National Hospital/University of Nairobi Ethical and Research committee and consent from both the patient and hospital management before collecting data. Data was collected using a predesigned structured questionnaire. The participants were interviewed to acquire socio-demographic characteristics and outcome of the treatment. Treatment modalities were obtained from the hospital records.

Data Analysis*:* The data was analyzed using Statistical Package for Social Sciences version 20. Frequency tables and charts were used to summarize the data. Measures of central tendency and dispersion such as means, standard deviation, and interquartile ranges were used to analyze continuous data. Chi square was be used to find relationship between variables at 5% level of significance.

Results: The ratio between males and females was 5:3 and the mean age of the participants was 53.15 (±14.47). There was no isolated chronic kidney disease because all the participants had at least one comorbidity. Comorbidity was associated with polypharmacy ($p<0.0001$) where the mean number of drugs prescribed was 6.54 (±2.05) per patient. A total of 478 different types of drugs were prescribed for the participants of which 39.75% required dose adjustment. Almost a quarter of the drugs that required dose adjustment were done incorrectly and half (51.39%) of the participants had adverse drug reactions after treatment. Occurrence of adverse drug reactions was associated with the number of drugs the patient was taking ($p=0.025$) and inappropriate prescribing ($p=0.001$).

Conclusion: There is polypharmacy in patients with chronic kidney disease because of associated comorbidities. Doses of a substantial number of drugs prescribed to patients with chronic kidney disease are not appropriately adjusted. This leads to poor treatment outcomes such as adverse drug reactions.

CHAPTER ONE: INTRODUCTION

1.1 Background

Renal failure is a global health problem (1). It is estimated that 200 million people have Chronic Kidney Disease (CKD) in the world (2). In the USA, it is estimated that 13% of the population has CKD. The population-based study representative of New Delhi and surrounding areas reported a prevalence of CKD at 4.2% in India whereas Thailand and Congo report a prevalence of 8.6% and 8% respectively (3).

Prevalence of renal disease in developing countries is usually unknown due to lack of complete data. With rapid urbanization, high prevalence of non-communicable diseases and Human Immune-deficiency Virus (HIV), the population is vulnerable to renal diseases. A meta-analysis done by Stanifer *et al* showed that the overall prevalence of CKD was 13·9% in Sub-Saharan Africa. In this study, the estimates varied from 2% in Cote d'Ivoire to 30% in Zimbabwe. Half of the countries represented had prevalence estimates ranging between 4% and 16% (4).

It is estimated that the prevalence of End Stage Renal Disease (ERSD) in Kenya is 4% (4). The Kenya Renal Association estimates the number of patients with renal failure in Kenya to be 6000 per year (5). This figure could be higher since CKD is a silent condition and vast population unaware of the disease (6).

Over the years, causes of morbidity and mortality have shifted from communicable diseases to chronic non-communicable diseases (2,7). Renal failure is one of these diseases whose prevalence is on the rise due to increased risk factors. This increase in the prevalence of renal failure can be attributed to changes in diet, physical inactivity, increased cases of diabetes, hypertension, and infectious diseases (2). Renal failure leads to ESRD that requires expensive renal replacement therapies that include dialysis and renal transplant. However, the availability of these procedures is limited in much of sub-Saharan Africa because of high costs. It is estimated that over two million people worldwide need Renal Replacement Therapy (RRT) (8).

Management of renal failure includes treatment of the comorbid conditions while considering the renal insufficiency (8,9). Most of these comorbidities are responsible for progression to ESRD. Evidence shows that appropriate treatment of these comorbid conditions by appropriate use of the drugs delay progression of CKD and development of complications (10). Therefore, careful drug selection during prescription for patients with renal failure and dosage adjustment has to be done to ensure safe and optimized therapy for each patient. This study intended to find out the type of drugs used by patients with renal failure, their appropriateness, and consequences of irrational treatment. This is expected to significantly contribute to safe treatment of patients with renal failure and avoidance of progression of renal damage.

1.2 Problem statement

Treatment of patients with renal failure is important to prevent increased morbidity and mortality. However, the clinicians are faced with numerous challenges in choice of drugs and diagnostic agents that would not injure the renal system and in making the correct dose adjustments. Lack of information on drug dosing in renal failure forces most prescribers to rely on their experience or advice from superior colleagues (8). Errors in treatment may lead to renal damage which can prolong hospitalization or cause death which could otherwise be avoided. Prolonged hospitalization also leads to wastage of resources.

Literature from Kenya indicates the lack of data on information on all drugs used in patients with renal failure since research has been done on selected classes of drugs. For instance, a study done at KNH on antibiotic dose adjustments in patients with CKD noted that 59.9% antibiotic prescriptions needed dose adjustment of which 72.3% were inappropriate (6). Another study done in western Kenya in 2007 on renal disease in anti-retroviral naïve HIV infected patients showed that renal disease is common and the need of dose adjustment is necessary (11). These studies, however, focused on anti-infectives and failed to give adequate attention to appropriateness of other prescribed drugs in renal disease and their correct dose adjustments which would boost literature on drug selection and dose adjustment.

1.3 Justification

Renal failure is a rising health concern and a major cause of morbidity and mortality all over the world. Cases of renal failure keep on rising due to increased risk factors which include hypertension, diabetes, heart failure, and HIV/AIDS. Most patients with CKD have other comorbid conditions requiring multiple therapies. These comorbid conditions will necessitate these patients to be on multiple medications for long periods. Therefore, careful selection of drugs during prescription in patients with CKD is necessary and the dose should be adjusted appropriately to avoid drug interactions, renal damage, side effects and poor outcomes. However, errors in prescription and dose adjustments in patient with CKD do occur which are important and costly. A study done by Decloedt 2010 *et al* show that 19% of prescriptions done for CKD patients needed dose ajustments but only 32% were adjusted correctly (12).

Studies done to assess drug utilization among CKD patients in Kenya are scant. Few have been done on selected classes of drugs. For instance a study done in western Kenya found that renal failure is common among people living with HIV and dose adjustment is necessary (11). Onyango *et al* noted that 59.9% antibiotic prescriptions among CKD patients in KNH needed dose adjustments but 72.3% were inappropriate (6). This was only an isolated instance of a particular class of drugs but similar findings may be found among other agents utilized by CKD patients.

This study has assessed drug utilization among CKD patients and their appropriateness at KNH . This data will be used to improve rational use of drugs among patients suffering from chronic renal failure and will form a basis of evaluating how the drugs are used used with the aim of improving the situation.

1.4 Objectives

1.4.1 General objective

To assess the rational utilization of drugs among adult patients with chronic renal failure at Kenyatta National Hospital.

1.4.2 Specific objectives

1. To find out the type of drugs used by patients with CKD.
2. To evaluate the appropriateness of drugs prescribed to patients with CKD.
3. To identify the potential consequences of irrational use of drugs in patients with CKD.

1.5 Research questions

1. Which drugs are used in patients with CKD?
2. Are drugs prescribed in patients with CKD appropriate?
3. What are the potential consequences of irrational drug use among patients with CKD?

1.6 Significance and anticipated output

Rational drug use in patients with renal failure and appropriate dose adjustments is possible. This would reduce the risk of getting adverse effects and ineffective treatment of patients. However, the health professionals have many challenges regarding accessing appropriate data and the experience in dose adjustments. Rising cases of renal failure and limited data related to drug utilization in patients with renal failure necessitates more research to provide more information. This study will provide health care professionals with retrievable practical information relating to drug prescription and dose adjustments in renal failure. This will reduce serious drug interactions, adverse effects and provide optimized drug therapy and hence better treatment outcomes.

The data will also be useful to health planners and providers, policy makers, governments (county and national) and other health sector stakeholders. The information generated will contribute to the literature on the correct drug utilization in patients with renal failure in Kenya and Africa in general.

1.7 Delimitations

This study focused on patient with renal failure who were attending outpatient clinic or admitted at Kenyatta National Hospital. The study involved interviewing the patients, reviewing their medical records for data fill ups.

CHAPTER TWO: LITERATURE REVIEW

2.1 Introduction

This chapter reviews literature on the epidemiology of CKD, the drugs used in CKD, their appropriateness and the consequences of irrational drug prescription in chronic renal failure.

2.2 Epidemiology of chronic kidney disease

The health problem created by renal failure is enormous. CKD contributes to global burden of disease with an estimated 850,000 deaths and 15,010,167 disability adjusted life years making it the 12th cause of death and 17th cause of disability (13). High prevalence is reported worldwide. The US estimates that 9.6% of the population has CKD. Studies done in Australia, Europe, and Asia confirm similar high prevalence. Anand *et al* reports similar high prevalence with USA and Australia having 13% while India having 4.2% (3). In 1999 data from the U.S indicated that 4-10 million Americans have CKD with almost 350,000 being managed for ESRD (14).

The epidemiology of CKD in African countries is not well described. However, recent studies indicate that the prevalence is substantial (15). A meta-analysis study by Stanifer *et al* also showed that renal failure is prevalent and increasing in Sub-Saharan Africa making the burden for renal failure high. It has been estimated that by 2030, 70% of patients with renal failure will be in developing countries. This is due to increased risk factors which include hypertension, diabetes, HIV, leshmaniasis, and schistosomiasis. In this study, it was showed that the overall prevalence of CKD was 13·9% in Sub-Saharan Africa with estimates varying from 2% in Cote d'Ivoire to 30% in Zimbabwe. Half of the countries represented had prevalence estimates ranging between 4% and 16% (4). However, epidemiological data is low and of poor quality. It has been estimated that 30% of patients with diabetic nephropathy will progress to ESRD. This prevalence may be even higher since CKD is a silent condition (14).

It is estimated that the prevalence of ERSD in Kenya to be 4% (4). In another study, it was noted that the prevalence of chronic kidney disease in Kenya is 4.8% (16). The Kenya Renal Association estimates the number of patients with renal failure in Kenya to be 6000 per year (5). In a cohort sudy conducted by Wools-Kaloustian *et al* to assess renal disease in an

antiretroviral-naïve HIV infected outpatient population in Western Kenya found that 11.5% had a creatinine clearance less than 60 ml/min and 4.8% less than 50 ml/min (11). This estimated prevalence could be higher since CKD is a silent condition and lack of increased awareness. In Kenya, diagnosis is mostly done during clinical practice (6).

Old age is a risk factor for chronic kidney disease. The incidence of CKD in patients aged over sixty years was estimated to be 4.3% whereas the prevalence was 7.6%. Hospitalization due kidney failure has been estimated to be between 2 to 5%. Due to the increasing risk factors, the prevalence of CKD is increasing worlwide with higher rates in developing countries (4,17).

2.3 Drugs used in renal failure and their appropriateness

Renal failure is the decline or reduction of renal function over time. Acute renal failure occurs when this decline is abrupt or rapid. Chronic renal failure is a progressive disease that persist at least three months with destruction of renal mass and function with irreversible sclerosis and nephron loss (18,19).

K/DOQI notes that CKD should be diagnosed if structural renal damage or reduced renal function indicated by decreased GFR for three months, less than 60ml/Min/1.73M^2. GFR is used to classify CKD in to 5 stages as shown in the table 1. Lack of the right intervention can lead to end-stage renal disease that needs dialysis or kidney transplantation (10,18,20).

Table 1: K/DOQI classification of CKD

Stage	Description	GFR(ml)/Min/1.73M^2
1	Kidney damage with normal or increased GFR	More than 90
2	Kidney damage with a mild decrease GFR	60-89
3	Moderate decrease in GFR	30-59
4	Severe decrease in GF	15-29
5	Kidney Failure	Less than 15 or dialysis

Source: National Kidney Foundation. K/DOQI Clinical Practice Guidelines for Chronic Kidney Disease: Evaluation, Classification, and Stratification. Am J Kidney Dis 39:S1-S266, 2002 (suppl 1) (20).

