ASSESSMENT OF EXPENDITURE AND BUDGET IMPACT ANALYSIS OF POST-KIDNEY TRANSPLANT CARE AT KENYATTA NATIONAL HOSPITAL

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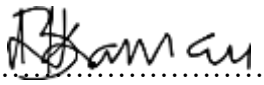
Signature……  …… Date……10/17/2022……

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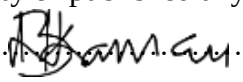
Signature…….  ……. Date……10/17/2022……

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DEDICATION

To my parents, Prof Isaac Kimengi and late Jane Wanjiru; Thank you for instilling in us the value of education and sacrificing in one way or another. I will be eternally grateful

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ABSTRACT

Background

In Kenya, the Ministry of Health reported that 4 million Kenyans have chronic kidney disease with a significant proportion of this population progressing to kidney failure. In the event that kidneys fail, renal replacement therapy by dialysis or transplantation is the only means of survival**.** Renal transplantation therapy (RTT) is a cost-effective therapy compared to hemodialysis or peritoneal dialysis in patients with end-stage renal disease (ESRD) despite being associated with a huge economic burden. The major factor limiting transplantation rates is availability of donor kidneys. Currently in Kenya, the NHIF benefit package only caters for dialysis and kidney transplantation omitting post-kidney transplant care. This signifies a gap service provision and policy which has devastating financial consequences on KTRs. Consequently, many healthcare providers in Kenya have lamented about this cost and resultant impact of non-adherence. It is possible that this cost can be comfortably borne by the NHIF.

Objective

The main objective of this study was to determine the expenditure and budget impact of post kidney transplant care from a provider perspective.

Methods

This was a mixed methods study comprising of a retrospective cohort study and a predictive Markov model. The study was done from the perspective of the healthcare provider (KNH). Patients who had undergone a kidney transplant and receiving care at the renal unit from 2010 to 2019 were identified. One hundred and fourteen files were identified after simple random sampling with replacement. Files of patients were selected using simple random sampling technique with replacement. This was carried out using a coin. The files that satisfied the inclusion criteria were gathered and a coin was tossed. Whichever file coincided with the head was included. The process was repeated until the calculated sample size was attained. A pre-tested data abstraction tool was used to collect socio-demographic and resources used in the management post-kidney transplant patient while an interview guide was used to collect cost data.

For each patient file, the principal investigator identified resources consumed in each year using the data abstraction form and estimated the quantities by counting the number of tablets/ tests used in each year to determine the total resources consumed. This process was repeated for a period of five years' post-transplant. Data was entered into an Excel based database and descriptive analysis was done using STATA version 10. A micro ingredient approach was used to cost all the resources used to manage kidney transplant recipients (KTRs). Resources used were identified and quantified and the unit cost were obtained from the procurement and billing departments. These were used to compute the total expenditure incurred by each patient per year. The expenditure data were converted to US dollars at the prevailing rate of 1 dollar to Ksh 102.9. The contribution of each cost category was computed. One-way sensitivity analysis was done to identify the cost categories whose uncertainty in value had the most impact on the total expenditure incurred and the findings presented in the form of a tornado charts. Budget impact analysis was done to determine the impact of including the care after transplant into the Kenyatta National Hospital and National Hospital Insurance Fund budgets. To predict the costs associated managing post kidney transplant patients, time varying discrete states markov modelling was done. A kidney transplant recipient (KTR) could exist in 3 possible states. The three states were survival with a viable kidney; hemodialysis following graft rejection; and death. Markov modeling was done and the transition probabilities for the three states were calculated using Heemod package version 0.14.2 in R. The cycle length was one month. A diagrammatic representation of the model is shown in Figure 4.13. We constructed a Markov model that was used to estimate the number of patients that would need post-kidney transplant services in five years. It was conducted from the perspective of Kenyatta National Hospital. The R code that was used to compute the costs associated with each health state is presented in Appendix five and the actual costs are presented in Appendix six.

Results

The three main categories whose expenditure contributed significantly to the total cost of post-kidney transplant care were immunesuppressants, laboratory investigations and services. We demonstrated that expenditure was highest in the first year post-kidney transplantation; a cost of Ksh 32,882 per patient per month (PPPM) followed by year three at Ksh 25,639 (PPPM)and the trend decreased gradually from year one to year five.

In addition, in the years following kidney transplant, the annual medicine and hospital budget increased by Ksh 369,568,640 and Ksh 3,824,569,720 respectively over a five-year period. Results from the budget impact analysis of KTRs in Kenya showed that expenditure for NHIF Outpatient budget will increase from Ksh 175,729,217 million in year one to Ksh 275,508,106 million in year five which is an increment of Ksh 99,778,889 million shillings.

Discussion

The results demonstrate that the first year post-kidney transplant is associated with the greatest expenditure of approximately Ksh 32,882 per patient per month. This amount is more than twice Kenya's monthly minimum wage of Ksh 13,572. Immunosuppressive medicines in particular were a major contributor to the yearly total expenditure signifying their important role in post-transplant care. In the budget impact analysis for all the kidney transplant recipients in Kenya, we have demonstrated that the incremental expenditure change over a five-year period for NHIF outpatient budget was Ksh 1,132,459,571 representing a 23% change from their baseline expenditure (2020).

We propose that post-kidney transplant care be incorporated into the NHIF benefit package since this amount is reasonable considering the important role of post-transplant care, to ease access and the financial burden associated with out of pocket expenditure.

Conclusion

The main expenditure drivers after kidney transplantation were immunosuppressants, laboratory investigations and services offered to KTRs. The first year post-kidney transplant is associated with the greatest expenditure of approximately Ksh 32,882 per patient per month. This amount is 2.4 times Kenya's monthly minimum wage of Ksh 13,572. Immunosuppressive medicines and laboratory investigations in particular were a major contributor to the yearly total expenditure signifying their important role in post-transplant care. We recommend that these expenditures to be covered by NHIF.

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ABBREVIATIONS

ACR	Albumin Creatinine ratio
AR	Acute Rejection
BPAR	Biopsy Proven Acute Rejection
CMV	Cytomegalovirus
Cs A	Cyclosporine
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CNIs	Calcineurin Inhibitors
CKD	Chronic Kidney Disease
DGF	Delayed Graft Function
ESRD	End Stage Renal Disease
GFR	Glomerular Filtration Rate
GBDS	Global Burden of Disease Study
KTR	Kidney Transplant Recipient
KNH	Kenyatta National Hospital
KDIGO	Kidney Disease Improving Global Outcomes
LMICs	Low and Middle Income Countries
MMF	Mycophenolate mofetil
MDRD	Modification of Diet in Renal Disease
m TORS-I	Mammalian target of rapamycin inhibitors
NHIF	National Hospital Insurance Fund
RAAS	Renin Angiotensin Aldosterone System
RRT	Renal Replacement Therapy
WHO	World Health Organization

DEFINITION OF TERMS

Anemia in this population is a hemoglobin level less than 12 g/dL in males and less than 11 g/dL in premenopausal women.

Chronic Kidney Disease (CKD) a decline kidney function measured using Glomerular Filtration Rate(GFR) of less than 60 mL/min per 1·73 m^2.

Cardiovascular disease (CVD) is any condition that damages the heart and blood vessels. This includes stroke, congestive heart failure, hypertension, coronary artery disease.

Delayed graft function is defined as a need for dialysis in the first week following transplantation.

Dyslipidemia is any abnormality in plasma lipoprotein concentration.

End Stage Renal Disease (ESRD) is a severe irreversible damage to the kidney characterized by proteinuria and a glomerular filtration rate of less than 15 ml/minute.

Kidney transplant is a surgical procedure that involves the replacement of a diseased kidney with a functional one from a donor.

Post-transplantation Diabetes Mellitus (PTDM) refers to sustained hyperglycemia developing in any patient without history of diabetes before transplantation.

Proteinuria is presence of proteins in urine and it is an indicator of kidney damage.

CHAPTER ONE: INTRODUCTION

1.1 Background

Africa is the second largest continent in the world, with a population of over 1 billion (Elhafeez et al., 2018). Most countries are undergoing epidemiological changes and are confronted with the double burden of communicable and non-communicable diseases. (Kaze et al., 2018). Chronic kidney disease is prevalent in Sub Saharan Africa as a result of diabetes, hypertension, and HIV pandemic. (Stanifer et al., 2014). Approximately 12–23% of adults have CKD and are potential candidates for End Stage Renal Disease (ESRD). (Ashuntantang et al., 2017).

In Kenya, the Ministry of Health reported that 4 million Kenyans have chronic kidney disease. Of these, approximately 10,000 have ESRD and require dialysis, yet only 10% of those who need dialysis are able to access the services. In addition, the prevalence is estimated to be at 4%. (Maritim et al.,2021). In Kenya, there are 214 dialysis units countrywide and the number of patients on regular dialysis increasing from ~300 patients to ~5000 patients today as a result of reimbursement hemodialysis by NHIF. (Ministry of Health, Kenya 2021).

In ESRD, dialysis or transplantation offers the only remedy for survival. (Ashuntantang et al.,2017). In the past ten years, more than 1.4 million people have undergone kidney replacement therapy. Transplantation is preferred because it is cost effective. However, donor availability limits the number of transplants carried out. (Chamberlain et al., 2014). Renal transplantation therapy (RTT) is a cost-effective therapy compared to dialysis despite the financial cost associated with it. Developed countries spend more than 2–3% of their health-care budget on the treatment of end-stage kidney disease. In 2015, Medicare (USA) expenditure on chronic and end-stage kidney disease were more than 64 and 34 billion United States dollars, respectively. (Luyckx & Stanifer, 2018)

A study by Tanriover et al., (2013) found that to abolish benefits after three years creates a burden of patients. Approximately 29% of the recipients were uninsured and 40,000 recipients were in danger of non-adherence resulting in loss of approximately 1300–1500 grafts yearly. (Tanriover et al., 2013). A study from a hundred Living Kidney Donors (LKDs) and found that about 96 % experienced costs associated with donation. (Klarenbach et al., 2014). A third of Living Kidney Donors incurred more than 3000 Canadian dollars, and 15% had costs of more than $8000. (Rodrigue et al 2015). These findings highlighted the costs associated with

donation to be a key factor responsible for the fall in donation rates. Therefore, it may be counterproductive for Kidney Transplant Recipients (KTRs) to receive grafts and then be denied optimal post-transplant care necessary for the survival of the graft and improved quality of life.

1.2 Problem statement

In Kenya, according to the National Hospital Insurance Fund (NHIF) Benefit Utilization report (2018), the fund spent Ksh 1.76 billion for the treatment of kidney failure. Further, the fund paid Ksh 64.7 million towards kidney transplants, up from Ksh 21.7 million the previous year and Ksh 922.8 million for 73,757 kidney dialysis sessions. These statistics indicate a rise in the uptake of renal transplant therapy services. (Top expenditure per healthcare Benefits Packages NHIF,2018).

Under the package, NHIF pays up to a maximum of Ksh 500,000 for a kidney transplant, for both local and overseas transplants while; dialysis is offered at a maximum of ksh 9,500 per session twice weekly. Currently NHIF does not fund post-kidney transplant care. Consequently, many healthcare providers in Kenya have lamented about this cost and resultant impact of non-adherence. It is possible that this cost can be comfortably borne by the NHIF. This study therefore sought to estimate the 5 year costs of post-transplant care in order to make a case for insurance funded care. The output of this study may be used by policy makers to convince NHIF to include post-kidney transplantation care in the health benefit package. This will be achieved by way of an unsolicited policy note to the NHIF.