This decline in function affects drug elimination and metabolism. Therefore, caution should be taken in selection of drugs and dose adjustment to avoid progression of renal damage, adverse effects due to drug accumulation and ineffective treatment due to low dose administration. Renal failure is common especially among hospitalized patients. Other conditions are affected by renal failure which increases the morbidity and mortality of such patients (21).

Drugs in the body are eliminated primarily via the liver and the renal system. Due to this function together with maintenance of a homeostatic environment through plasma filtration, the kidney receives 25% of the cardiac output (9,22). With this high blood supply the delivery of drugs, diagnostic agents and their metabolites is high making the renal system vulnerable to injury especially when this exposure is regular and over a long period. This can lead to alteration of nephron structure and function. Such injury may be insignificant or result to end stage renal disease. It may also aggravate underlying AKI or CKD (9,23,24).

It is evident that the prevalence of CKD increases with age. It will therefore be associated with other comorbidities. These comorbidities will highly influence the morbidity and mortality for these patients. Hypertension and diabetes are the most common comorbidities associated with CKD. Collins 2003 *et al* estimated the prevalence of

Cardiovascular Disease (CVD) in patient with CKD between 1984 and 1999 to be 40% while that of diabetes at 38%. It was estimated that diabetes causes ERSD in 19-15% of the patients with CKD in kenya. Other comorbidities associated with chronic kidney disease include cerebrovascular disease, anemia, thyroid disease, chronic respiratory diseases, HIV and other infectious diseases. These comorbidities increase the treatment burden for such patients which is estimated to be greater than the kidney component only (16,25,26). In many instances, several drugs are used in management of such patients. Good medication management is important in the choice of drugs to be used to avoid further renal damage, adverse effects due to drug accumulation and ineffective treatment. There is also the risk of drug - drug interactions since CKD is associated with polypharmacy. The majority of the patients with CKD are over sixty years and this makes them more susceptible to these adverse effects. For instance, a study done by Fraser 2015 *et al* found that only 4% of the participants had isolated CKD, 26% had at least one comorbidity, 29% had two comorbidities and 40% had more than two comorbidities. In this study 59% of the participants were on five or more drugs, 11% were on ten or more while only 3% were not taking any drugs (10,27).

The choice of medications is an important factor in management of patient with CKD. Patient education on drugs to be avoided in CKD is also important. Various drugs are used to manage these comorbid conditions. Therapy is done in combination to ensure effectiveness. Drugs used include antihypertensives, antidiabetics, antibiotics, anticonvulsants, haematinics, analgesics, antithrombotics, among others (10).

A study done by Dasari 2014 *et al* showed that the most prescribed antihypertensives is calcium channel blockers followed by betablockers, diuretics, ACEIs and ARBs. Calcium channel blockers and beta blockers was the most widely prescribed combination. Aspirin was effective and safe in prevention of thromboembolism. However, the effectiveness of clopidogrel was reduced. In this study, insulin was used to manage diabetes. Decreased excretion of low molecular weight heparins is associated with bleeding episodes. These anticoagulants like enoxaparin should be avoided in renal failure. Artovastatin and rosuvastatin are used to reduce cholesterol. The use of statins increases survival rates.

Erythropoetin was used to manage anemia caused by renal failure. Admistration of erythropoetin raises the haematocrit levels and reduce progression to ERSD (10).

However, inappropriate drug prescriptions occur in patients with renal failure. In a large case control by Chertow 2001 *et al* found that 14% of medication orders for patients with renal failure were nephrotoxic and renally excreted (21). In another study, the participants with renal failure received at least one medication that was renally cleared and/ or potentially nephrotoxic. 14% of drugs contraindicated in patients with renal failure were administered. These medications administered were aspirin, gliclazide, nitrofurantoin, and spironolactone with aspirin. This error has been attributed to lack of conclusive data on nephrotoxic drugs (28).

A cross section study done by Cho 2014 *et al* showed noncompliance to renal dosing guidelines among prescribers. Most prescribers chose the "patient has tolerated this drug in the past" to override the warning system. The rates of excess dosing of kidney disease related drugs is still high among ambulatory patients (29).

Injuries by drugs to the renal system may occur via several mechanisms. Prerenal injury occurs when renal perfusion is compromised which impairs GFR. This is mostly caused by antihypertensives especially in combined therapy. NSAIDs inhibit prostaglandin synthesis which is important for vasodilation of the afferent ateriole to maintain GFR. This inhibition will result to vasoconstriction which may cause renal impairment. CKD patients with other comorbid conditions like CVD are at high risk of developing further renal damage when taking antihypertensives since the drugs can decrease renal perfusion (9).

Immunosupressants like ciclosporin and tacrolimus injure the renal vasculature while aminoglycosides and amphotericin B exhibit direct drug toxicity to the renal system (6). Other drugs cause hypersensitivity reactions after being deposited in the interstium. These drugs include penicillins, cephalosporins, phenytoin, thiazide, ranitidine and rifampicin (9).

Renal injury can also result from renal tubular obstruction. This is caused by drugs that can precipitate in the renal tubules. This is seen with sulphonamides, aciclovir and gancyclovir. Hydralazine, methyl dopa, pindolol, atenolol and ergotamine cause obstruction due to retroperitoneal fibrosis (9).

Renal function is important in the pharmacokinetics and pharmacodynamics of administered drugs. These processes include drug effects, absorption, distribution, clearance, and protein binding. These parameters profoundly change in renal failure due to physiologic changes in multiple body organ systems (19,23). Almost half of all drugs or their metabolites are excreted by the kidneys, and it is estimated that 30% of all adverse effects will be caused on the renal system or affect it (30). This therefore necessitates appropriate dosing in such patients to avoid errors that can result to toxicity and under dosing in renal failure. For instance, toxicity of aminoglycosides can lead to deafness whereas low dose adjustments can lead to longer stay in the hospital or death.

GFR or creatinine is used to calculate individual doses to avoid adverse effects and poor outcomes. The dose can either be reduced depending on the GFR or creatinine clearance or reducing the frequency of administration or both (19,30). GFR is the standard for measuring renal function. Cockroft Gault equation or Modification of Diet in Renal Disease (MDRD) are used for estimation of GFR. In renal failure with GFR less than 60ml/min/1.73M^2 or in older patients with GFR less than 90ml/min/1.73M^2, MDRD is better in estimation of GFR than Cockcroft Gault equation. The eGFR is normalised to an average sized man body surface area of 1.73M^2 inorder to allow accurate result comparisons between people of different weights. Though the actual GFR must be used in prescribing drugs with narrow therapeutic indices like chemotherapeutics or in the extremes of body weight (19,23,31,32). These two equations are illustrated below

The cockcroft Gault equation. The units is ml/min (32)

$$\mathbf{CLcr} = \frac{(\mathbf{140} - \boldsymbol{age\ (years)}) * (\boldsymbol{weight\ (kg)}) * \mathbf{0.85}\ (\boldsymbol{female})}{\boldsymbol{Scr}\left(\frac{\boldsymbol{mg}}{\boldsymbol{dl}}\right) * \mathbf{72}}$$

MDRD. The units is ml/Min/1.73M^2 (32)

GFR (ml/mim/1.73M^2) = 186 *$Scr^{-1.154}$ *$Age^{-0.203}$ * (1.212 *if black*) * (0.742 *if female*)

The goal of dosage adjustment is to achieve drug concentration profiles in renal failure similar to those in normal renal function. This means similar peaks, troughs, achievement of steady state or Minimum Inhibitory Concentration (MIC) for antibiotics. Since the half life will be increased due to the compromised drug clearance the attainment of the steady state will be delayed. Therefore all the parameters of each drug must be considered in stepwise process to ensure the steady state is attained in a timely fashion (32).

This stepwise approach will involve obtaining the patients history and demographics. This includes getting the relevant demographic information, medical history, social history, clinical and laboratory information. Estimate the GFR of the client and evaluate if the drugs prescribed need to be individualized. The dose is then estimated considering the eGFR, pharmacokinetics of the drug and the volume status of the patient. The drug is then monitored considering the clinical response, toxicity or therapeutic drug monitoring (32)

Most literature indicate that dosage adjustment should be done to the maintenance dose but not to the loading dose. However other data indicate that the loading dose is not necessary in patients with renal failure, but if its necessary it can be adjusted depending on the volume of distribution of the drug in the CKD patient as shown below (19,32).

$$\textbf{Patients loading dose} = \frac{(\boldsymbol{usual\ dose}) * (\boldsymbol{patients\ Vd})}{\boldsymbol{Normal\ Vd}}$$

Source: Matzke GR, Aronoff GR, Atkinson AJ, Bennett WM, Decker BS, Eckardt K-U, et al. Drug dosing consideration in patients with acute and chronic kidney disease—a clinical update from Kidney Disease: Improving Global Outcomes (KDIGO). Kidney Int [Internet]. 2011;80(11):1122–37 (32).

The maintenance dose can be adjusted according to the renal function by either reducing the frequency of administration or reduction of the amount administered. More constant drug levels are attained in reducing the dose while maintaining the frequency of

administration. But the risk of developing toxicities is high is if the time for drug clearance is inadequate. Less risk of developing toxicities is observed in giving the normal dose but lengthening the administration interval. However this approach is associated with sub-therapeutic drug concentrations (19,23,31,32).

In dose adjustments the prescribers should be aware that the goal is to maintain similar plasma concentrations of the unbound drug to that of normal population. The maintenance dose can be calculated using the formula below:

$$\mathbf{Cu(ss,ave)} = \frac{F.\left(\frac{\mathbf{Dm}}{\mathbf{T}}\right)}{\mathbf{CLu}} = \frac{F*.\left(\frac{\mathbf{Dm}}{\mathbf{T}}\right)*}{\mathbf{CLu}*}$$

Where Cu (ss,ave) = Steady State plasma concentration of the unbound drug

CLu = plasma clearance of the unbound drug

$(\mathbf{Dm/T})$ = maintenance dose regimen in normal patients

T = the time interval for administration

The asterisk superscripted notes the parameters in a CKD patient

Therefore the maintenance dose in patient with renal failure is given by this formula:

$$\left(\frac{\mathbf{Dm}}{\mathbf{T}}\right)*= \frac{\left(\frac{\mathbf{Clu}*}{F*}\right)}{\left(\frac{\mathbf{Clu}}{F}\right)} \mathbf{x}\left(\frac{\mathbf{Dm}}{\mathbf{T}}\right)$$

Source: Verbeeck RK, Musuamba FT. Pharmacokinetics and dosage adjustment in patients with renal dysfunction. Eur J Clin Pharmacol [Internet]. 2009 Aug 20;65(8):757–73 (23).

In dose adjustments the GFR is categorised in three broad categories. These categories range from GFR being less than 10ml/Mn/1.73M^2, 10 – 20ml/Mn/1.73M^{2}and 20 - 50ml/Mn/1.73M^2. these categories cover 10 fold of renal function. The drugs are adjusted acording to these categories (23,32).

Inappropriate dosing errors is an one of the important problems in management of patients with renal failure. A study done by Henok *et al* showed that 31% of prescription made for CKD patients required dose adjustments. Fifty eight percent of the dose adjustments was inappropriate and 74% of the patients received more than one drug that required dose adjustment (33). In another study the prevalence of drug dosing inadequacy was 17.5% in phase 1 and 15.5% in phase 2 (34).

A study done to assess the dosing errors in old patients found that prior to eGFR reporting, the average rate of antibiotic prescriptions dosed in excess of guidelines was 64 per 100 antibiotic prescriptions. Nevertheless, no impact was noted after introduction of dosing using renal function with over-dosing being seen in 68 per 100 antibiotic prescriptions. In addition, 169 prescriptions of nitrofurantoin were made irrespective of the drug being contraindicated in renal failure (35).

In management of patients with renal failure this information is an important guide in selecting the drugs to be administered. Therapeutic benefit against the risks should be considered to avoid further renal damage and adverse effects. In prescribing in renal failure individual patients risks should be considered. Frequent renal monitoring will help to diagnose deteriorating renal function (9,32).

2.4 Potential consequences of irrational use of drugs in patients with renal failure

In renal dysfunction, pharmacokinetics processes are impaired with changes in drug absorption, distribution and clearance. Absorption is slightly higher than in normal population due to delayed gastric emptying, decreased rate of elimination or reduced presystemic elimination. The extent of absortion will also be dependent on the volume of distribution. Such cases are seen with propranolol, dihydrocodeine and sildenafil. Concomitant drug administration due to comorbid conditions may also affect absorption. This drug interaction is seen with phosphate binders when administered with flouroquinolones. For instance sevelamer will reduce absorption of ciprofloxacin (12,19,32).

In addition to decreased plasma albumin concentration in renal failure, the binding sites for drugs in albumin may undergo conformational changes. This decreases the quantity of bound drug due to accumulation of endogeneous substances leading to competition for binding sites of albumin. Most affected is acidic drugs causing higher plasma unbound drug concentrations which is the active form and easily eliminated. However elimination will depend on the ability to metabolise and excrete which is already impaired. This increases the risk of developing adverse drug effects. In patients with renal failure there is a high risk of developing fluid overload. Together with altered protein and tissue binding, there is increased volume of distribution of certain drugs. But the volume of distribution of digoxin and pindolol is decreased in renal failure (12,32).

Metabolism of drugs occurs in the gut, plasma, liver and the kidneys. This metabolism is impaired in renal failure. After metabolism, the metabolites maybe pharmacologically active. Normally these metabolites are eliminated by further renal metabolism and excretion. Therefore in renal failure these metabolites may accumulate as seen with morphine-3-glucuronide and morphine-6-glucuronide which can lead to morphine intoxication exhibited by respiratory depression, mental obtundation and hypotension (32).

Lack of dose adjustments or errors in adjustments in CKD patients can cause adverse effects or poor outcomes. The worst scenario is when these adverse effects are nephrotoxic which will worsen the already injured renal system (12,32). Dose adjustments are often neglected by prescribers and a study done by Eric *et al* on dose adjustments in medical patients with renal failure noted that renal impairment occurred in 31% of admitted patients within 24 hours. Nineteen percent of the prescriptions needed dose adjustments and only 32% were correctly adjusted (12). Errors in prescription for patients with renal is important and costly. These errors are associated with adverse drug reactions (21).

Precise estimation of adverse drug reaction occurrence is unknown. In a study done to assess adverse drug events in patients with renal failure showed that 159 events were recorded among 300 participants with 40.7% having a suspected Adverse Drug Reaction (ADR). Occurrence of ADRs resulted to longer hospitalization of such patients as

compared to patients without ADRs. However, it was noted that 30.2% of these adverse event could have been prevented. Inappropriate dose or frequency, prescription of inappropriate drugs in renal failure, lack of therapeutic drug monitoring or presence of drug to drug interaction were the causes of preventable adverse drug reactions. In this study ADRs included electrolyte disturbances, hypotension, hypoglycemia, neutropenia, intestinal bleeding and respiratory depression. Diuretics, antidiabetics, antibiotics, antithrombotics, antihypertensives and mineral supplements were the major causes of adverse effects (36).

Irrational drug prescriptions will lead to adverse effects due to drug and metabolite accumulation or ineffective treatment. This leads to increased morbidity, increased therapeutic costs, increased hospitalizations, increased length of hospital stay and mortality.

CHAPTER THREE: METHODOLOGY

3.1 Introduction

The chapter details how the study was conducted in order to achieve the outlined objectives. Tools, participants, data required, and method of analysis are described in the chapter.

3.2 Research design

A cross-sectional research design was used. This design was appropriate since it involves one time contact between the researcher and the respondents and therefore seeking current data on the issues being investigated.

3.3 Study area and site

The study was conducted in the renal unit and wards in KNH. It is an 1800 bed hospital offering tertiary services most of which are referrals from other hospitals and some from the neighboring countries. Being the largest referral and teaching hospital in East Africa, KNH receives an annual average of 800,000 outpatient visits and 90,000 inpatients from within Kenya and outside the country. It is estimated that KNH receives at least five new renal failures every week (6). The choice of the location of study was based on the Kenya's geographical representativeness of the patients who seek medical services at KNH. This was an important aspect in boosting the reliability of data in generalizing the Kenyan situation.

3.4 Target population

The study population was adult patients aged above 18 years diagnosed with chronic renal failure who were either admitted or attending outpatient renal clinic at KNH during the period of the study. Both male and female patients were included in the study.

3.4.1 Inclusion criteria

The patients included in the study had the following characteristic:

- Diagnosed with chronic renal failure and admitted or attending outpatient clinic at KNH.
- The plasma creatinine of the patient must be measured and recorded in the file.
- Aged 18 years and above.
- Patients of either sex.
- Patients who have voluntarily given consent to participate in the study.
- Patients who have signed the informed consent.

3.4.2 Exclusion criteria

Eligible patients with the following characteristics were excluded from the study:

- Pregnant women.
- Failure to sign the written informed consent form.
- Patients with psychiatric illnesses.

3.5 Sampling

3.5.1 Sample size

The sample size for the study was estimated using the formula as proposed by Cochran (37).

$$\mathbf{n} = \frac{\mathbf{pqZ^2}}{\mathbf{e^2}}$$

Where;

n is the sample size,

p is the prevalence renal failure in Kenya, 4%(4)

q is the level of precision that is 1-p,

Z is the standard deviation for 95% confidence interval which is 1.96 (from tables) and

e is the allowable margin of error that is 5%.

$$n = \frac{(0.04) * (1 - 0.04) * 1.96^2}{0.05^2} = 59.01 \approx 60$$

The sample size was inflated with 20% to cover for incomplete data

$$n = \frac{120 * 60}{100} = 72$$

3.5.2 Sampling technique and participants' recruitment

Recruitment was done in the internal medicine wards and at the renal clinic. A list of admitted patients having renal failure was sourced from records in each of the eight wards of internal medicine and renal clinic. The files of these patients were perused to assess their eligibility using the screening and eligibility form. The files of the eligible patients were selected using simple random sampling where a coin was tossed and the file that scored the tail was included in the study. The patient whose file was selected wads approached and the researcher read the consent form, explained, and answered any question from the participant. If the participant could only speak in their mother tongue, the next of kin was used to make them understand the purpose of the consent. The participants were then requested to voluntarily sign the consent form or put a thumb print. The same process was utilized when recruiting participants in the renal clinic. This was done after the patients finished their appointments with the clinicians.

3.6 Research instruments

A structured questionnaire was administered to the participants by the principal investigator. The questionnaire was used to collect relevant data which included demographics, comorbidities, drugs prescribed and dose adjustment done.

3.7 Pre-testing

Before the commencement of the main data collection exercise, the predesigned questionnaire was administered to 10 participants selected from the eight wards of internal medicine and renal outpatient clinic in KNH. This exercise assisted in identification of any gaps, inconsistencies, or information flow difficulties that may be encountered during the main data collection. Ultimately, the identified gaps were amended to minimize likely difficulties during the main data collection exercise.

3.8 Variables

The main outcomes were the drugs being utilized by the patients with renal failure, their appropriateness in renal failure, and the consequences of irrational drug use in chronic renal failure.

Drug prescriptions and dose adjustment depended on the comorbidities and renal function respectively. Prescription of nephrotoxic drugs and lack of or incorrect dose adjustments were classified as inappropriate prescriptions. The MDRD equation was used to estimate GFR. The doses of drugs prescribed were compared with the recommended doses in the dosing guidelines at different eGFRs as directed by the Renal Drug Handbook.

Both chronic and curable comorbidities were considered. Remission was considered to have occurred when the symptoms of chronic comorbidities became less severe after treatment. The participants suffering from curable diseases were considered cured if the symptoms resolved after the treatment.

Independent variables included age, gender, education, and occupation of the participants.

3.9 Data management

3.9.1 Accuracy and completeness

Data on patient demographics, drugs prescribed and dosage adjustments were sourced from the files. The questionnaire was checked for completeness. Data from each patient was coded and entered into MS Excel version 2010 to create database. This was done

from the point of origin of the data to analysis in order to avoid information loss. This ensured safe and adequate data flow which was easily traced.

3.9.2 Data forms and data entry

The pretested questionnaire was used to abstract drug utilization information from the files. This data included the participants' demographic characteristics, stage of renal failure, comorbidities, type drugs used to manage the comorbidity and the dose adjustments. This data was entered in MS Excel. Median, standard deviation, and interquartile ranges was used to report continuous data while proportions were used to report categorical data at 95% confidence interval. Associations between dependent and independent variables were assessed using Chi square with alpha value of 0.05.

3.9.3 Quality assurance

Consistency of the data was monitored during data collection to ensure it was uniform and reliable. This was done by ensuring thorough checking and double checking by a different investigator. The final report was inspected and audited as Good Clinical Data Management Practices (GCDM) 2007 dictates.

3.9.4 Data security

Computer hard discs were used to store the cleaned data sets. Back up files were saved in the DropBox, CDs, and flash disks.

3.9.5 Data analysis

The data entered in Microsoft Excel was then exported to STATA. Frequencies, tables, and charts were used to summarize the data. Measures such as means, standard deviation, and interquartile ranges were used to analyze the data. Therefore, the data was analyzed as means plus/minus standard deviation, counts, or proportions. The t test was used to compare continuous variables. Chi square was used to compare categorical variables. The P value was set at 0.05. The data was represented as in the dummy tables shown below.

3.10 Logistical and ethical considerations

In order to commence the study, the consent was sought from the University of Nairobi/Kenyatta National Hospital Ethics and Research Committee (Ref: KNH-ERC/A/301). The consent of respondents was also requisite. The study was conducted during the time that the respondents and the hospital management considered appropriate. All the data collected during the study was handled with confidentiality and used for purposes of the research only. In addition, the names of the respondents and patients were not recorded for confidentiality reasons. Instead, the completed questionnaires were numbered for identification purposes.

CHAPTER FOUR: RESULTS

4.1 Introduction

This chapter contains the results of the study in three main parts. They are socio-demographic characteristics, the drug prescribed in CKD, their appropriateness and the outcome of the treatment.

4.2 Socio-demographic and clinical characteristics of the study population

Socio-demographic characteristics of the participants are presented in table 2 shown below. A total of 72 participants were included in the study and 41(56.94%) prescriptions were made in the wards and the rest in the renal clinic. Forty-five (62.50%) of the participants were males. The average age of the participants was 53.15 (SD +/- 14.47) years. The youngest participant was 20 years and the oldest was 90 years. Majority of the participants were over 50 years. Almost a third of the participants (n=21, 29.17%) were over 60 years. Only 4 (5.56%) participants were thirty years and below.

The education level of the participants was divided into four categories, tertiary, secondary, primary, and informal. More than a half of the p articipants (n=43, 59.72%) had either informal or primary level of education. Only 5 (6.94%) participants had tertiary level of education.

Thirty-eight (52.77%) participants were self-employed and only sixteen (22.22%) were salaried. However, majority of the participants earned KShs 1 – 5,000 per month. Only 6.94% earned more than KShs 30,000.

More than a half of the participants were at stage five of CKD. Only a few (4.17%) were at stage 2. Most patients were newly diagnosed and had CKD for less than one year.