1.3 Research question

i. What are the direct medical costs associated with post-kidney transplant care from the perspective of the providers?
ii. What would be the budgetary impact of inclusion of post-transplant cost of care on the budgets of Kenyatta National Hospital and National Hospital Insurance Fund?

1.4 Study objectives

1.4.1 General objectives

The main objective of this study was to determine the cost of post kidney transplant care from a provider perspective and the impact on the budget of Kenyatta National Hospital.

1.4.2 Specific objectives

i. To determine the direct medical expenditure associated with post-kidney transplant care from the perspective of the provider.
ii. To conduct a Budget Impact Analysis from a providers' perspective for a scenario where the NHIF pays for post-transplant care.

1.5 Study justification

Expenditure on post-kidney transplant care; immunosuppressive drugs, laboratory tests, radiology, re-admission imposes a huge financial burden on Renal Transplant Recipients. Consequently, this results in poor adherence to immunosuppressive medications, decline in graft function post- transplant and reduced quality of life. Studies to identify and quantify the direct medical costs have not been carried out. Consequently, there is need to identify expenditure to be incurred by the health provider and insurer.

Funding for post-transplant care would be a relief to Kidney Transplant Recipients (KTRs) as government through the National Health Insurance Scheme (NHIF) will be able to provide subsidized, affordable and accessible care. Consequently, this will lessen the financial burden of care incurred by KTRs resulting in longer graft life outcomes, resumption of normal work routine and improvement of quality of life. For NHIF, this study sought to provide estimates of projected costs of post-transplant care into the Benefit Package and sensitize other health insurance providers to provide more funding for post-transplant care. For government, this study sought to assist in planning, budgeting and allocation of additional funding by factoring in the incremental expenditure associated with post-transplant care with the goal of providing the highest quality of health care.

CHAPTER TWO: LITERATURE REVIEW

2.0 Theoretical review

In economic evaluation of health care interventions, emphasis is placed on actual resource consumption. In particular, Markov models have been used frequently in decision making. (Briggs and Sculpher, 1998). The theoretical foundation of Markov model is described by (Sonnenberg *et al.*, 1993) and (Briggs and Sculpher, 1998). The model categorizes a disease into different life states and an individual has a given probability of existing in a given state within a given cycle length. The first step is to categorize the disease into states which represent important events in the disease being modelled. (Briggs and Sculpher, 1998)

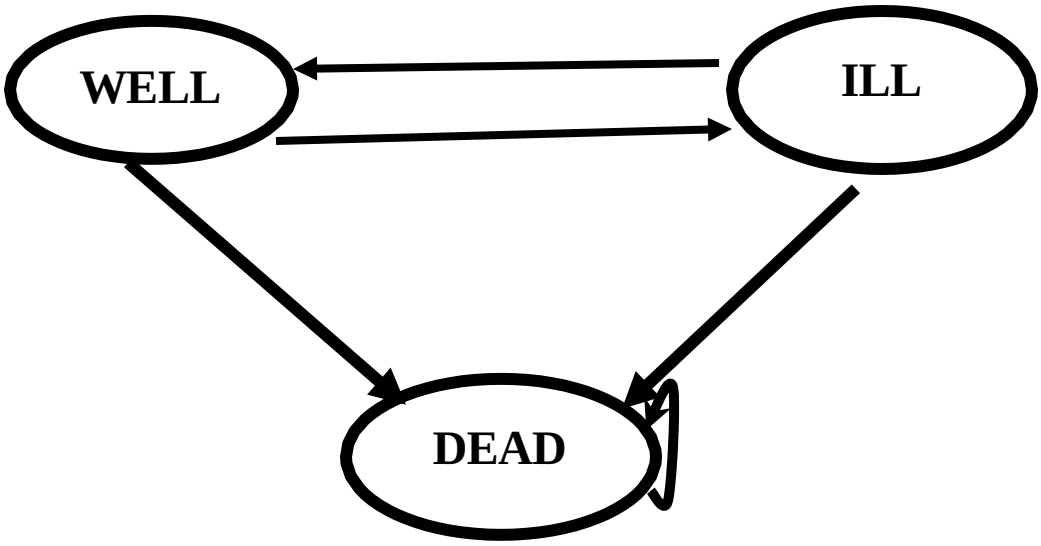


Figure 1: Transition state diagram model that consist of three health states:

In this model comprising of three states, the possible transitions between these states is given by a 3*3 transition matrix. The "Dead" state is referred to as an "absorbing state" because once a patient has transitioned into it, it is impossible to leave. It is assumed that transitions from "Dead" to "Ill" and "Dead" to "Well" are ruled out because these are impossible transitions. Out of a possible nine transitions, only three probabilities can be estimated: moving from Well to Ill (tpWell), from Well to Dead (tpDead) and Ill to Dead (tpIll) in this example. The transition from one state to another in a cycle should add up to one.

Table 2. 1: Transition matrix for 3 state model

Transition from	To: WELL	ILL	DEAD	TOTAL
WELL	1-tpWELL-tpDEAD	tpWELL	tpDEAD	1
ILL	0	1-tpILL	tpILL	1
DEAD	0	0	1	1

(tpWELL); moving from WELL to ILL, (tpDEAD) from WELL to DEAD and (tpILL) ILL to DEAD.

Each state has its own associated costs and the probability of transitioning from one state to another was summarized in a transition matrix. The transition matrix as well as the costs associated with each state will be used to compute yearly and 5 yearly costs associated with kidney transplantation. In cohort simulation, a hypothetical group of patients will be used to demonstrate the experience of patients as predicted by the model. (Briggs and Sculpher, 1998). At the start, the assumption was that the whole group of patients begin at time zero in this case after kidney transplant. At each cycle, the transition probabilities between states was used and the movement of subjects within the cycle was adjusted accordingly. The model was run for a number of cycles to create a database subjects in each health state.

2.1 Empirical Literature review

Organ transplantation is a life-saving and cost-effective treatment for patients with end-stage organ failure. (Helmuth *et al.*, 2019). About 1.4 million individuals have received a transplant and this number keeps rising by 8% annually. (Chamberlain *et al.*, 2014). Yet, challenges such as use of risky deceased donor kidney transplants (DDKTs) and costs of offering these services have not been addressed. (Jay and Abecassis, 2018). In recent years, because of economic crises, policy makers have faced difficulties in allocating limited available budget to several diseases. (Salamzadeh *et al.*, 2014).

Few studies have systematically analyzed expenditure associated with post kidney transplantation despite the fact that transplantation is a very resource-intensive intervention. (Barnieh *et al.*, 2011). These costs include; initial work up and laboratory evaluation, immunesuppressants, and comorbidities. (Rodrigue, Schold and Morrissey, 2016). Maintenance drug treatment and post-transplant events are the primary cost drivers in the study. (Chamberlain *et al.*, 2014).

Table 2. 2: A summary of the cost of maintenance therapy (2011-2012)

Table 2.2 is a summary of cost of maintenance therapy done in Iran. The main expenditure drivers were immunosuppressive drugs; cyclosporine, Mycophenolate mofetil, Sirolimus and tacrolimus. (Salamzadeh et al., 2014). Maintenance immunosuppression, post-transplant events accounted for most of the cost (37.7 and 24.7 % respectively) while management of cytomegalovirus infection had the least cost (0.95 %). (Chamberlain et al., 2014).

Maintenance therapy	Dosage	Unit price (IRR)	Total cost/day/patient (IRR)	Cost (USD)
Cyclosporine (generic)	150mg qd	300,1500,1200	5167800	153854
Mycophenolate mofetil	2gqd	11000	44000	2881892
Prednisolone	5mg/d/qd	130	130	8515
Tacrolimus	0.2mg/kg/d	1000	28000	183393
Total cost				3227654

2.1.1 Epidemiology of Chronic Kidney Disease

Chronic kidney disease (CKD) contributes to the disease burden in developing countries. WHO estimates that approximately 1·5% of deaths are due to CKD. (Webster *et al.*, 2017). Chronic Kidney Disease (CKD) is the deterioration kidney function measured a by Glomerular Filtration Rate (GFR) of less than 60 mL/min per 1·73 m^2 for at least three months. (Webster *et al.*, 2017). A GFR of less than 15 mL/min per 1·73m^2 signifies kidney failure and treatment options for such patients entails dialysis or kidney transplantation. (Webster *et al.*, 2017).

The Global Burden of Disease (GBD) study estimated that there were approximately 1.2 million deaths as a result of kidney failure. (Luyckx and Stanifer, 2018). Rapid urbanization, environment changes, non-communicable risk factors increase the prevalence of CKD. (Stanifer *et al.*, 2016). In Sub-Saharan Africa, the prevalence of CKD ranges from 5 to 17%. Majority of these countries are unable to provide dialysis or transplantation services and are unprepared to treat the cardiovascular adverse events of CKD. (Stanifer *et al.*, 2016). According to Webster *et al.*, 2017, disease progression is influenced by determinants of health. Epidemiological studies on CKD are poorly conducted in developing countries due to inconsistent assessments of renal function and the use of divergent techniques. (Stanifer *et al.*, 2016). Kaze *et al.*, 2018 reported that Africans are at increased risk for CKD and progression to end-stage renal disease (ESRD).

2.1.2 Causes and Risk factors for Chronic Kidney Disease

Stanifer *et al.*, 2016 reported that in developing countries, urbanization has created unique public health challenges. Diabetes and hypertension remain the main causes of CKD. (Webster *et al.*, 2017). These causes are summarized in Table 2.3

Table 2. 3. Known causes of Chronic Kidney Disease

Non Communicable Diseases	**Communicable & Infectious Diseases**	**Environmental & Occupational exposures**
Diabetes Mellitus; Type I&II	Human Immunodeficiency Virus	Non-steroidal analgesics
Hypertension	Hepatitis B & C	Traditional/Herbal medicines; Chinese herbs, Aloe vera
Obesity	Chronic Pyelonephritis	Agricultural pesticides & Industrial waste products
Acute kidney injuries	Syphilis	Heavy metals; Lead, mercury, Gold, Arsenic

2.1.3 Diagnosis of Chronic Kidney Disease

Estimated GFR is preferred over serum creatinine concentration for determination of kidney function. (Hill *et al.*, 2016). The two equations used to estimate GFR are the Chronic Kidney Disease Epidemiology Collaboration Equation (CKD-EPI) and Modification of Diet in Renal Disease Study (MDRD) equation. (Vassalotti *et al.*, 2016). The MDRD study equation underestimates GFR in patients with normal function while the CKD–EPI equation overestimates GFR in patients who are at high risk of CKD. (Wouters *et al.*, 2015).

2.2 Management of the Post-Transplant Patient

The management of Kidney Transplant Recipients (KTR) is divided into two phases; an immediate post-operative phase to reduce the incidence of acute rejection and a later phase to preserve kidney function and minimize effects of immunosuppressants. (Baker *et al.*, 2017). Induction phase poses the greatest risk compared to the maintenance phase. (Muntean and Lucan, 2013). Approximately all allografts are allogenic and will induce an immunological rejection response destroying the kidney. (Baker *et al.*, 2017). Most transplant centers use an initiation agent immediately post transplantation, followed by two to three drugs in the maintenance phase. (Kalluri and Hardinger, 2012). This protocol has resulted in reduced incidences of acute rejection events to 12% in year one. (Pascual *et al.*, 2017).

2.2.1 Risk Stratification of Kidney Transplant Recipients

In the past, selection of immunosuppressants was based on effectiveness to minimize episodes of rejection. However, currently the practice has shifted to selection of an individual drug on the basis of risks and benefit it poses to the patient. (Hardinger *et al.*, 2013).

Table 2. 4. Risk based strategy for selection of immunosuppressants in kidney transplantation

Risk Type	Low	Medium	High	Strategy
Immunological	First graft, older 60 years	Afro-Caribbean recipient, older donor	Previous early immunological graft loss, ABO-incompatible	Increase total immunosuppressive load
Metabolic	Low BMI Age<40 years	Positive family history	BMI >35, HCV positive, Age >60, Previous CVD, Race	Avoid/minimize steroids and tacrolimus
Neoplastic	Age <40	Pre-malignant lesion	Previous cancer Hereditary syndrome	Consider low immunosuppression load or sirolimus
Ischemic-reperfusion injury	Living donor, Deceased donor	Donor aged 50–60 years	Extended criteria donor	Reduce CNI exposure
Non-adherence			Poor RRT compliance, Age <20, Transition from paediatric to adult	Education Simple drug regime alemtuzumab or belatacept

BMI; body mass index, CNI; calcineurin inhibitors, RRT; renal replacement therapy, HCV; hepatitis C virus, CVD; cardiovascular disease. Table 2.3 illustrates risk stratification matrix used to classify individuals according to the level of risk (immunological, metabolic, neoplastic, ischemic and non-adherence). The matrix assists in decision analysis for selection of the appropriate immunosuppressant for KTRs.

2.2.2 Induction Agents after Kidney Transplant

All Kidney Transplant Recipient should receive an induction agent before or at the time of the transplant to minimize the chances of rejection. Transplant patients with low risk receive an interleukin 2-Receptor antagonists while those at higher risk lymphocyte depleting antibodies. (Baker *et al.*, 2017). The most commonly used antibodies are basiliximab, antithymocyte globulin, and alemtuzumab. (Hardinger, Brennan and Klein, 2013).

Basiliximab administration leads to down-regulation of IL-2R expression altering circulating lymphocyte concentrations. (Atlani, Sharma and Gupta, 2013). Alemtuzumab is a recombinant antibody directed against the cell surface glycoprotein CD52. (Muntean and Lucan, 2013). It causes depletion of all T cells in blood and in the graft. (Afaneh *et al.*, 2011). The dose is 0.3 mg/kg over 3 hours. Pre-medication with prednisolone, paracetamol, and diphenhydramine usually minimizes the risk of cytokine release syndrome. (Afaneh *et al.*, 2011). Antithymocyte globulin (ATG) comprises of purified polyclonal antibodies generated in rabbits (rATG) or horses (equine ATG) (Atgam,). (Bakr, Nagib and Donia, 2014). It is frequently used as an induction therapy in approximately 56 % of KTRs. (Alloway *et al.*, 2019). The typical dose of 1.5 mg/kg for 7- 14 days. (Kalluri and Hardinger, 2012).

2.2.3 Maintenance Therapy in Kidney Transplant Recipients

Immunosuppressive therapy should have maximal efficacy. However, these agents have a narrow therapeutic index and the toxic dose is close to the optimal immunosuppressive dose. (Pedroso and Citterio, 2015). The therapeutic approach involves a regimen of 2-3 drugs targeting various immune responses. The choice of the regimens depends on the transplant center and the patients' immunological risk. (Ghanta et al., 2013). There are five classes of maintenance immunosuppressive agents: calcineurin inhibitors (CNI), anti-proliferative agents, mammalian target of rapamycin inhibitors (mTOR), corticosteroids, and co-stimulation blockade (belatacept). (National Kidney Foundation).

Calcineurin inhibitors (CNIs) are the mainstay agents of immunosuppression for kidney transplantation. Tacrolimus is preferred over cyclosporine because it is less nephrotoxic. (Ghanta et al., 2013). Therapeutic drug monitoring (TDM) is critical to optimize the immunosuppressive treatment. (Pedroso and Citterio, 2015). Tacrolimus dose is 0.15 to 0.30 milligrams per kilogram and cyclosporine is 6 to 10 milligrams per kilogram. (Ghanta et al., 2013). Chronic calcineurin inhibitor nephrotoxicity is the major limitation of CNI-based regimens. (Taylor *et al.*, 2015). The establishment of minimization and withdrawal protocols have minimized nephrotoxicity and graft survival. (Ghanta et al.,2013). Therefore, therapeutic monitoring of calcineurin inhibitor concentrations is important because of their variability in pharmacokinetics, and concentration--toxicity relationships. (Taylor *et al.*, 2015). A meta-analysis of tacrolimus versus cyclosporine demonstrated that tacrolimus was positively associated with better allograft survival. (Taylor *et al.*, 2015).

Table 2.5. Comparison of the adverse events associated with calcineurin inhibitors (Azzi et al., 2019)

Adverse Effects	Cyclosporine	Tacrolimus
Vasoconstriction	++	+
Fibrogenesis	++	+
Serum creatinine (30)	-	+
Graft survival (31)	-	+
Diabetes	+	++
Tremor	+	++
Hirsutism	++	-
Gingival Hyperplasia	++	+
Dyslipidemia	++	+

++ More pronounced side effects; + less pronounced side effects; - no side effects.

Four alternative approaches to reduce exposure to the toxicity (to full-dose CNI therapy have emerged. (Agency for Healthcare Research and Quality, 2016). These are presented in Table 4

Table 2. 6. Strategies to minimize Calcineurin inhibitor-induced Nephrotoxicity

Risk strategy	Definition	Timing
Minimization	Reduction of dose	At time of transplant or post-transplant
Conversion	Reduction of dose until eliminated and substituted by another agent	Timing of side effect
Withdrawal	Reduction of dose until eliminated	At time of transplant or time of side effect
Avoidance	No CNI used	Planned de novo

Anti-Proliferative agents such as Mycophenolate mofetil (MMF) is the inactive precursor of mycophenolic acid (MPA). Owing to the lack of nephrotoxicity, a neutral cardiovascular risk factor profile and its good efficacy, MPA is the backbone of all immunosuppression regimens worldwide. (Naik, Glander and Budde, 2011). Azathioprine is no longer being used in transplant centers as a first line maintenance agent with the introduction of CNIs and MMF. (Ghanta et al., 2013).

Mammalian target of rapamycin inhibitors (mTOR inhibitors) are used either in combination with a CNI or not. The aim is to minimize adverse effects related to CNI use. (Russ, 2013). This strategy allows reduction of CNIs during the early post-transplant period. (Pascual *et al.*, 2017). Everolimus (EVR) works 100 times better than cyclosporine. (Liu *et al.*, 2017). Everolimus is a sirolimus derivative dosed at 0.75 mg orally twice daily. (Arbagy *et al.*, 2015). Sirolimus has a half-life of 60 to 70 hours. (Ghanta et al., 2013).

2.3 Conceptual Framework

Cardiovascular disease and kidney failure are responsible for most of the post-transplant complications and death independent of graft rejection. (Snyder and Bremerton, 2016). In particular, hypertension, diabetes, dyslipidemia and smoking are very common. (Rangaswami *et al*., 2019).

Hypertension is the most prevalent cardiovascular disease affecting up to 80% of patients. (Schaefer, 2012). Immediately following transplantation, blood pressure targets are more liberal (<160/ 90mmHg). The aim to maintain blood flow and reduce the incidence of thrombosis. A blood pressure target of less than 130/80mmHg is recommended to reduce end organ damage. (Rangaswami et al., 2019). The majority of KTRs require treatment to achieve the target blood pressure in addition to lifestyle modifications. (Schaefer *et al*., 2012). Calcium channel blockers are recommended because they improve GFR. Calcium channel blockers reverse intra-renal vasoconstriction and vascular resistance associated with calcineurin inhibitors use. (Rangaswami et al., 2019).

However, verapamil and diltiazem should be avoided because they interact with and raise CNI levels with potential for nephrotoxicity. (Schaefer *et al.,* 2012). ACE inhibitors and ARB blockers are recommended if urinary protein excretion exceeds 1 g per day. Thiazide diuretics are used to counteract the sodium-related effects of calcineurin inhibitors. (Snyder and Bremerton, 2016).

Dyslipidemia is highly prevalent in the post-transplant period (60-80%). Exacerbating factors include obesity, diabetes mellitus, proteinuria (Rangaswami *et al*., 2019) and immunesuppressants (cyclosporine, sirolimus and everolimus). (Baker et al., 2017). Fluvastatin reduces the risk of death or myocardial infarction by 35 %. (Baker *et al*., 2017). Diabetes mellitus in the post-transplant period (PTDM) is prevalent in approximately 20 % of KTRs. Risk factors include increasing age, obesity, metabolic syndrome and family history. Transplant-specific risk factors are use of tacrolimus and steroids. (Baker et al., 2017). Patients experience insulin resistance and elevated triglyceride levels. (Roth *et al*., 2017). Transient hyperglycemia is a consequence of use of high dose steroids, tacrolimus or cyclosporine. (Baker et al., 2017). Transplant societies recommend screening and treatment of diabetes with a target hemoglobin A1C of less than 7%. (Snyder and Bremerton, 2016).

Anemia is common in approximately 30 to 40 % of patients awaiting kidney transplant. (Roth *et al*, 2017). In men, hemoglobin of less than 12g/dl and less than 11 g/dL in women is a definitive diagnosis of anemia in this population. (Roth *et al.*, 2017). Predisposing factors include immunosuppressants (MMF, azathioprine, sirolimus), infections (EBV, CMV), and allograft dysfunction. (Schaefer, 2012). Kidney transplant patients have an increased risk for common infections. (Snyder and Bremerton, 2016). This is dependent on the immunosuppression therapy and pathogen exposure. (Roth *et al*, 2017). Antimicrobial prophylaxis has greatly reduced the degree and occurrence of post-transplant infections. (Schaefer, 2012).