Table 2: Socio-demographic and clinical characteristics of the participants (n=72)

Variable	n(%)	Variable	n(%)
Gender		**Occupation**	
Female	27 (37.5%)	Salaried	16 (22.22%)
Male	**45 (62.5%)**	Casual waged	7 (9.72%)
		Self employed	**38 (52.77%)**
Age in categories		Un-employed	11 (15.28%)
18 – 30 years	4 (5.56%)		
31 – 40 years	10 (13.89%)	**Monthly Income**	
41 – 50 years	15 (20.83%)	KShs 1 – 5,000	**40 (55.56%)**
51 – 60 years	**22 (30.56%)**	KShs 5,001 – 15,000	21 (29.17%)
>60 years	21 (29.17%)	KShs 15,001 – 30,000	6 (8.33%)
		>KShs 30,000	5 (6.94%)
Age distribution			
Mean	**53.15**	**Duration of the illness**	
Standard Deviation	14.47	Below 1 year	**30 (41.67%)**
Minimum	20	1 – 3 years	15 (20.83%)
Maximum	90	3 – 5 years	16 (22.22%)
		More than five years	11 (15.28%)
Education level		**Baseline stage of CKD**	
Tertiary	5 (6.94%)	Stage 2	3 (4.17%)
Secondary	24 (33.33%)	Stage 3	13 (18.06%)
Primary	**38 (52.78)**	Stage 4	17 (23.61%
Informal	5 (6.94%)	Stage 5	**39 (54.17%)**

4.3 Assessment of drugs used in CKD and their appropriateness

4.3.1 Comorbidities

Figure 1 presents the number of comorbidities per patient. There was no isolated CKD and all the participants had comorbidities. Only fourteen (19.44%) had one comorbidity but the majority (n=36, 50%) had two comorbidities.

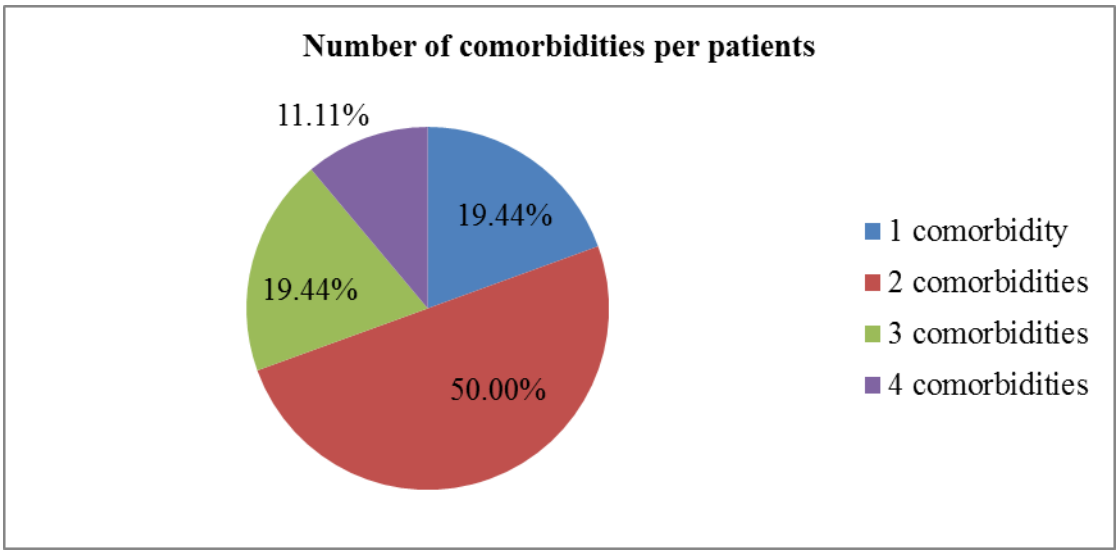

Figure 1: Number of comorbidities by per patient

The most prevalent comorbidities were hypertension, followed by diabetes mellitus, anemia, atherosclerosis, and RVD. Figure 2 presents the prevalence of comorbidities among the participants.

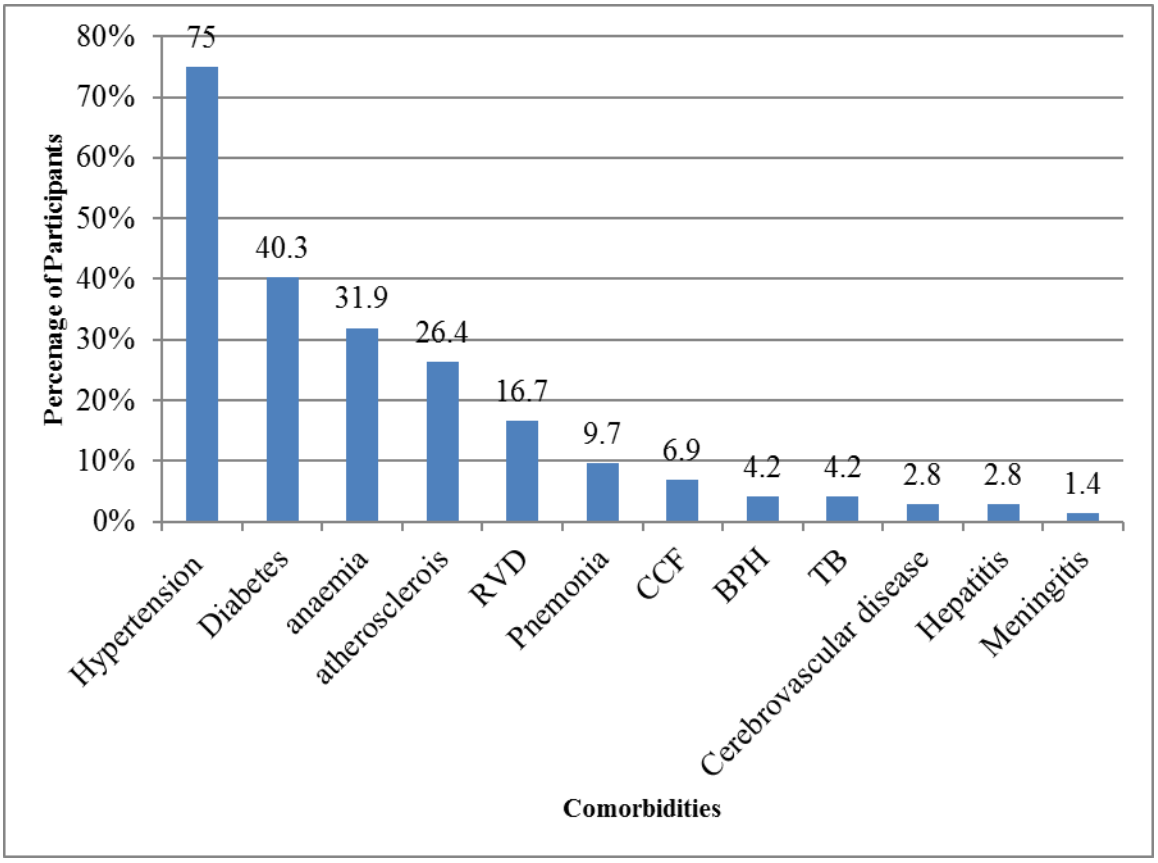

Figure 2: Types of comorbidities encountered

Key: RVD- Retroviral Disease, CCF- Congestive Cardiac Failure, BPH- Benign Prostrate Hyperplasia, TB- Tuberculosis

4.3.2 Types of drugs prescribed

Several drugs were prescribed for treatment of comorbidities occurring in CKD. Appendix 4 presents the drugs that were prescribed and for those that needed dose adjustment whether it was appropriate or not. Table 3 summarizes this information. A total of 478 drugs were prescribed for the participants. Majority (60.25%) of the drugs did not require dose adjustment. Majority of the drugs requiring dose adjustments were done correctly (74.74%) but 25.26% were not adjusted correctly.

Table 3: Assessment of dose adjustment and its appropriateness

Variable	n	%
Requirement for dose adjustment (n=478)		
Drugs not requiring dose adjustment	288	**60.25**
Drugs requiring dose adjustment	190	39.74
Appropriateness of dose adjustments (n=288)		
Appropriate dose adjustment	142	74.74
Inappropriate dose adjustment	48	**25.26**

4.3.3 Classes of drugs prescribed

Different classes of drugs were prescribed depending on the comorbid the participant was suffering from as illustrated in appendix six. Figure 3 summarizes this information. The most prescribed drugs were antihypertensives (75%) and antacids.

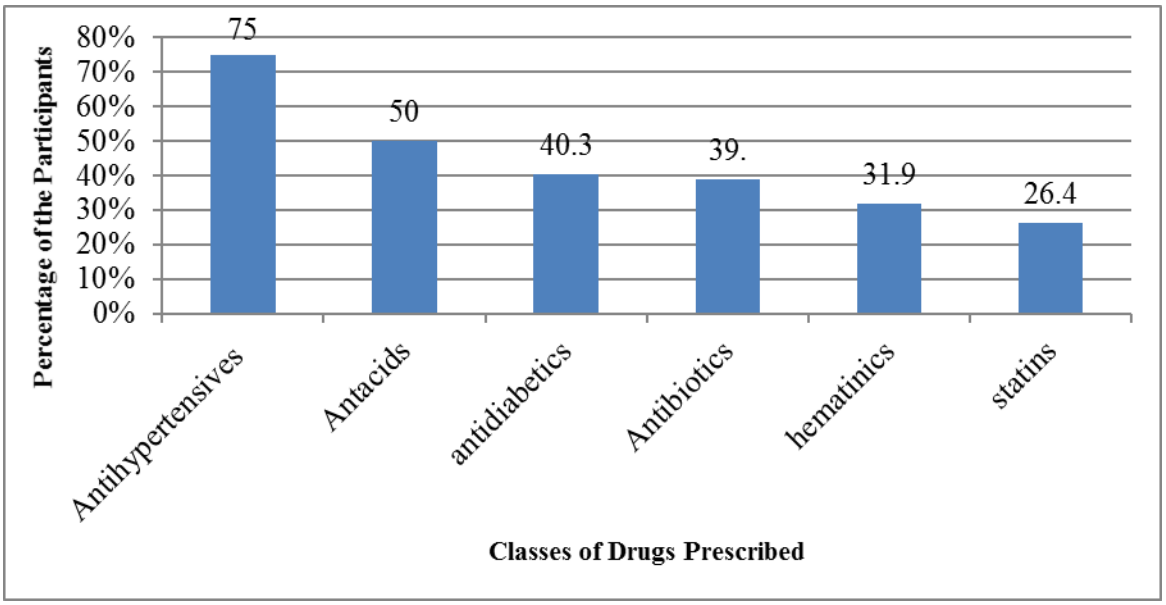

Figure 3: Classes of drugs prescribed

4.3.4 Number of drugs prescribed per patient

Seventeen (23.83%) participants were taking seven drugs. However, 1.39% of the participants were taking twelve drugs, 5.56% eleven drugs, 1.39% ten drugs and 6.94% nine drugs. The mean of the number of drugs per patient was 6.54 +/-2.05. The minimum number of drugs was two and the maximum was 12 per prescription.

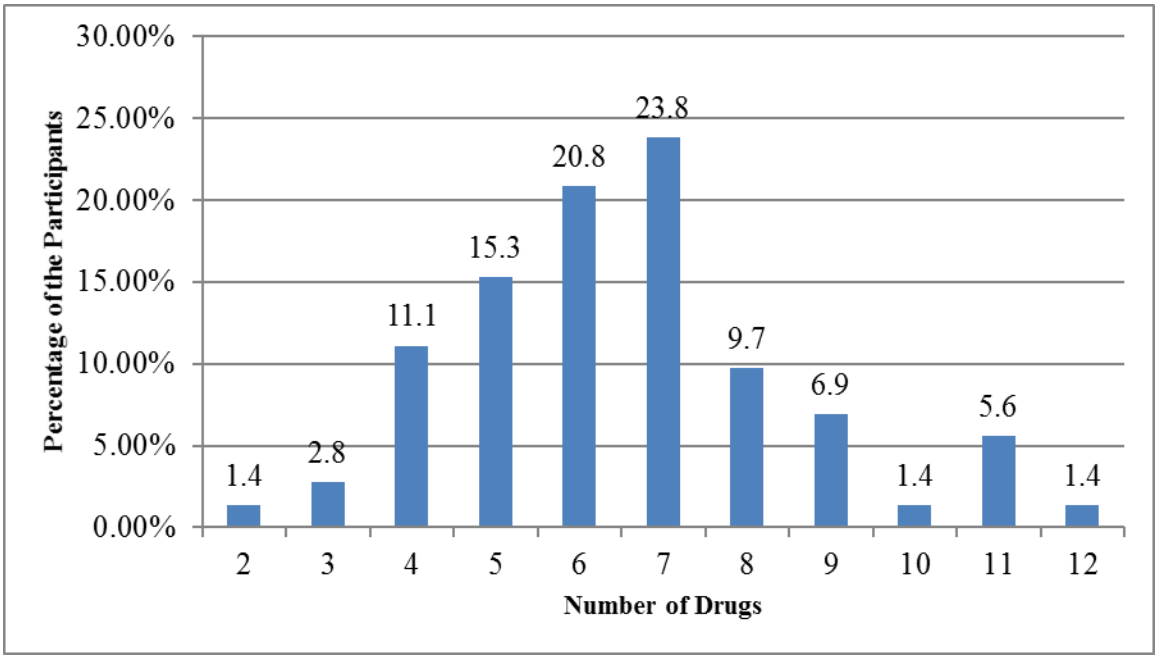

Figure 4: Number of drugs per participants

The number of drugs prescribed to the patient was associated with the number of comorbidities present (p<0.0001).