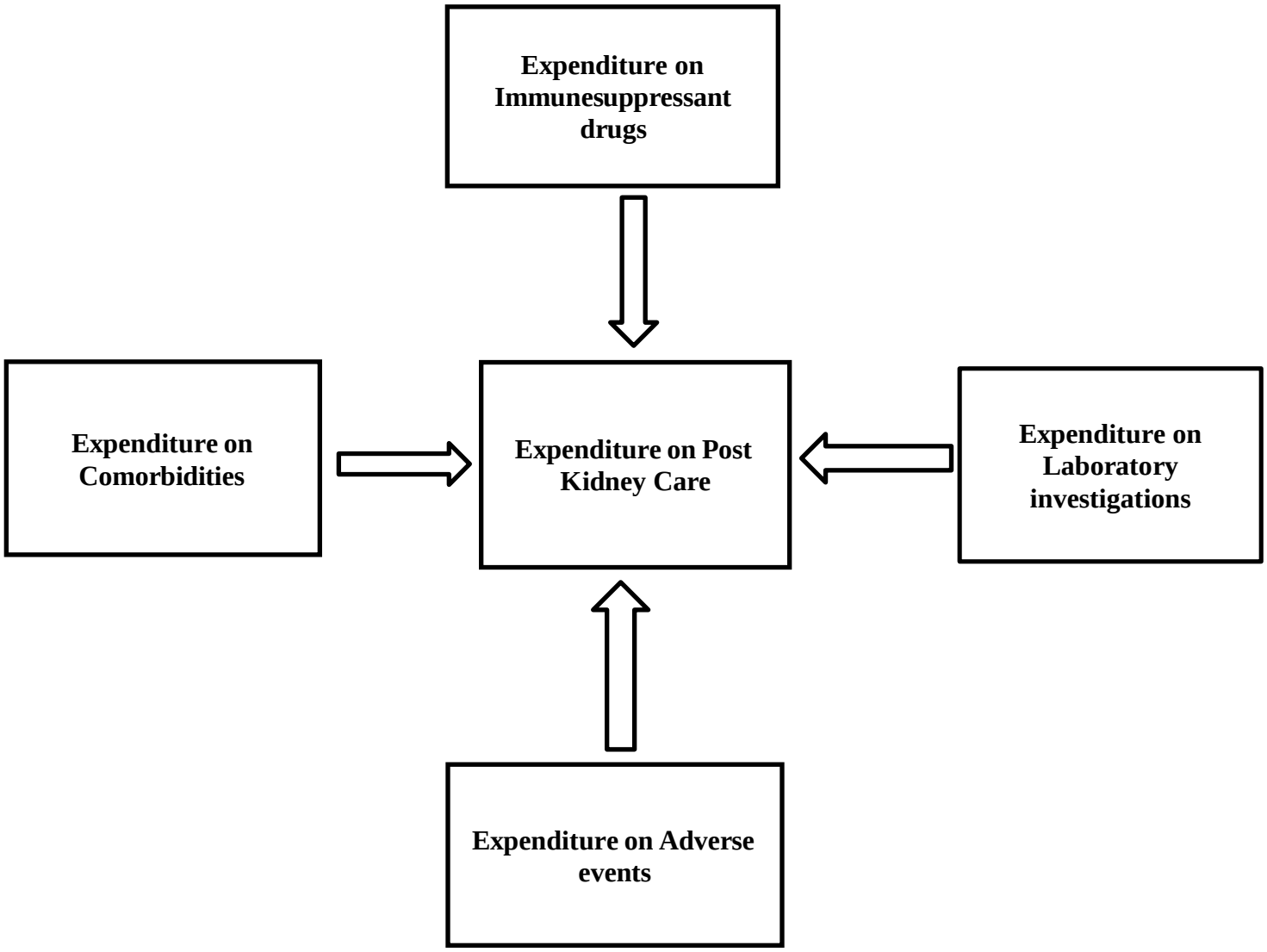


Figure 2.1: Conceptual framework for expenditure on post-kidney transplant care

Table 2. 7. Prevalence of Risk factors for graft rejection in kidney transplant recipients (KTRs)

Variable	Frequency	Prevalence (%)	95 % Confidence Interval	Publication
Hypertension	87	95.6	88.5-98.6	(Wagude, 2012)
Dyslipidemia	67	73.6	63.2-82.1	(Wagude, 2012)
Dysglycemia	45	49.5	38.9-60.1	(Wagude, 2012)
Obesity	44	48.4	37.8-59.0	(Wagude, 2012)
Proteinuria	41	45.1	34.7-55.8	(Wagude, 2012)
Anemia	20	22.0	14.2-32.1	(Wagude, 2012)
Smoking	3	3.3	0.9-10.0	(Wagude, 2012)
Impaired kidney function (CrCl <60 ml/min)	15	16.5	9.8-26.1	(Wagude, 2012)
Cytomegalovirus infection		90		(Arogundade, 2013a)
Chronic rejection	3	6.8		(Kisanga *et al.*, 2017)
Biopsy proven acute rejection	9	20		(Adamu *et al.*, 2012)
Infections	19	42.2		(Adamu *et al.*, 2012)

Table 2.5 summarizes studies on the prevalence's of risk factors for graft rejection among renal transplant recipients managed at different transplant centers in Africa.

Laboratory monitoring is a widely accepted practice of post-transplantation management. The aim is to monitor graft function. (Josephson, 2011). Early detection of graft dysfunction allows prompt treatment. (National Kidney Foundation). Table 2.8 summarizes the monitoring schedule for different investigations post-transplant.

Table 2.8: Routine screening tests following kidney transplantation

Test	Screening intervals after transplantation					
	1 week	1 month	2-3 months	4-6 months	7-12 months	>12 months
Creatinine	Daily	2-3 per week	Weekly	Every2 weeks	Monthly	Every2-3months
Urine protein	Once		Quarterly			Yearly
Complete blood count	Daily	2-3 per week	Weekly	Monthly		Yearly
Diabetes	Weekly		Every 3 months			Yearly
Lipid profile			Once			Yearly
Tobacco use	Prior to discharge					Yearly
Blood pressure	Every visit					

CHAPTER THREE: METHODOLOGY

3.1 Study Design

This was a mixed methods study of a predictive Markov model to compute five year costs associated with kidney transplant and a retrospective cohort study. It was divided into four sections namely; A key Informant Interview (KII), review of patient files, costing study and budget impact analysis.

3.2. Study Location

The study was conducted at Kenyatta National Hospital (KNH) Renal Transplant Unit clinic. KNH is the largest public tertiary referral hospital located in Upper Hill area and serves as the teaching hospital for the University of Nairobi. The hospital has a capacity of approximately 2000 beds and receives patients from the whole of Kenya and parts of East and Central Africa. It offers preventive, curative and clinical diagnostic health services. It is a training and research center for different cadres of healthcare professionals. It has several specialized clinics including a nephrology clinic which is one of the very few centres in the country. The unit offers specialized services such as dialysis, transplantation and management of KTRs. The clinic runs its reviews every Tuesday from 8am to 1pm and approximately 15-20 pre and post-transplant patients are attended to on a given day with a cumulative number of approximately 960 patients on follow up. The healthcare team comprises of physicians, pharmacists, nurses, laboratory technicians and registry staff.

3.3 Study Population

3.3.1 Key Informant Interview

The participants included individuals were involved in the management of KTRs and those from the procurement department. They included Pharmacists, laboratory staff, billing managers and supply chain staff to obtain tender prices for commodities and services offered to KTRs.

3.3.2 Review of Patient files

The study population comprised of adult patients who have undergone a kidney transplant between 1st January 2010 to 31st December 2019 and who were attending the transplant clinic at KNH. This period was chosen to allow inclusion of a cumulative number of post-transplant patients. Secondly, expenditure associated with care increases with time such that immediately after the transplant, expenditure was high but reduces with time. Therefore, a larger time frame allowed for assessment of delayed costs.

3.4 Inclusion/ Exclusion criteria

3.4.1 Inclusion criteria

Patient files were screened by the principle investigator for eligibility. Eligibility criteria included the following:

1) Renal transplant recipients who were 18 years and over
2) Renal transplant recipients on follow up in the transplant clinic at KNH even those who had their transplant done in other centres.
3) Voluntarily gave informed consent and signed the consent declaration form

3.4.2 Exclusion criteria

All renal transplant recipients were on follow up at the transplant clinic in KNH who were back on dialysis.

3.5 Sampling

3.5.1 Sample size determination for a Key Informant Interview

The principles of sampling in qualitative studies were used (Sandelowski, 1995). According to this principle, a sample size of one key individual per organization was considered. This was considered sufficient as the tender prices for commodities and billing fees for laboratory investigations and services offered to KTRs were uniform for the institution. The final sample size was determined by the principle of saturation; a study was terminated if no additional information will be obtained by interviewing more respondents.

3.5.2 Sample size determination of Patient files

Sample size was determined using Yamane's formula.

$$\mathbf{n= N/ 1+ N (e)^2}$$

where;

n= sample size
N= size of the study population
e= degree of precision= 0.05

n = $200/ 1+ 200(.05)^2 = 133$ patient files

Therefore 133 patients' records were included in the study

3.6 Sampling Technique

3.6.1 Sampling technique for a Key informant interview

Purposeful sampling was used and the following criteria was used to include participants into the study. A minimum of two individuals per department were interviewed.

1. Individuals who worked in supply chain or procurement department at KNH such as billing officers.
2. Individuals who were involved in the management of kidney transplant recipients and these included Pharmacists, renal nurses, laboratory technicians.
3. Individuals who gave informed consent

3.6.2 Sampling technique of Patient files

Files of patients were selected using simple random sampling technique with replacement. This was carried out using a coin. The files that satisfied the inclusion criteria were gathered and a coin was tossed. Whichever file coincided with the head was included. The process was repeated until the calculated sample size was attained.

3.7 Participant recruitment

3.7.1 Key informant interview

A letter of introduction was sought from the KNH research office and delivered to the respective departments of KNH. Identified key informants were requested for an interview at a time and place of their convenience.

3.8 Data collection

3.8.2 Key Informant Interview

An oral interview was conducted using an interview guide (Appendix 2). The purpose was to obtain market prices and quantities of various goods and services used the in management of KTRs. The principal investigator explained the purpose of the study and proceeded to request the key informant to be included into the study by signing the informed consent form. For each of the key informants, a date, time and venue of their convenience for the interview was set where the

principal investigator proceeded to ask questions regarding the fees and prices levied on commodities and services. Prices were then entered into an MS Excel sheet and exported to STATA version 13 for valuation of resources used.

3.8.3 Patient files

Data on patient demographics, laboratory investigations, comorbidities and drugs was extracted from the files using a data abstraction form (Appendix 1). The cost categories involved include; costs to manage comorbidities, laboratory, immunosuppressant's, and drugs to manage adverse effects. For each patient file, the principal investigator identified resources consumed in each year using the data abstraction form and estimated the quantities by counting the number of tablets/ tests used in each year to determine the total resources consumed. This process was repeated for a period of five years' post-transplant. Quantities used for each expenditure category were entered into an MS excel sheet and exported to STATA version 13 for computation of total expenditure.

3.9 Cost Analysis

Cost analysis involved the following: identification of resources, quantification, valuation, estimation of future costs by Markov modelling and sensitivity analysis.

3.9.1 Resource Identification

Resource identification was done using two approaches namely; Review of treatment guidelines and identification of all resources mentioned and key informant interview with providers of health commodities and services; renal transplant nurse, pharmacists, laboratory staff and physicians. In addition, the findings of the pilot study were used to fine tune the data abstraction tool. The findings were triangulated to come up with all resources needed for patient management. Costs were divided into four categories namely; costs of immunesuppressants, laboratory, adverse events and comorbidies.

3.9.2 Quantification

Quantification entailed identification of exact amounts of resources used. Given that treatments may be sub-optimal in terms of dose and frequency, as far as possible the recommended doses and frequencies in the guidelines were used. For each patient, the exact quantities of each expenditure category was calculated in each year post-transplant for a period of five years. The expenditure categories included; immunosuppressant drugs, laboratory investigations and radio-imaging studies, management of comorbidities and adverse effects.

3.9.3 Valuation

Valuation is defined as attaching of a price to a given resource. As recommended in guidelines, the market rates as per 2020 were used for all marketable resources. The prices of key health commodities and services were obtained from the tender document of Kenyatta national hospital for financial for year 2019/2020 and from billing officers for various departments. Figure 3 shows the steps involved in the costing of each resource item involved in the management of post- kidney transplant patients.

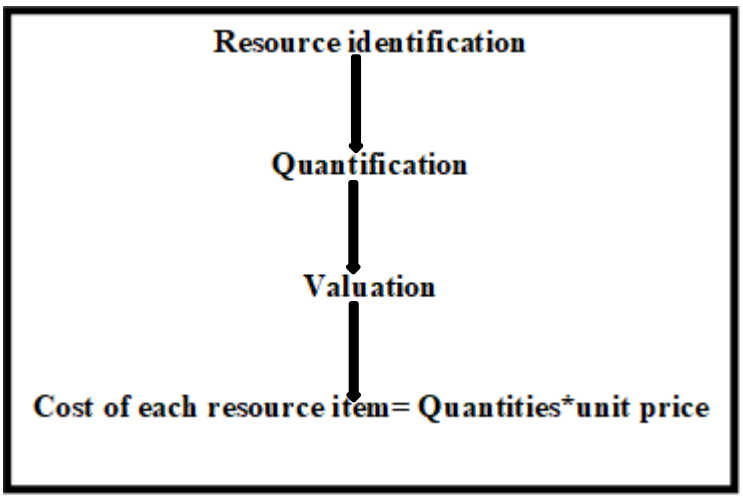


Figure 3. 1: Steps involved in costing of resource items

The total expenditure involved in managing post-kidney transplant patients was determined using the following cost function.

$$TC=\sum a+b+c+d$$

Where

a; cost of immunosuppressant drugs

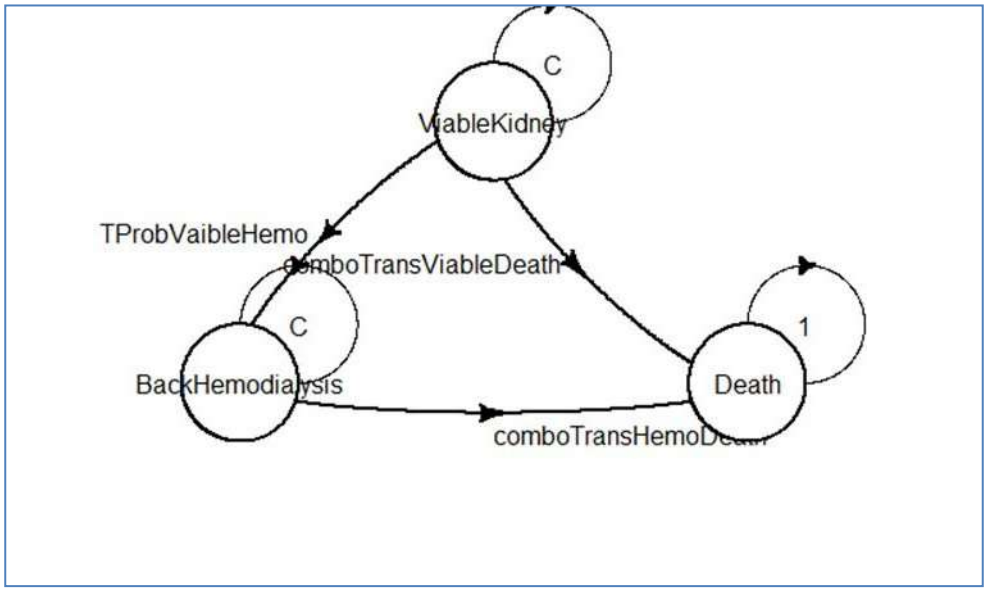
b; cost of laboratory investigations and radio-imaging studies

c; cost of antimicrobials

d; cost of managing comorbidities

3.9.4 Markov modeling for kidney transplant states

We constructed a Markov model that was used to estimate the number of patients that would need post-kidney transplant services in five years. It was conducted from the perspective of Kenyatta National Hospital. To predict the costs associated managing post kidney transplant patients, time varying discrete states markov modelling was done. A kidney transplant recipient (KTR) could exist in 3 possible states. The three states were survival with a viable kidney; hemodialysis following graft rejection; and death. Markov modeling was done and the transition probabilities for the three states were calculated using Heemod package version 0.14.2 in R. The cycle length was one month. A diagrammatic representation of the model is shown in Figure 4.13.



KEY: *TProbViableHemo was the transition probability for loss of a viable graft leading to return to dialysis, TransViableDeath was the probability of death in patients with a viable kidney post-transplant and TransHemoDeath was the probability of death in patient on hemodialysis*

Figure 3.2: Transition state diagram for post-kidney transplant patients

The data inputs that were required to run the model were: transition probabilities between the 3 states, costs associated with each state and current data current number of patients who have received a transplant.

3.9.4 Transition matrix for the three state markov model for a post kidney transplant patient

This model was a 3 state transition matrix resulting in a possible 9 transitions. The transition probabilities that were computed are summarized in the matrix presented in Table 4.4. The absorbing state was death. TProbViableHemo was the transition probability for loss of a viable graft leading to return to dialysis after graft loss. TransViableDeath was the probability of death in patients with a viable kidney post-transplant; TransHemoDeath was the probability of death in patient on hemodialysis. C represented the probabilities of remaining given state at the end of a cycle and were computed as 1 minus the sum of the probabilities of the probabilities of the cells in a given row. Parametric survival analysis was conducted to obtain the time varying transition probabilities.

Table 3.1: Transition matrix for the 3 state post-kidney transplant model

	Viable kidney	**Back to Hemodialysis**	**Death**
Viable kidney	**C**	**TProbViableHemo**	TransViable Death
Back to Hemodialysis	0	**C**	TransHemo Death
Death	0	0	1

3.9.5 Parametric Survival analysis to obtain the time dependent transition probabilities

The data for survival analysis was reconstructed from the life tables from the thesis by (Githinji, 2014) who conducted a cohort study on treatment outcomes following kidney transplant at Kenyatta National Hospital. Survival data analysis was done using the survHE package in R version 4.0.4. The following distributions were used: exponential, weibull, log logistic, gompertz, gamma and log normal. The survival model was fitted with no covariates. This generalized gamma model gave the lowest AIC and BIC values as specified in Table 4.7. Three separate models were generated for the outcomes loss of a viable kidney and death. For all the outcome, the appropriate distribution was generalized gamma (Table 4.5). However, generalized gamma distribution was not suitable for computation of the transition probabilities. Therefore, we settled for weibull distribution. The one-month transition probabilities were computed using the calc_prob_from_surv function in the Heemod package from the conditional probabilities. The reconstructed data is represented in Appendix one.

Table 3.2 Model fit for parametric data analysis on survival data for post-transplant kidney patients

	Exponential	**Weibull**	**Gamma**	**Log Normal**	**Log Logistic**	**Gen Gamma**
DEATH						
AIC	152.0126	147.4614	147.6139	146.1398	147.2935	138.2674
BIC	154.5976	152.6314	152.7839	151.3097	152.4635	146.0223
BACK TO HEMODIALYSIS						
AIC	119.6878	117.7394	117.7335	117.3127	117.7606	112.712
BIC	122.2727	122.9093	122.9034	122.4826	122.9305	120.4669
LOST TO FOLLOW UP						
AIC	678.311	647.514	651.9409	660.6295	665.2	620.3
AIC	680.896	652.6839	657.1108	665.7994	670.3	628.1

The transition death was adjusted for the all-cause mortality given that a patient could either have died from kidney related complications or other natural causes. Transition probability with respect to the all-cause mortality was obtained from the World Health Organization, WHO. (2021). Global Health Observatory Website. https://www.who.int/data/gho which provides the one-year probability of death for different age groups. The age specific mortality rate for Kenya for either sex was retrieved for the age group 45 to 49 years. This age group was selected as it is the most to undergo transplant. The one-year probability was converted to a one-month transition probability using the rescale_prob function in Heemod. A value of 0.0458 was obtained. A graph displaying the computed time varying transition probabilities are presented in Figure 4.13 while the actual values are presented in Appendix four.

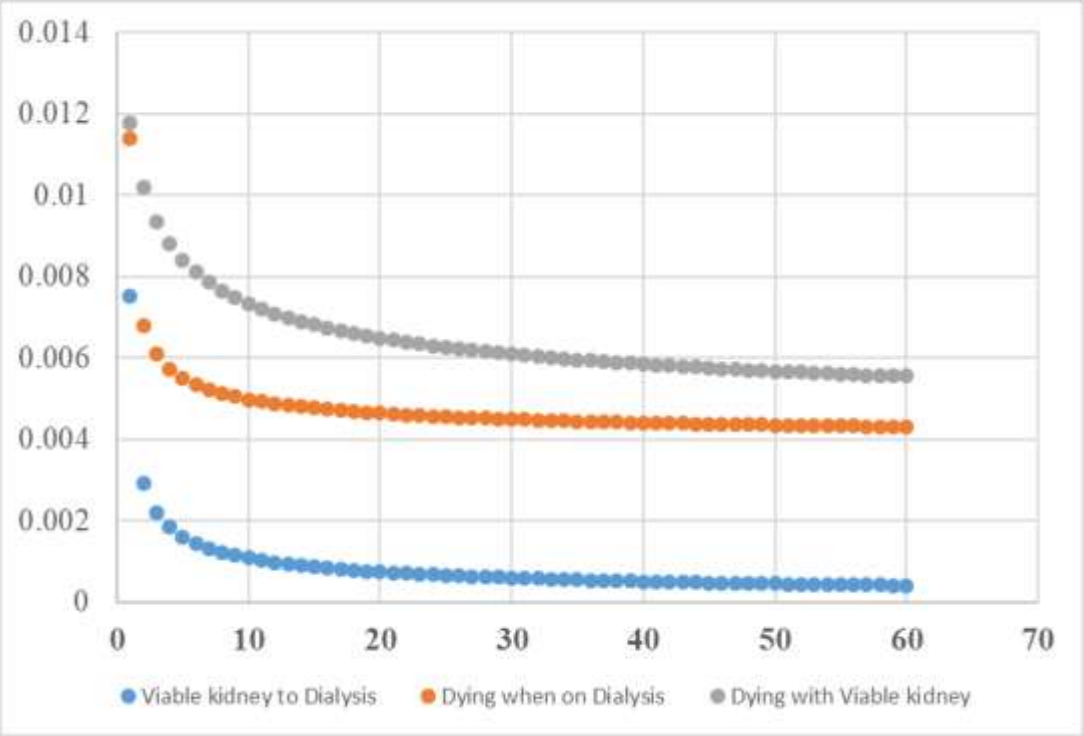


Figure 3.3 Time varying transition probabilities for Post kidney transplant patients in Kenyatta National Hospital

3.9.6 Cost estimates used in the Markov model

Data on the expenditure incurred by post-kidney transplant patients was obtained from a study done at the Kenyatta National Hospital Renal unit. We employed the micro ingredient approach to determine the type and amount of resources required to manage a KTR through sampling of 114 patient files. The resources identified were cost of immunesuppressants, laboratory investigations and radio imaging studies, costs to manage comorbidities. Tender prices for the financial year 2019/2020 were obtained from the procurement department and charges for the services were requested from the billing department of Kenyatta National Hospital. The median expenditure per year per month was computed using STATA software while data on the prevalence's of the various comorbidities were obtained from literature. The R code that was used to compute the costs associated with each health state is presented in Appendix five and the actual costs are presented in Appendix six. The costs were not discounted and were obtained for a total of 60 months (5 years) post-dialysis. From the analysis, the costs of medicines and services post-transplant over a five-year period are significantly lower than those incurred by patients on dialysis who still have to undergo a transplant at some point in the future. This trend decreased gradually from year one to year three where it remained fairly constant till year five.

Expenditure incurred in provision of therapeutic drug monitoring for tacrolimus and cyclosporin and immunosuppressants remained constant throughout the five-year period similar to that incurred in provision of dialysis.