Table 4: Associations between comorbidities and treatment burden

Number of drugs prescribed	Number of comorbidities				p value
	1	**2**	**3**	**4**	
2 – 5	11	9	2	0	
6 – 9	3	27	11	3	
10 or more	0	0	1	5	**<0.0001**

4.3.5 Frequency and severity of drug interactions among the study participants

One of the drug combinations had two drugs contraindicated to be given together. A fifth (20.83%) of the drug combinations did not have a potential drug to drug interaction. However, 19.44% of the combinations had potential serious drug interaction that required the use of an alternative agent. Seventy-five percent of the cases had potential significant interaction which required close monitoring while 43.06% combinations had minor interactions.

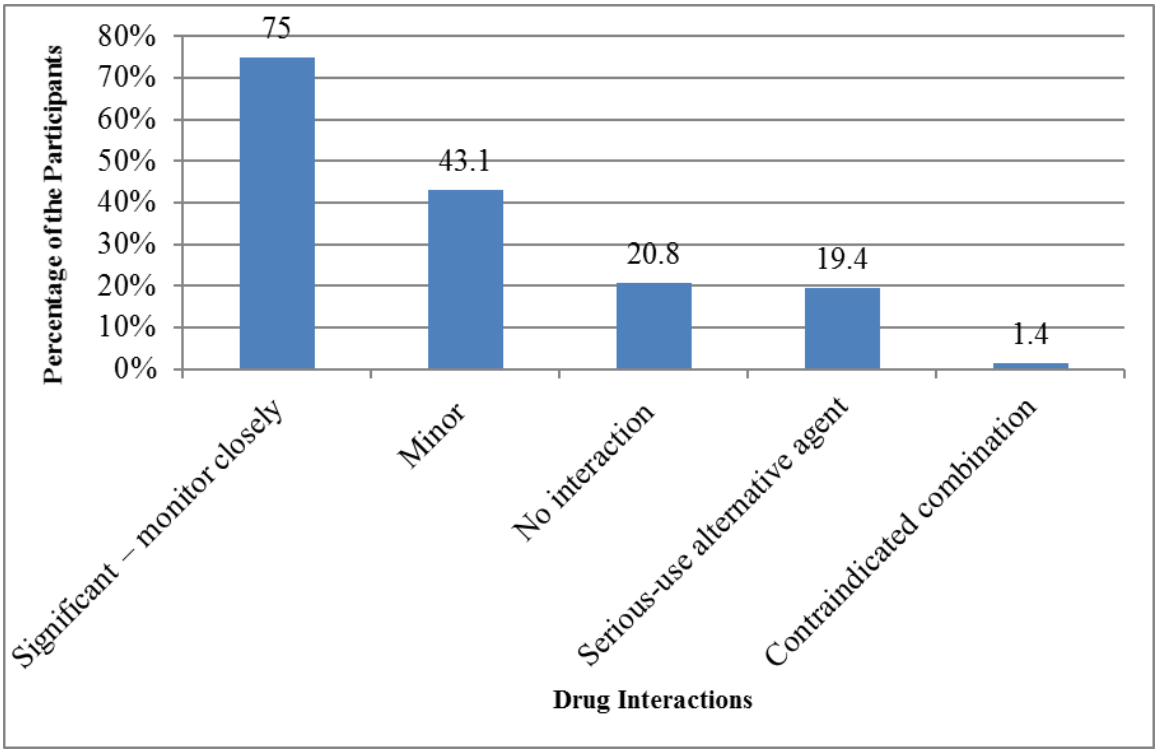

Figure 5: Frequency and severity of drug interactions

4.4.1 Assessment of the outcome of the treatment

The renal function of 47(66.20%) participants worsened after the prescription as indicated by elevation of serum creatinine. About half (51.39%) of the participants had ADRS after treatment. Thirty-three (45.83%) participants had resolution of the symptoms of the comorbidities. One participant was cured and one death occurred.

Table 5: Outcome of the treatment

Variable	n	%
Elevation of serum creatinine	47	66.20
Cured	1	1.39
Remission	32	**45.83**
ADRs	37	**51.39**
Death	1	1.39

Key: ADRs – Adverse Drug Reactions

4.4.2 ADRS encountered

The most common adverse effect was nausea and vomiting followed by, dizziness, diarrhea, difficulties in breathing, musculoskeletal pain and neuropathy as illustrated in figure 6.

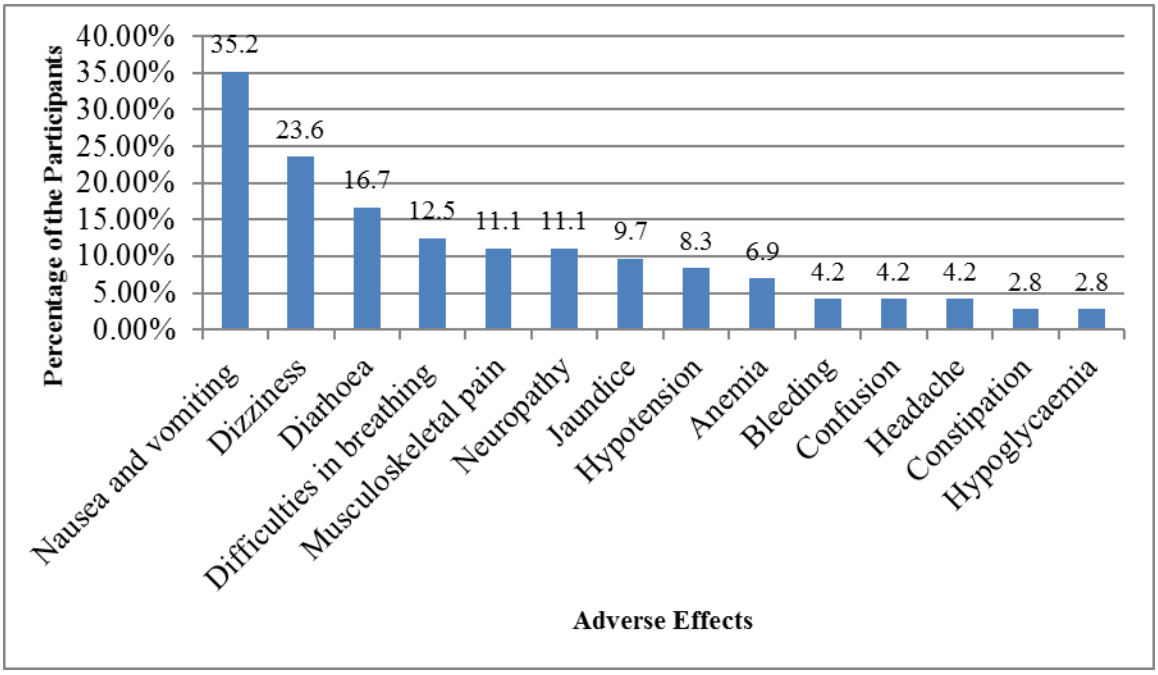

Figure 6: ADRS encountered among the participants

4.4.3 Associations between ADRS and the number of drugs prescribed

ADRS were observed more in patients taking more than five drugs than those taking fewer drugs. Occurrence of ADRS was associated with the number of drugs the patient was taking p=0.025).

Table 6: Association between ADRS and the number of drugs per patient

Variable	**ADRS**		**P value**
	Present	**Absent**	
Less than 5 drugs	15	7	
More than 5 drugs	20	50	**0.025**

4.4.4 Relationship between independent variables and appropriateness of dose adjustments

Appropriateness of the prescriptions was not associated with gender (p=0.067). In addition, renal function was also not associated with the number of drugs prescribed (p=0.08). The clinical set up was associated with appropriateness of the prescription (p=0.04) with more cases seen in the wards. Remission and occurrence of ADRS was associated with the inappropriateness of the prescription (p<0.0001 and p=0.001 respectively). Potential serious and significant drug to drug interactions were associated with the inappropriateness of the prescription (p=0.001 and p=0.004 respectively).

Table 7: Relationship between independent variables and appropriateness of dose adjustment

Variables	Was the prescription appropriate?		P-value
	Yes	No	
Gender			
Male	31	14	
Female	13	14	0.067
Clinical set up			
Wards	21	20	
Outpatient	23	8	**0.04**
Outcome of the treatment			
Higher Cr	32	15	0.08
Cured	1	0	0.611
Remission	27	5	**<0.0001**
ADRS	16	21	**0.001**
Death	1	0	0.611
Interactions			
No interaction	10	23	0.427
Serious	3	11	**0.001**
Significant	28	26	**0.004**
Minor	15	16	**0.046**

CHAPTER FIVE: DISCUSSION, CONCLUSION, AND RECOMMENDATIONS

5.1 Introduction

The findings of this study are compared with similar studies done elsewhere by other researchers in this chapter. Conclusions and recommendations are also given.

5.2 Discussion

There were more males than females similar to findings from other studies as reported by Seck *et al* (38). The young were few while more than a half of the participants were aged between 51 – 60 years. Studies done elsewhere have also demonstrated a linear increase in CKD with increase in age (38,39).

More than a half of the participants had either informal or primary level of education. Studies have noted that patients with different education levels have different health habits and give different treatment outcomes. The population which is more educated has fewer risks for CKD than less educated population. Furthermore, poor health outcomes in patients with CKD are associated with the level of education with lower level having higher risks (40,41).

Only about a tenth of the study population was unemployed. The rest had income generating activities with the majority being self-employed. However, the remuneration was minimal with the majority of the participants earning between KShs 1 – 5,000 monthly. Only 6.94% earned more than KShs 30,000 per month. A study done by Beech *et al* indicates that association between CKD and economic status is not linear but the more stable economically a population is, the fewer the risks for CKD and therefore a lower prevalence (40).

The participants presented with several comorbidities and there was no isolated chronic renal failure. Other studies report that patients with CKD suffer from other conditions and it is very rare to find CKD without comorbidities. Isolated CKD take a small percentage of the total population. The results of this study are consistent with findings by Fraser *et al* (12).

Several studies report that hypertension and diabetes are the most common comorbidities in CKD. The other comorbidities include anaemia, atherosclerosis and RVD among others (10,27). In the present study, the most common comorbidities were hypertension, diabetes, anaemia, atherosclerosis, and RVD. Studies have suggested that correct treatment of these conditions is necessary to delay the progression of the disease and occurrence of complications (10,27).

Presence of comorbidities forces patients with CKD to be on multiple medications. Taking multiple drugs concomitantly will increase the cost needed for treatment, affect adherence and increase the risk of adverse drug reactions (42,43). Different drug combinations are used in management of comorbidities in CKD. In this study, the mean of drugs per patient was 6.54 +/-2.05. Fraser *et al* reports similar results on the number of medications prescribed per patient. In their study, the median number of drug was five and 59% of the participants were taking five or more drugs. Eleven percent was taking ten or more drugs (27). The number of comorbidities was associated with the number of drugs prescribed ($p < 0.0001$).