3.10 Data Analysis

3.10.1 Descriptive data analysis

The Shapiro-wilk test was performed to determine if continuous variables were normally distributed or not. Normally distributed variables were summarized as the mean and standard deviation of the mean. Continuous variables that were not normally distributed were summarized as median, interquartile range and range. Categorical variables were summarized as frequencies and percentages. Exploratory data analysis was performed to determine if there were any significant correlations between continuous variables and associations between categorical variables. The descriptive and exploratory data analysis was done using STATA version 13 software. The level of significance was set at 0.05. Markov cohort simulation was done using the Heemod package in R. The costs were presented in Kenyan shilling (Ksh) before conversion into US dollars. The prevailing rate is 1 USD=Ksh 102.90.

3.11 Costing Study & Time Horizon

This study was done from the perspective of the provider with a time horizon of 5 years. In addition, the perspective of the NHIF (payer) was considered since the outcomes of this study have an impact on the budgetary allocation for KTRs. The costing methodology was divided into two sections namely: Cost analysis, and Budget impact analysis.

3.12 Quality Assurance

The interview guide and data abstraction form was piloted and amended before the actual study. Data collected was cleaned and coded. Two research assistants were trained on the data collection tool and how to extract key information from patient files.

3.13 Data Management

Data on costs, resources used and the key informant interviews were entered was entered into MS Excel. Thereafter, the data was exported and analyzed using STATA version 13.0 and Heemod package in R. This database was password protected to guarantee data privacy and backed up on an external hard drive.

3.14 Ethical considerations

Permission to carry out the study was sought from both the Kenyatta National Hospital-University of Nairobi (KNH-UoN) Ethics and Research Committee and the KNH research office. A letter of approval to conduct the study Ref P953/11/2019 was granted and is attached on Appendix 3. The review of patient files was done within the renal unit to assure confidentiality of patient information.

CHAPTER: FOUR RESULTS

4.1 Participant recruitment and reasons for exclusion

At the time of the study, the renal unit had approximately 192 post-kidney transplant patients. Of these, those who were ineligible were 12 children and 15 patients who were back on dialysis. Out of th 165 patient files that met the eligibility criteria, 133 files were sampled by random sampling with replacement. However, the due to missing records only 114 files could be traced. The consort diagram in Figure 4.1 summarizes reasons for exclusion.

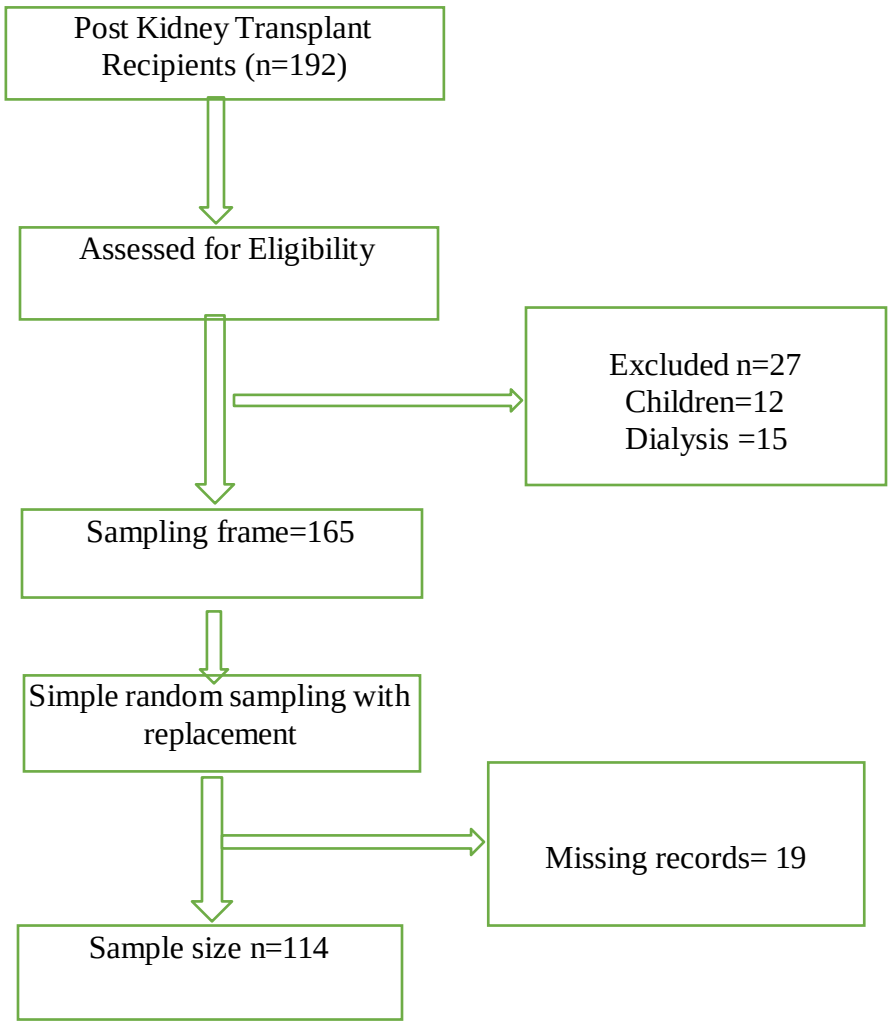


Figure 4.1 Summarizes reasons for participant exclusion

4.2 Socio-demographic characteristics of Study Participants

Table 4.1 summarizes the sociodemographic characteristics of kidney transplant recipients at Kenyatta National Hospital. A majority of the kidney transplant recipients were male (86, 76%) and the rest were females (22%). The mean age of the recipients was 46 years (SD=11.7) with a majority (41, 36%) being in the 41-50 age group. Only 2 patients were above the age of 70 years. The median height of the recipients was 168cm.The median weight was 62kg with an interquartile range of 56kg to 65kg. The mean body mass index was 22kg/m^2 (SD=3.23).

Table 4.1: Sociodemographic characteristic of post-kidney transplant recipients at Kenyatta National Hospital.

Variable	Frequency
Sex	
Male	86 (75.4%)
Female	28 (4.6%)
Age category	
20-30	1 (0.9%)
31-40	38 (33.3 %)
41-50	41 (36 %)
51-60	21 (18.4 %)
61-70	11 (9.7 %)
>70	2 (1.8 %)
Age (Mean ± SD)	45 (11.7)
Weight (Median, IQR)	62 [56,65]
Height (Median, IQR)	168 [168,168]
BMI (Mean ± SD)	22 (3.23)
Marital status	
Married	65 (57.5%)
Single	17 (15 %)
Unknown	31 (27.4%)

4.3 Medical characteristics of Kidney transplant recipients at Kenyatta National Hospital

Table 4.2 summarizes comorbidities amongst kidney transplant patients and the types of immunosuppressants used for treatment. Hypertension (113, 99.1%%) and bacterial infections (109, 95.7%) were the most prevalent comorbidies. Seven of these patients had dyslipidemia while a minority had anemia (12, 10.5 %). Most of the post kidney transplant patients at Kenyatta National Hospital are on a backbone of a cyclosporine regimen (59, 51.8%) followed by (36, 32.8%) on tacrolimus. A small number (19, 15.4%) had been on both regimen of tacrolimus and cyclosporin.

Table 4.2: Comorbidities among kidney transplant patients and Immunosuppressant therapy

Comorbidity	**n (%)**
Hypertension	113 (99.1 %)
Diabetes mellitus	33 (29 %)
Anemia	12 (10.5 %)
Dyslipidemia	7 (6.1 %)
Bacterial infection	109 (95.7 %)
Viral infections	14 (12.3 %)
Type of Immunosuppressant	
Tacrolimus	36 (32.8 %)
Ciclosporin	59 (51.8 %)
Tacrolimus and Ciclosporin	19 (16.7 %)

4.4 Five-year expenditure by category for kidney transplant recipients at Kenyatta National Hospital

The three main categories whose expenditure contributed significantly to the total cost of post-kidney transplant care were immunesuppressants, laboratory investigations and services. Expenditure on immunosuppressants in particular contributed significantly in the first year post-transplant with an annual cost of about Ksh 240,000 per patient. This trend dipped in the second year to about Ksh 160,000 and rose in year three gradually to decline at Ksh 165,000 in year five.

The decline in expenditure on laboratory investigations and radio-imaging tests was almost gradual from Ksh 70,000 year one post-transplant to less than Ksh 3000 in year five. Expenditure on services offered to post-transplant recipients rose in year two to about Ksh 27,000 and declined gradually. Other expenditure categories such as antibiotics, anti-diabetic, anti-hypertensive medicines and consumables were minimal with patients spending less than Ksh 5,000 yearly.

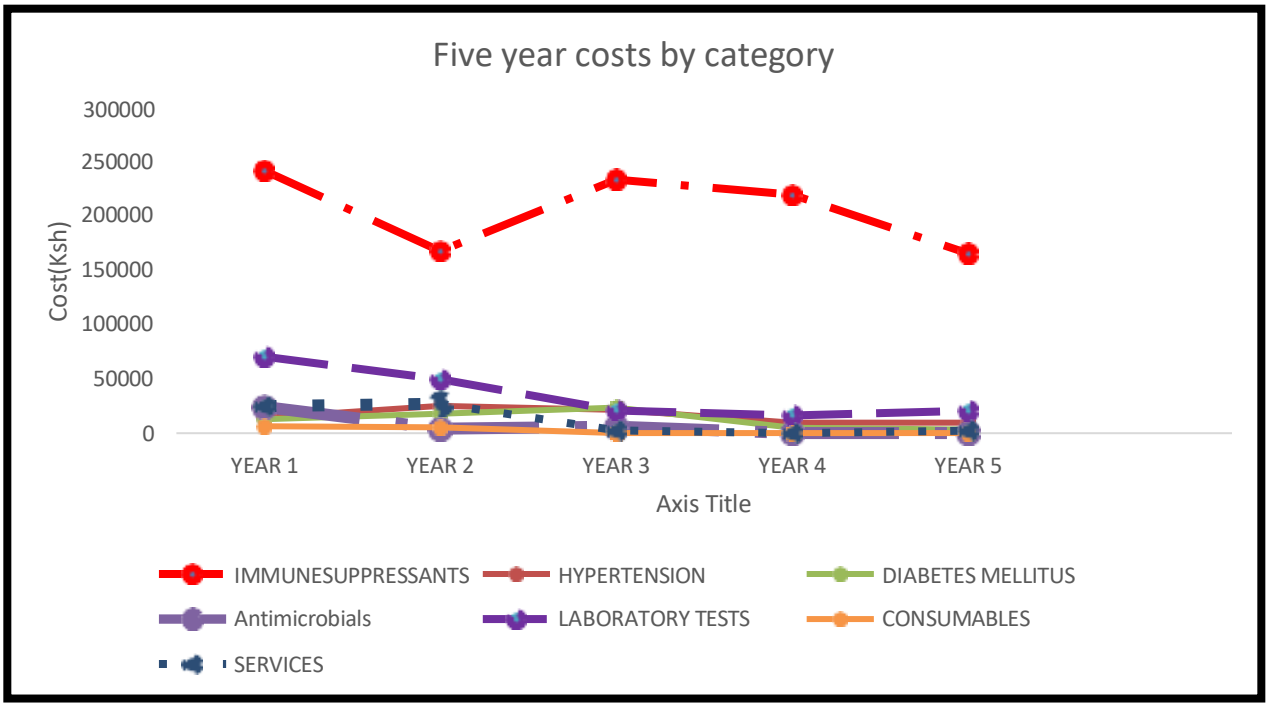


Figure 4.2: Five-year expenditure by category for kidney transplant recipients at Kenyatta National Hospital

4.5 Expenditure on Drugs by kidney transplant recipients at Kenyatta National Hospital

4.5.1 Expenditure on Immunosuppressants

Figure 4.2 summarizes the 5-year expenditure on immunosuppressants by individual kidney transplant recipients by drug. Expenditure on ciclosporin and mycophenolate were highest in year one and accounted for most of the expenditure for the remaining years. However, expenditure on ciclosporin dipped sharply in year two before rising again in year three. Expenditure on tacrolimus was fairly constant for the five-year period. Expenditure on azathioprine and methylprednisolone were minimal.

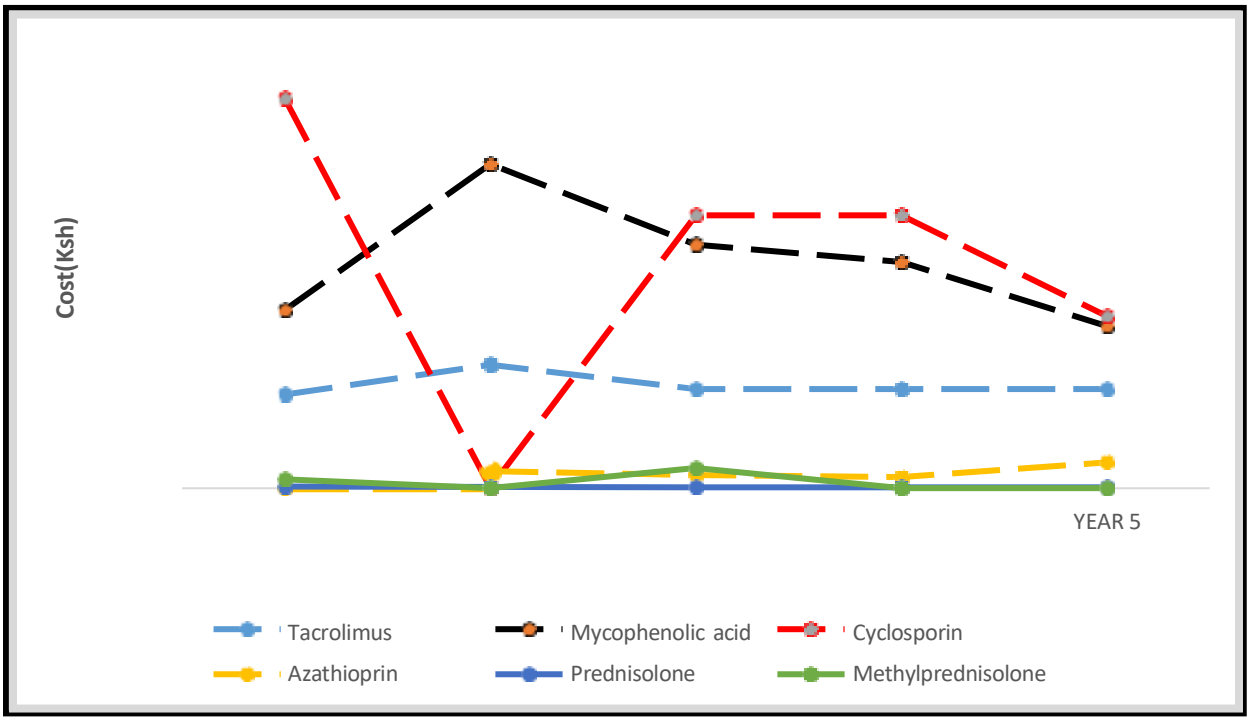


Figure 4.3: Expenditure on Immunesuppressants by kidney transplant recipients at Kenyatta National Hospital

4.5.2 Expenditure on Anti-hypertensives by kidney transplant recipients at Kenyatta National Hospital

Figure 4.3 represents the five-year expenditure on hypertensive medicines by kidney transplant recipients. The expenditure on nebivolol, methyldopa and metoprolol was found to contribute significantly to the post-transplant costs in the first three years post kidney transplant in this cohort of patients. Year two and three expenditure on nebivolol was ksh 13,000 compared to methyldopa where expenditure was less than ksh 4,000. Therefore, expenditure on nebivolol was approximately four times and that on other drugs. Atenolol, nifedipine, and amlodipine were associated with minimal expenditures.

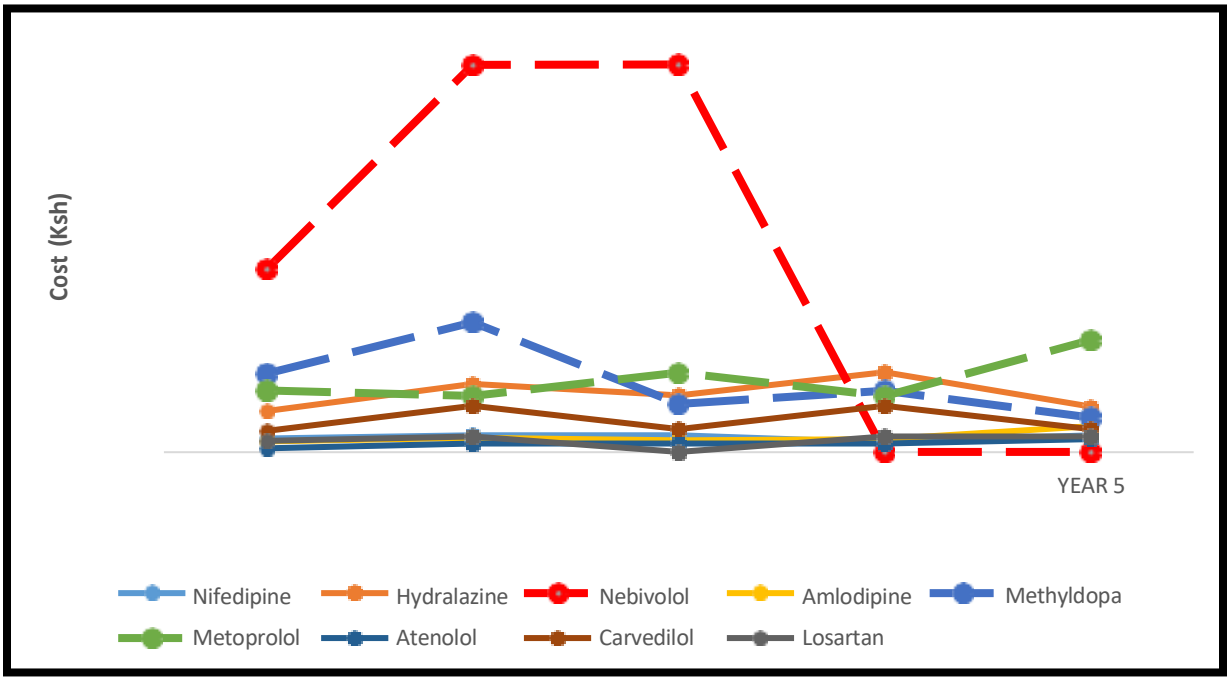


Figure 4.4: Expenditure on Anti-Hypertensive medications by kidney transplant recipients at Kenyatta National Hospital

4.5.3 Expenditure on Anti-diabetic drugs by kidney transplant recipients at Kenyatta National Hospital

Figure 4.4 represents expenditure on anti-diabetic drugs incurred by kidney transplant recipients. The highest expenditure was on gliclazide in year three post-transplant with an annual expenditure of about ksh 20,000. Unexpectedly, expenditure on Gliclazide dropped to nil in year four. The second costliest anti-diabetic was Mixtard R insulin whose annual expenditure increased annually from year one to year four. Expenditure on metformin and soluble insulin was almost negligible.

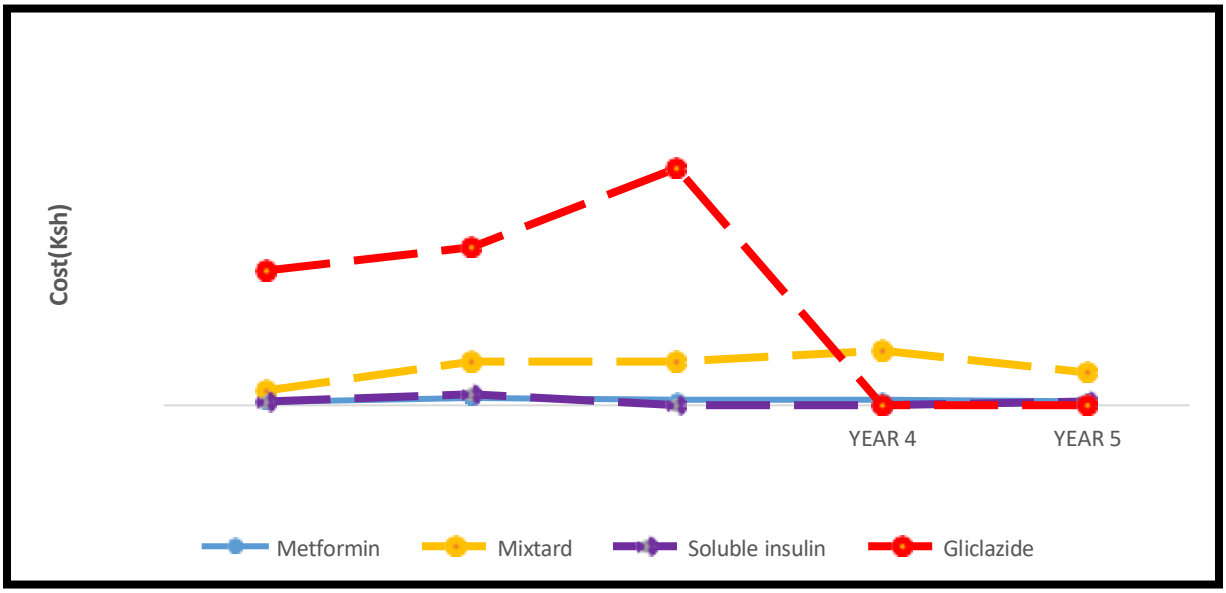


Figure 4.5: Expenditure on Anti-diabetic medicines by kidney transplant recipients at Kenyatta National Hospital

4.5.4 Expenditure on Antibiotics by kidney transplant recipients at Kenyatta National Hospital

As presented in Figure 4.5, yearly expenditure on antibiotics was highest in the first year post-transplant and thereafter fell sharply for most of the drugs to less than ksh 1,000 yearly. The exception to this was isoniazid whose expenditure remained high in the second year and meropenem whose expenditure spiked sharply in the third year by about ksh 4000. The highest expenditure on antibiotics was on linezolid whose cumulative expenditure was at Ksh 7000 per individual compared to other antimicrobials.

Meropenem expenditure dipped in year two then spiked in year three. Other antimicrobials accounted for minimal expenditure. In year four and five, expenditure on antibiotics was almost nil and beta lactams were the most widely used classes of antibiotics.