In the present study, CCB, diuretics, and beta blockers were mostly used, for the management of hypertension, the commonest comorbidity. A few participants were on vasodilators, ACEIs and ARBs. These results are comparable to findings by Dasari *et al* (10). Studies have revealed that multiple antihypertensive drugs are required to manage hypertension associated with CKD. Most studies report that three to four drugs may be needed to achieve this. ACEI and ARBs are safe and effective in reduction of proteinuria and are therefore used as first line treatment of hypertension in CKD. In another study conducted by Dasari *et al*, 60.5% of the hypertensive patients were on CCB, 55.4% on beta blockers and 42.8% were on diuretics. However, the patients on ACEI and ARBs were 10% and 3.3% respectively due to contraindications (10). From our findings, majority of participants were on CCBs, beta blockers, diuretics, and vasodilators. Use of ACEI and ARBS accounted for 19.44% and 13.89%, respectively.

A study conducted by Strid 2003 *et al* on the use of Acid Suppression therapy (AST) in CKD noted that these patients have many gastrointestinal symptoms and prescription of AST is high. In this study 41% of the total study was on either proton pump inhibitors or

H2 receptor antagonist. However the majority of the cases for AST had no adequate indication (44). In the present study, half of the study population was on acid AST. Assessment of the indications for AST was beyond the scope of this study.

The present study revealed that insulin was used mostly to manage diabetic participants. However, a few participants were on biguanides and sulphonylureas. In the study conducted by Dasari *et al*, insulin was mostly used to manage diabetes with CKD (10). Studies have shown that sulphonylureas, glinides and insulin carry a higher risk of inducing hypoglycemia and therefore they require close monitoring when given in CKD (45,46). The relationship between different anti-diabetic medications and the reasons for their preferences in CKD was beyond the scope of present study

In this study all participant with anemia were treated with erythropoietin and iron sucrose. Probably Recombinant human erythropoietin (RHE) and iron were prescribed because they are safe and effective in treatment of anemia in CKD as it has been revealed by Nurko *et al*. Furthermore greater increases in hemoglobin and ferritin are seen when anemic patients with CKD on RHE are given iron intravenously as compared to oral iron (47,48) .

Dyslipidemia in patients with CKD are safely managed by statins. Any statin can be used but atorvastatin is the commonly used in management of dyslipidemia in CKD. In the study conducted by Dasari *et al*, 90.1% of the patients with atherosclerosis were on atorvastatin and 9.8% were on rosuvastatin (10). In the present study all participants with atherosclerosis were treated with atorvastatin.

In CKD patients, it is recommended that the most appropriate agents in management of the comorbidities would be ones not requiring dose adjustment. However, this is not always possible and in this study almost a third required dose adjustment based on the baseline stage of CKD at prescription. But 25.26% of these drugs that required adjustment were incorrectly done. The results of this study are comparable to a study done by Ababa *et al*. In their study, only 26% of the study population did not have drugs that needed dosage adjustment. Of the prescriptions that had drugs requiring dose adjustment, 31% had inappropriately dose adjustments (33).

Prescriptions with at least one pair of drugs with a potential serious interaction which required the use of an alternative drug were made to almost a fifth (19.44%) of the participants. The severity of most potential drug interactions was significant which requires close monitoring. They were found in seventy-five percent of the participants. Occurrence of potential serious, significant, and minor drug interactions were associated with appropriateness of the prescription (p value 0.001, 0.004, and 0.046 respectively) Marquito *et al* report similar results. In their study, potential serious interactions were found in 16.8% of the participants and significant in 76.9% (49). Drug interactions affect the outcome of treatment due to ineffective treatment, poor adherence and ADRS which maybe higher in CKD. This may be avoided by careful drug evaluation especially where there is polypharmacy (43).

Patients with CKD are also prone to have multiple adverse events which have important consequences in the outcome of the treatment. In this study, half of the study population had either one or two ADRS. Seven percent had three or four ADRS. The results of the present study are similar to Chapin 2010 *et al* where they noted that patient with CKD carry a very high risk for occurrence of ADRS. In their study ADRS were observed in more than a half of the participants (50). ADRS were observed more in patients whose prescription were inappropriate (p = 0.001). ADRS were also associated with the number of drugs the patient was taking (p= 0.025). One of the determinants of occurrence of ADRS was the number of drugs being taken concurrently. Sato *et al* demonstrated that polypharmacy is associated with ADRS, [RR 4.3 95% CI, 3.8–4.8] (51).

A positive association was found between worsening of serum creatinine and appropriateness of the drug used in CKD by Ababa *et al* (33). In the present study, the renal function of 47 (66.20%) participants worsened after taking the prescribed drugs. However, this was not associated with appropriateness of prescribing (p=0.08). Perhaps the increase in serum creatinine levels could have been due to progression of the CKD or ADRs of some drugs.

CKD is associated with poor treatment outcomes and a higher risk of occurrence of ADRS due to changes in pharmacokinetics and pharmacodynamics of the administered drugs. Studies have revealed that this risk increases when inappropriate dosing is done

(19). In the present study, more than a half of the participants had ADRS. There was a positive association between ADRS with inappropriate prescribing (p=0.001). Appropriate drug prescribing ensure optimized therapy and avoidance of ADRS and unwarranted drug interactions (52). In this study resolution of comorbidities occurred in thirty-two of the participants. Twenty-seven of these participants had appropriate dose adjustments. This remission was associated with appropriateness of the prescriptions ($p < 0.0001$).

5.3 Limitations

The study site was limited to patients admitted or attending outpatient renal clinic at KNH. In addition, the study relied on the willingness of the patient to participate. This limitation was minimized by adding 20% to the estimated sample size.

Other parameters that clinicians may have used to adjust the doses were not considered. For instance, different blood pressures or heart rates require different doses. In addition, the guidelines used by the clinicians were not considered and they may have different reference ranges from the ones used in this study. The study used The Renal Drug Handbook third edition to get the cut off points for dose adjustments.

In KNH, the serum creatinine levels are routinely reported. However, creatinine clearance has to be calculated by the clinicians who may use different formulae from the one used in this study. The formulae may give varied eGFR and consequently underestimate the renal function. This would affect dose adjustments. In this study MDRD formula was used to estimate eGFR. MDRD incorporates the weight of the patient and has adjustment factors for men and women to avoid variances.

5.4 Conclusion

Comorbidities were associated with CKD and isolated cases occurred rarely. This necessitated polypharmacy with a mean number of drugs prescribed per patient being 6.54 +/-2.05. Antihypertensives, antacids, and antidiabetics were the most prescribed drugs. A substantial number of drugs prescribed to patients with CKD were not appropriately adjusted. Prescriptions with at least one pair of drugs with a potential

serious interaction were made for almost a fifth (19.44%) of the participants. Inappropriate prescribing was associated with ADRS, and drug interactions.

5.5 Recommendations

5.5.1 Recommendations for policy and practice

This study recommends provision of simplified aids like charts and handbooks on drug selection and dose adjustments in CKD to ameliorate poor treatment outcomes and ADRS. Installation of automated systems that compute eGFR and offer computed dosing in CKD or give alerts on the need for dose adjustments should also be considered.

5.5.2 Recommendations for research

This study did not assess the effects of socio-economic indicators like education level, employment, and income on the outcome of comorbidity treatment in CKD. In addition, the various drugs that were prescribed were not assessed for the specific ADRS they cause and associations thereof. Further research is needed to assess the effects of these factors on drug selection and treatment outcome.

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APPENDICES

APPENDIX 1: STUDY ELIGIBILITY SCREENING FORM

Study information

Assessment of rational utilization of drugs in adult patients with chronic renal failure at Kenyatta National Hospital

Investigator: Philip Macharia Karani

Signature:_____

Date: _____

Patient information

Patient identification code: _____

Gender Male ☐ Female ☐

Inclusion criteria

Five items must be answered yes for the subject to be included in the study.

Criteria	**Response**	
	Yes	**No**
1. Is the patient diagnosed with chronic renal failure and admitted or attending outpatient clinic at KNH?		
2. Is the plasma creatinine of the patient measured and recorded in the file?		
3. Is the patient over 18 years?		
4. Has the patient given consent to participate in the study?		
5. Has the patient signed the consent form?		

Exclusion criteria

Three items must be answered no for the subject to be included in the study.

Criteria	Response	
	Yes	No
1. Is the participant pregnant?		
2. Has the subject declined to sign consent to form?		
3. Does the patient have a psychiatric illness?		

APPENDIX 2: CONSENT

Part 1 Information sheet

Study Tittle

Assessment of rational utilization of drugs in adult patients with chronic renal failure at Kenyatta National Hospital

Investigators

Lead investigator: Dr. Karani Philip Macharia, a post graduate student in the School of Pharmacy, University of Nairobi.

Institutional affiliation: Department of Pharmaceutics and pharmacy practice, School of Pharmacy, University of Nairobi, Kenya.

Supervisors:

Dr. Peter Ndirangu Karimi Lecturer, Department of Pharmaceutics and Pharmacy Practice, University of Nairobi.

Dr. David Gitonga Nyamu. Lecturer, Department of Pharmaceutics and Pharmacy Practice, University of Nairobi.

Introduction

This consent form is for the intended study of patients with chronic renal failure admitted in the medical wards or attending renal clinic at KNH. The consent is to be sought from participants with chronic renal failure and questions will be asked regarding the disease. The study in which you are requested to participate is titled "Assessment of rational utilization of drugs in adult patients with renal failure at Kenyatta National Hospital."

Purpose of the study

The purpose of this study is to find out the drugs used by patients with chronic renal failure and assess their appropriateness in renal failure at Kenyatta National Hospital. It

also intends to find the association between poor drug use and adverse effects and poor treatment outcomes.

Your role of a participant in the study

If you participate in the study you will be requested to be interviewed using a questionnaire to gather your socio-demographics and adverse effects that you may have had during the course of treatment. Your treatment charts and files will also be reviewed to collect data on the treatment you are receiving at KNH. The study does not require any specimen from you and no procedure will be carried on you.

Benefits

Correction of any wrong prescription or dosage will benefit you as a participant. The result of the study will also provide crucial information to health care providers on drug use and adjustments in patients with renal failure in the Kenya's health system. No financial compensation will be given.

Risks or discomforts

There are no risks or harm anticipated to the participants in this study. Participation in the study will not attract any extra charges from KNH.

Confidentiality

All the information you give will be confidential and will be used only for the purpose of this research. Your name will not appear in the questionnaire to ensure that the identity is concealed.

Voluntary

Your participation in this study is completely voluntary. If you do not agree to participate you are free to withdraw at any time without giving reasons for the withdrawal. There will be no consequences attached to your treatment and you will continue receiving your treatment in KNH.

You are guaranteed that all ethical considerations and approvals have been undertaken. For any questions or any concern contact the principal investigator on email karanimbore@yahoo.com telephone number +254720411281, the supervisors Dr. Karimi Peter Ndirangu on email ndirang@yahoo.com telephone number 020-2119317and Dr. Nyamu David Gitonga on email dgnyamu@gmail.com telephone number 020-2119317or Kenyatta National Hospital/University of Nairobi Ethical and Research Committee Secretary: Email uonknh.erc@uonbi.ac.ke Tel +254 207 726300 ext 44102.

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

Part II: Consent certificate by the patient

I…… I willingly agree to participate in the research conducted by Dr. Karani Philip Macharia, whose nature has been explained by him/his research assistant. After explanation regarding the aim of the study, I understand that my participation is on my free will. The study results may be beneficial to my kin, other patients, and health care professionals through better understanding of appropriate drug use in renal failure.

…….Signature/thumb print

Date …… dd/mm/yy

Statement by the witness if the participant can only speak in mother tongue

I confirm that the consent form has been read to the above respondent (…….). He/she has been given the opportunity to ask questions regarding the study where the explanations were not clear. I also confirm that the respondent has given his/her consent.

Witness name……..……..……

Signature……..…….

Date ……

Part III: Statement by the researcher

I have accurately read out the information sheet to the participant, and to the best of my ability made sure that the participant understands that participation requires his/her consent without coercion, information given will be handled confidentially and that refusal to participate or withdrawal from the study will not in any way determine the quality of care and treatment given to the patient. I also confirm that the participant was given an opportunity to seek clarifications regarding the information read and or explained to the respondent

A copy of this Informed Consent Form has been provided to the participant.

Name of researcher taking consent……

Signature of researcher taking the consent……

Date……

KIAMBATISHO 2: IDHINI

Sehemu ya kwanza

Jina la utafiti

Tathmini ya matumizi ya busara ya madawa kwa watu wazima walio na ugonjwa wa figo katika Hospitali ya Taifa ya Kenyatta.

Watafiti

Mtafiti mkuu: Dkt. Karani Philip Macharia, Mwanafunzi uzamili katika Shule ya Pharmacy, Chuo Kikuu cha Nairobi

Uhusiano wa Kitaasisi: Idara ya Pharmaceutics na Pharmacy practice, Shule ya Pharmacy, Chuo Kikuu cha Nairobi, Kenya

Wasimamizi: Dkt. Peter Ndirangu Karimi Mhadhiri, Idara ya Pharmaceutics na Pharmacy Practice, Chuo Kikuu cha Nairobi

Dkt. David Gitonga Nyamu Mhadhiri, Idara ya Pharmaceutics na Pharmacy Practice, Chuo Kikuu cha Nairobi

Kuanzishwa

Fomu hii ya idhini itatumika kwa utafiti uliokusudiwa kwa watu wazima walio na ugonjwa wa figo waliolazwa katika wodi au kuhudhuria kliniki ya figo katika Hospitali ya Taifa ya Kenyatta. Idhini itatafutwa kutoka kwa wagonjwa na baadaye mahojiano dodoso yatafanywa. Utafiti unaombwa kushiriki unaitwa "Tathmini ya matumizi ya busara ya madawa kwa watu wazima walio na ugonjwa wa figo katika Hospitali ya Taifa ya Kenyatta"

Malengo ya utafiti

Lengo la utafiti ni kutathmini matumizi ya busara ya madawa kwa watu wazima walio na ugonjwa wa figo katika Hospitali ya Taifa ya Kenyatta

Kama mshiriki natarajiwa kufanya nini?

Kama mshiriki kwa huu utafiti, utahojiwa kwa kutumia muundo wa dodoso kukusanya nakala za kijamii na historia ya matibabu yako na matokeo yake. Rekodi zako za matibabu unayopokea hapa Hospitali Kuu ya Kenyatta zitaangaliwa ili kuchukua nakala za matibabu zichukuliwe. Utafiti huu hauhitaji sampuli yoyote kutoka kwako na kwa hivyo hakuna operesheni yoyote utafanyiwa ili kufikia malengo ya utafiti huu.

Faida

Marekebisho ya matumizi mabaya ya madawa itakuwa faida ya kwanza na ya haraka kwako kama mshiriki kwa huu utafiti. Matokea ya utafiti huu utatoa taarifa muhimu ya matumizi ya madawa kwa wagonjwa walio na ugonjwa wa figo kwa wataalamu wa afya katika mfumo wa afya nchini Kenya. Hautalipwa fidia yoyote kwa kushiriki kwa utafiti huu.

Hatari

Hakuna hatari yoyote inayokusudiwa kwa huu utafiti. Ushiriki wako katika utafiti huu hautavutia malipo yoyote ya ziada kutoka Hospitali ya Taifa ya Kenyatta.

Usiri

Nakala utakazotoa zitatumika kwa madhumuni ya utafiti huu pekee na pia hizo nakala zitakuwa za siri. Jina lako halitaandikwa kwa karatasi ya maswali ili kuhakikisha kuwa usiri unazingatiwa.

Kujitolea

Ushiriki katika utafiti huu ni kwa hiari yako. Iwapo hautakubali kushiriki unaweza kujiondoa wakati wowote bila kupatiana sababu yoyote ya kujiondoa. Pia unadhibitishiwa kuwa kutoshiriki katika utafiti huu haitabadilisha ubora wa huduma unazopokea kutoka kwa Hospitali ya Taifa ya Kenyatta.

Pia unahakikishiwa kuwa masuala yote ya kimaadili na ruhusa ya kufanya utafiti huu zimefanyika.

Kwa maswali yoyote kuhusu ukweli wa utafiti tafadhali wasiliana na mtafiti mkuu kwa barua pepe karanimbore@yahoo.com nambari ya simu +254720411281, wasimamizi Dr. Karimi Peter Ndirangu barua pepe ndirang@yahoo.com nambari ya simu 020-2119317 and Dr. Nyamu David Gitonga barua pepe dnnyamu@gmail.com nambari ya simu 020-2119317au katibu wa Kamati ya Utafiti ya Chuo Kikuu cha Nairobi/ Hospitali ya Taifa ya Kenyatta: Email uonknh.erc@uonbi.ac.ke Tel +254 207 726300 ext 44102.

Nakualika ushiriki katika utafiti huu. Ushiriki wako utakuwa tu kupitia idhini yako ambayo unaweza kutoa sasa au baadaye. Pia unaweza kuuliza ufafanuzi wowote juu ya jambo ambalo linatatiza katika utafiti huu.

Sehemu ya Pili: Cheti cha idhini ya mgonjwa

Mimi……kwa mapenzi yangu napeana idhini ya kushiriki katika utafiti utakaofanywa na Dkt. Karani Philip Macharia, ambao asili yake nimeelezwa naye ama msaidizi wake wa utafiti. Baada ya maelezo kuhusu lengo la utafiti , nimeelewa kwamba kushiriki kwangu ni kwa mapenzi yangu. Matokeo ya utafiti huu inaweza kuwa na manufaa kwa jamaa zangu na wagonjwa wengine. Pia wataalamu wa huduma za afya wataelewa vizuri utumizi sahihi wa madawa kwa wagonjwa walio na ugonjwa sugu wa figo.

…….

Sahihi / alama ya kidole

Tarehe …… siku/mwezi/mwaka

Kauli ya mshahidi kama mshiriki anaweza tu kusema kwa lugha ya mama

Nathibitisha kuwa kwamba fomu ya idhini imesomwa na kuelezwa kwa mshiriki aliyeandikwa hapo mbeleni (…….). Mshiriki amepewa nafasi ya kutafuta ufafanuzi kwa kuuliza maswali kuhusu utafiti huu . Pia nimethibitisha kuwa mshiriki amewapa watafiti idhini yake ya kushiriki kwa utafiti huu .

Jina la Mshahidi …….……..

Sahihi……..…….

Tarehe ……..……

Sehemu ya tatu: Kauli ya mtafiti

Nina usahihi kuwa nimemsomea mshiriki fomu ya idhini kadri ya uwezo wangu na nimehakikisha kuwa mshiriki ameelewa kuwa idhini yake ya kushiriki katika utafiti huu amepatiana bila kulazimishwa. Pia maelezo yoyote mshiriki atatoa yatabebwa kwa usiri na kwamba akikataa kushiriki au kujiushuru kutoka kwa utafiti huu haitabadilisha ubora wa huduma anazopokea kutoka kwa Hospitali ya Taifa ya Kenyatta. Pia nathibitisha kwamba mshiriki alipewa nafasi ya kutafuta ufafanuzi kuhusu taarifa alizosomewa au kuelezwa kutoka kwa fomu ya maeelezo ya idhini.

Mshiriki pia amepewa nakala ya fomu ya maelezo ya idhini.
Jina la mtafiti anayechukua idhini ……

Saini ya mtafiti anayechukua idhini

……

Tarehe……

APPENDIX 3: QUESTIONNAIRE

STUDY TITLE: Assessment of rational utilization of drugs in adult patients with chronic renal failure at Kenyatta National Hospital

NOTE: Tick or fill in the questionnaire appropriately

1. Respondent number _____
2. Patients identification code _____

Demographical data

3. Patient's gender

Male ☐ Female ☐

4. Date of admission_____
5. Current age of the patient _____Years
6. Current weight of the patient _____kg
7. Current height of the patient _____cm

8. What is the education level of the participant?

Tertiary ☐

Secondary ☐

Primary ☐

Informal ☐

9. What is the occupation of the participant?

Salaried ☐

Casual waged

Self employed

Unemployed

10. What is the participant's net monthly income category (KShs)?

1-5,000

5,001-15,000

15,001-30,000

30,001-50,000

50,000-100,000

>100,000

Diagnosis

11. When was the patient diagnosed with renal failure? _____Day/Month/Year
12. What was the creatinine level at admission? _____ ml/Min
13. What is the stage of renal failure at admission?

Stage 1

Stage 2

Stage 3

Stage 4

Stage 5

Assessment of drugs used in renal failure and their appropriateness

14. In which clinical setup was the prescription done?

Wards	
Outpatient clinic (Renal Clinic)	

15. Is the patient suffering from other illnesses?

Medical Condition	Tick where appropriate	Duration of illness (days)
Anaemia		
Atherosclerosis		
Cardiovascular disease (specify)		
Cerebrovascular disease		
Depression		
Diabetes		
Thyroid disease		
Respiratory condition (specify)		
Others		

16. Which drugs were prescribed to manage the comorbid conditions?

Medical Condition	Drug	Is the drug contraindicated in renal failure? Dosage		Was dose adjustment required?		Was the adjustment appropriate?	
		Yes	No	Yes	No	Yes	No
Anaemia							
Atherosclerosis							
Cerebrovascular disease							
Cardiovascular disease							
Depression							
Diabetes							
Ischemic heart disease							
Hypertension							
Thyroid disease							
Respiratory							
Others							

17. What was the creatinine level during prescription? _____ ml/Min

18. What was the eGFR when the prescription was made? _____ ml/Min/1.73M^2

Assessment of consequences of irrational drug use

19. To assess if the drug administered has worsened the renal disease, record at least two separate creatinine levels and compare with the levels at admission.

Reading	Date	Creatinine levels ml/Min
At admission		
Reading 1		
Reading 2		
Reading 3		

20. What was the outcome of the treatment?

A. Cured
B. Remission
C. ADRs
D. Death

If choice for question 20 is C, please answer question 21 and 22.

21. Have you suffered from the following?

Condition	Yes	No
Seizures		
Hemiparesis		
Neuropathy		
Bleeding		
Jaundice		
Difficulties in breathing		
Diarrhea		
Vomiting		
Constipation		
Mouth ulcers		
Anaemia		
Other		

22. Assessment of adverse effect in the participant file

Adverse effect	Assessment	Normal values	Patient values
Jaundice	ALP levels GGT levels AST levels ALT levels INR Platelet levels Protein levels		
Anaemia	Hemoglobin levels		
Seizures	RBS Sodium levels Calcium levels Potassium levels Acid base balance		
Bleeding	INR APTT Platelet levels		
Hemiparesis	INR APTT Platelet levels		
Hypotension	Pulse BP		
Hypoglycemia	Random blood sugar		
Neutropenia	Full blood count		

APPENDIX 4: DRUGS PRESCRIBED TO PARTICIPANTS

	Dose adjustment		Appropriateness of dose	
Drug prescribed	**Not required**	**Required**	**Appropriate n(%)**	**Inappropriate**
Erythropoietin	22			
Iron sucrose	23			
Atorvastatin	21			
Metformin		4	4(100%)	
Glimepiride		1	1(100%)	
Soluble insulin	6			
Mixtard	19			
Furosemide	31			
Metolazone	6			
Spironolactone		3	3(100%)	
Losartan		14	14(100%)	
Telmisartan		1	1(100%)	
Hydralazine		18	18(100%)	
Clopidogrel	3			
Enalapril		9	9(100%)	
Lisinopril		1	1(100%)	
Labetalol	1			
Atenolol	2			
Carvedilol		15	15 100%)	

	Dose adjustment		Appropriateness of dose	
Drug prescribed	**Not required**	**Required**	**Appropriate**	**Inappropriate**
Nebivolol		2	2(100%)	
Prazosin	1			
Clarithromycin		5	4(80%)	1(20%)
Ceftazidime		3		3(100%)
Metronidazole	3			
Meropenem		3	3(100%)	
Levofloxacin		1		1(100%)
Clindamycin		1	1(100%)	
Rifampicin		3	3(100)	
Pyrazinamide		3	3(100%)	
Ethambutol		3		3(100%)
Acyclovir		1		1(100)
Enoxaparin		8		8(100%)
Heparin	9			
Protamine	1			
Warfarin	2			
Tranexamic acid		1		1(100%)
AZT		1	1(100)	
EFV	6			
NVP	1			

	Dose adjustment		Appropriateness of dose	
Drug	**Not required**	**Required**	**Appropriate**	**Inappropriate**
ABC	4			
LPV/r	2			
Omeprazole	40			
Ranitidine	1			
Cetirizine	3			
Paracetamol		8	6(75%)	2(25%)
Tramadol		2	1(50%)	1(50%)
Meloxicam	1			
Pregabalin		3	1(33.33%)	2(66.67%)
Tamsulosin	3			
Phenytoin	1			
SPS	7			
Pyridoxine	3			
Lactulose	1			
Allopurinol		2	2(100%)	
Methylprednisolone	1			
Prednisolone	3			
Metoclopramide	11			
Ondansetron	3			

APPENDIX 5: DRUG COMBINATIONS PER PATIENT

Combination	n	%	Cumulative %
Recombinant Human Erythropoietin (RHE) + Hematinic + CCB + vasodilator + LMWH + Antihistamine + PPI	1	1.39	1.39
Insulin + CCB + ACEi + Antiplatelet (aspirin)	1	1.39	2.78
Loop diuretic + CCB + ACEI + anticonvulsant	1	1.39	4.17
Loop diuretic + CCB + ARB + Statin	1	1.39	4.56
Biguanides +NRTI + NNRTI + Sulphonamide + PPI + Dopamine 2 receptor antagonist	1	1.39	6.94
NRTI + NNRTI + Sulphonamide + PPI + Triazole antifungal + Paracetamol	1	1.39	8.33
Thiazide diuretic + ACEi + PPI + Dopamine 2 receptor	1	1.39	9.72
RHE + Iron supplement + Loop diuretic + vasodilator + B blocker + CCB + PPI	1	1.39	11.11
RHE + Iron supplement + Glycoside + Loop Diuretic + CCB + B blockers + Cephalosporin + Macrolide + LMWH	1	1.39	12.50
Insulin + vasodilator + loop diuretic + CCB + monobactam + antiplatelet (aspirin) + Heparin	1	1.39	13.89
RHE + Iron supplement + CCB + Opioid + PCM + Dopamine 2 receptor antagonist + PPI	1	1.39	15.28
Insulin + CCB + vasodilator + Antifibrinolytic + Monobactam + Heparin + PPI	1	1.39	16.67
Insulin + CCB + Loop diuretic + ARB + Cephalosporin + macrolides	1	1.39	18.06
Statin + Insulin + CCB + B blockers + Cephalosporins + Nitroimidazole + antiplatelet (aspirin)	1	1.39	19.44
RHE + Iron supplement + PPI + alpha antagonist + potassium chelating agents	1	1.39	20.83
Statin + Insulin + CCB + Loop Diuretic + LMWH + Nitroimidazoles + Cephalosporin + Macrolide + PPI	1	1.39	22.22

Combination	n	%	Cumulative %
Loop diuretic + CCB + vasodilator + B blocker + anticonvulsant + PPI + Cephalosporin + LMWH	1	1.39	23.61
Statin + Insulin + CCB + ARB + Fluoroquinolones + Clindamycin + PCM	1	1.39	25.00
RHE + Iron supplement + PPI + vitamin + Anti TB + Triazole antifungals + Heparin + potassium chelating agents	1	1.39	26.39
Statin + Insulin + vasodilator + ARB + loop diuretic + CCB + PPI + Dopamine receptor antagonist	1	1.39	27.78
RHE + Iron supplement + PPI + CCB + Peripheral vasodilator + Cephalosporin + Heparin	1	1.39	29.17
CCB + Peripheral vasodilator + Cephalosporin + Heparin	1	1.39	30.56
CCB + Loop diuretic + B blockers + Peripheral vasodilators + LMWH	1	1.39	31.94
Thiazide + loop diuretic + B blocker + cardiac glycoside	1	1.39	33.33
RHE + Iron supplement + PPI + NNRTI + NRTI + Sulphonamide	1	1.39	34.72
RHE + Iron supplement + PPI + statin + Insulin + CCB + ACEi + Thiazide + loop diuretic + heparin + dopamine receptor antagonist	1	1.39	36.11
CCB + Glycopeptide antibiotics + Beta lactams + opioids + Dopamine receptor antagonists + PPI	1	1.39	37.50
Loop diuretic + K sparing diuretic + Dopamine receptor + fluoroquinolone + laxative	1	1.39	38.89
RHE + Iron supplement + CCB + Peripheral vasodilator + Thiazide + loop diuretic + sulphonyl ureas	1	1.39	40.28
CCB + Peripheral vasodilator + B blocker + PPI + steroid	1	1.39	41.67
Statin + Insulin + B blocker + Loop diuretic + ARB	1	1.39	43.06

+ peripheral vasodilators + antiplatelet + CCB			
Combination	**n**	**%**	**Cumulative %**
Statin + Insulin + antiplatelet + CCB + ACEI	1	1.39	44.44
Statin + vasodilator + B blocker + CCB	1	1.39	45.83
RHE + Iron supplement + PPI + NNRTI + NRTI + Sulphonamide +ARB + loop diuretic + B blocker + Cardiac glycoside	1	1.39	47.22
Sulphonylureas + biguanides + CCB + B blocker + Antiplatelet + xanthine oxidase inhibitor	1	1.39	48.61
Statin + insulin + ACEi + Thiazide + Loop diuretic + B blocker + CCB + NSAID + PPI +	1	1.39	50.00
RHE + Iron supplement + PPI + statin + CCB + Lasix + B blockers + potassium chelating agents	1	1.39	51.39
Statin + CCB + loop diuretic + antiplatelet + Xanthine oxidase inhibitors + PPI	1	1.39	52.78
RHE + Iron supplement + ACEi + CCB + Thiazide diuretic	1	1.39	54.17
Statin + Insulin + CCB + Furosemide	1	1.39	55.56
Statin + Biguanide + Insulin + CCB + ARB + Loop diuretic + Fluoroquinolone + anticonvulsant	1	1.39	56.94
ACEi + PPI + analgesic, other	1	1.39	58.33
Statin + sulphonyl urea + ACEI + CCB + peripheral vasodilators + anti platelets	1	1.39	59.72
Statin + insulin + CCB + ACEI + LMWH + Monobactams + H2 antagonist	1	1.39	61.11
Antiviral + PPI + Heparin + Sulphonamide	1	1.39	62.50
CCB + Peripheral vasodilator + central vasodilator	1	1.39	63.89
Anti TB + NRTI + NNRTI + sulphonamide + vitamins	1	1.39	65.28
RHE + Iron supplement + CCB + loop diuretic + PPI + Potassium chelating agents	1	1.39	66.67
RHE + Iron supplement + PPI + peripheral vasodilator + B blocker + CCB + Furosemide +	1	1.39	68.06

Steroid + Selective 5HT3 antagonist

Combination	n	%	Cumulative %
RHE + Iron supplement + PPI + CCB + loop diuretic + potassium chelating agents	1	1.39	69.44
Anti TBs + insulin + cephalosporins + vitamins + PPI + sulphonamides + triazole antifungals	1	1.39	70.83
RHE + Iron supplement + PPI + B blocker + Enalapril + aldactone + dopamine receptor antagonist	1	1.39	72.22
RHE + Iron supplement + insulin + antiplatelet + ARB + CCB + cephalosporin + LMWH	1	1.39	73.61
Statin + insulin + peripheral vasodilator + CCB + central vasodilator + cephalosporins + PPI + anti histamines	1	1.39	75.00
RHE + Iron supplement + alpha blockers + analgesic, others +cephalosporins + potassium chelating agents	1	1.39	76.39
Insulin + loop diuretic + B blocker + analgesic, others + cephalosporins + heparin + potassium chelating agents	1	1.39	77.78
RHE + Iron supplement + PPI + CCB + macrolide + coumarin	1	1.39	79.17
Steroids + PPI + dopamine receptor antagonists	1	1.39	80.94
Insulin + CCB + NRTI + Protease inhibitors + sulphonamide	1	1.39	83.33
RHE + Iron supplement + CCB + Selective 5HT3 antagonists	1	1.39	84.72
Statin + B blocker + Coumarin + loop diuretic + Thiazide + ARB	1	1.39	86.72
Insulin + K sparing diuretic + loop diuretic + ARB + CCB + antiplatelet	1	1.39	86.11
CCB + PPI	1	1.39	87.50
Sulphonyl ureas + Biguanides + Thiazide + ARB + B blocker + CCB + Antiplatelet	1	1.39	88.89

NRTI + Protease + Sulphonamide + Selective 5HT3 antagonist + PPI	1	1.39	90.28

Cumulative	**n**	**%**	**Cumulative %**
Anti TB + ARB + Loop diuretic + Anticonvulsant + PPI NRTI + NNRTI + sulphonamide	1	1.39	91.67
Iron supplement + NRTI +NNRTI + Selective 5HT3 antagonist + PPI + Sulphonamide	1	1.39	93.06
Statin + Insulin + CCB + B blockers + antiplatelet	1	1.39	94.44
Insulin + central vasodilator + loop diuretic + B blocker + hydralazine	1	1.39	95.83
RHE + Iron supplement + PPI + CCB + dopamine receptor antagonist	1	1.39	97.22
Statin + ARB + CCB + thiazide + NRTI	1	1.39	98.61
B blocker + CCB + ARB + loop diuretic + PPI	1	1.39	100.00

APPENDIX 6: DRUGS PRESCRIBED IN CLASSES

Class	n	%
Anti-hypertensive	54	75.0%
Antacids	41	56.94%
Ant-diabetics	29	40.28%
Anti-diabetics	29	40.28%
Antibiotics	28	38.8%
Hematinic	23	31.94%
Statins	19	26.39%
Anti-coagulants	17	23.61%
Antivirals	13	18.05%
Antiplatelet	13	18.05%
Analgesics	11	15.27%
Antihistamines	8	11.11
Antifungals	3	4.17
Alpha receptor blockers	3	4.17

APPENDIX 7: ETHICAL APPROVAL FROM KNH/UON RESEARCH AND ETHIC COMMITTEE

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/301

10th August, 2016

KENYATTA NATIONAL HOSPITAL APPROVED 10 AUG 2016 KNH/UoN-ERC P.O. Box 20723-00202 NAIROBI

Karani Philip Macharia
Reg. No. U56/76059/2014
Dept. of Pharmaceutics and Pharmacy Practice
School of Pharmacy
College of Health Sciences
University of Nairobi

Dear Philip,

REVISED RESEARCH PROPOSAL: ASSESSMENT OF RATIONAL UTILIZATION OF DRUGS IN ADULT PATIENTS WITH CHRONIC RENAL FAILURE AT KENYATTA NATIONAL HOSPITAL (P359/05/2016)

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 10th August 2016 – 9th August 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.

"Protect to discover"

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 Chair, KNH- UoN ERC
The Dean, School of Pharmacy, UoN
The Chair, Dept. of Pharmaceutics and Pharmacy Practice, UoN
Supervisors: Dr. Peter Ndirangu Karimi, Dr. David Gitonga Nyamu

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