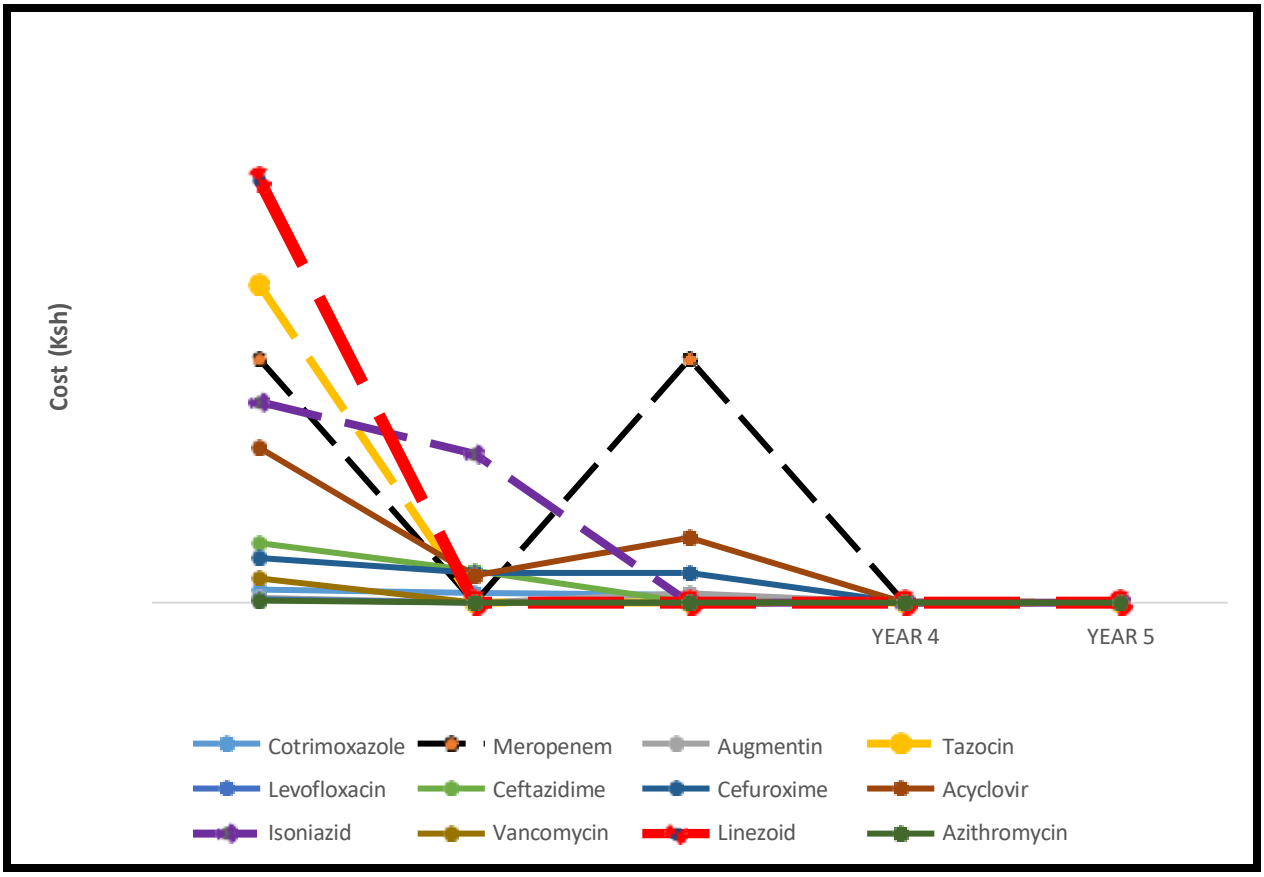
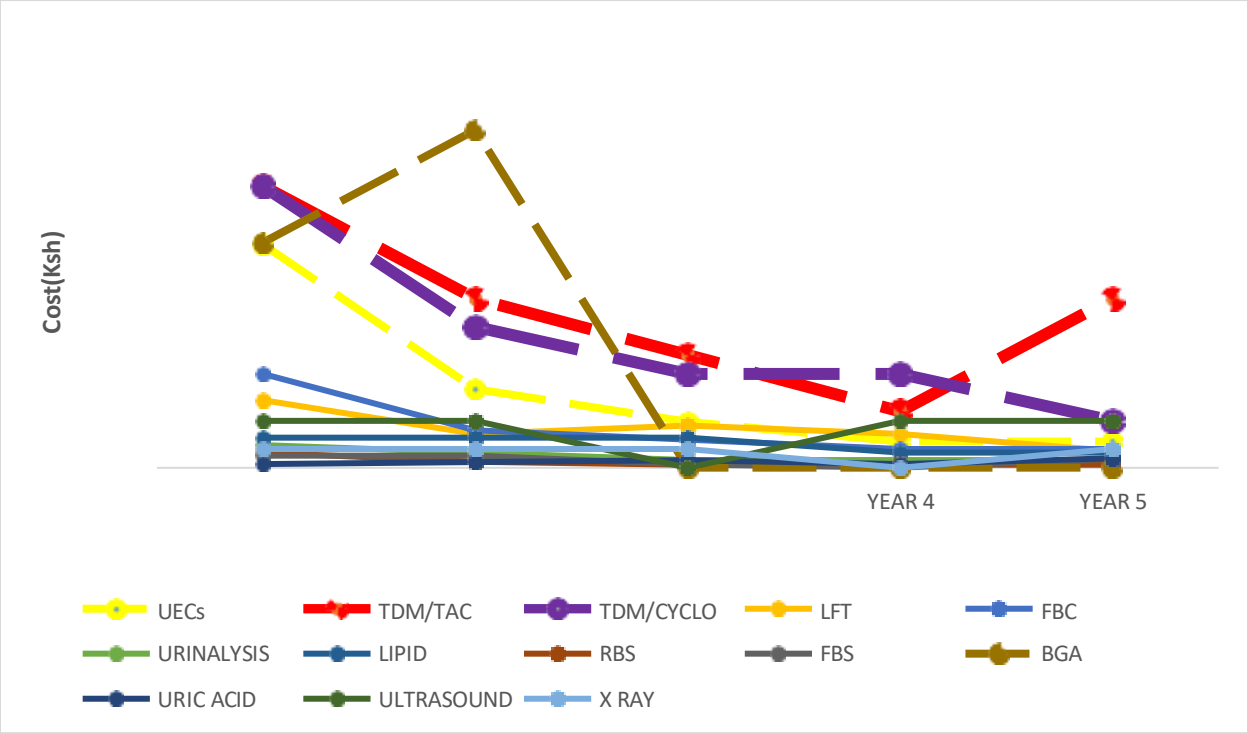


Figure 4.6: Expenditure on Antibiotics by kidney transplant recipients at Kenyatta National Hospital

4.6 Expenditure on Laboratory investigations and Radio-imaging by kidney transplant recipients at Kenyatta National Hospital

As presented in Figure 4.6, from the first to the third year post-transplant, the four investigative tests whose expenditure was highest were therapeutic drug monitoring for ciclosporin and tacrolimus, urea electrolytes and creatinine levels and blood gas analysis. In the first year post-transplant, expenditure on ciclosporin and tacrolimus was equivalent to about Ksh 15,000 yearly and it dropped gradually from year one to four. However, there was a spike in year five for therapeutic drug monitoring for tacrolimus.

Expenditure on blood gas analysis was the third highest in year one and it spiked sharply in year two such that it exceeded that of therapeutic drug monitoring of ciclosporin and tacrolimus individually. The decline in expenditure on urea electrolytes and creatinine was almost exponential and plateaued from the third year. Other investigations such as liver function tests, random blood sugar, fasting blood sugar were minimal with patients spending less than ksh 1,000 yearly and this trend remained constant throughout the five-year period.



KEY: TDM/TAC= Therapeutic drug monitoring/Tacrolimus, TDM/CYCLO= Therapeutic drug monitoring/Cyclosporin, UECs= Urea, Electrolytes and Creatinine, LFT=Liver function test, RBS=Random blood sugar, FBS=Fasting blood sugar, BGA=Blood gas analysis

Figure 4.7: Expenditure on Laboratory investigations and Radio-imaging of kidney transplant recipients at Kenyatta National Hospital

4.7 Expenditure on Services offered to post-kidney transplant recipients at Kenyatta National Hospital

Bed charges accounted for the highest expenditure in the first year of post-transplant followed by nursing services. Bed charges were almost two to ten-fold greater than other service expenditures in year one and two. Unexpectedly, expenditure on bed charges were higher in year two post-transplant compared to year one. By year four, expenditure on miscellaneous services declined significantly to almost zero.

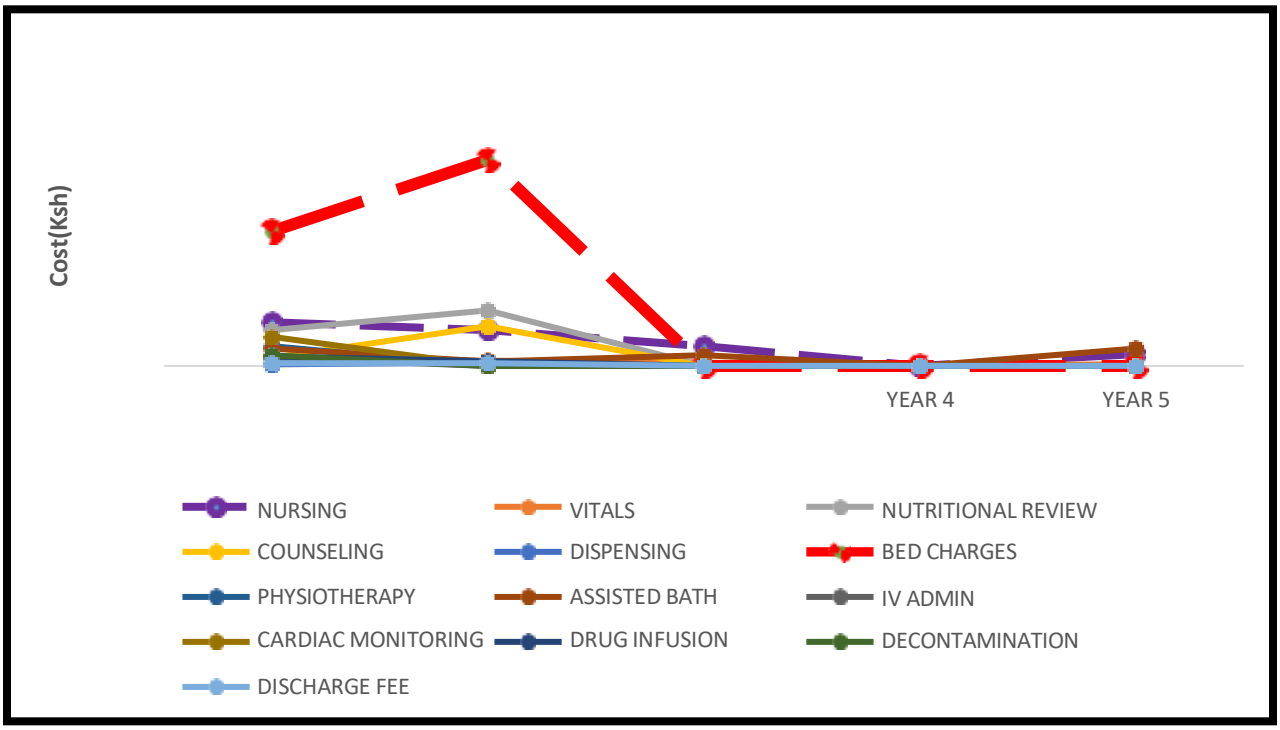


Figure 4.8: A representation of services offered to post-kidney transplant recipients at Kenyatta national hospital

4.8 Expenditure on Consumables by kidney transplant recipients at Kenyatta National Hospital

The minor consumables included infusion fluids, oxygen therapy, infusion sets and surgical masks. Expenditure on these was extremely minimal and no single item cost more than ksh 2,000. However, expenditure was highest in year two post-transplant and dropped sharply in the third year.

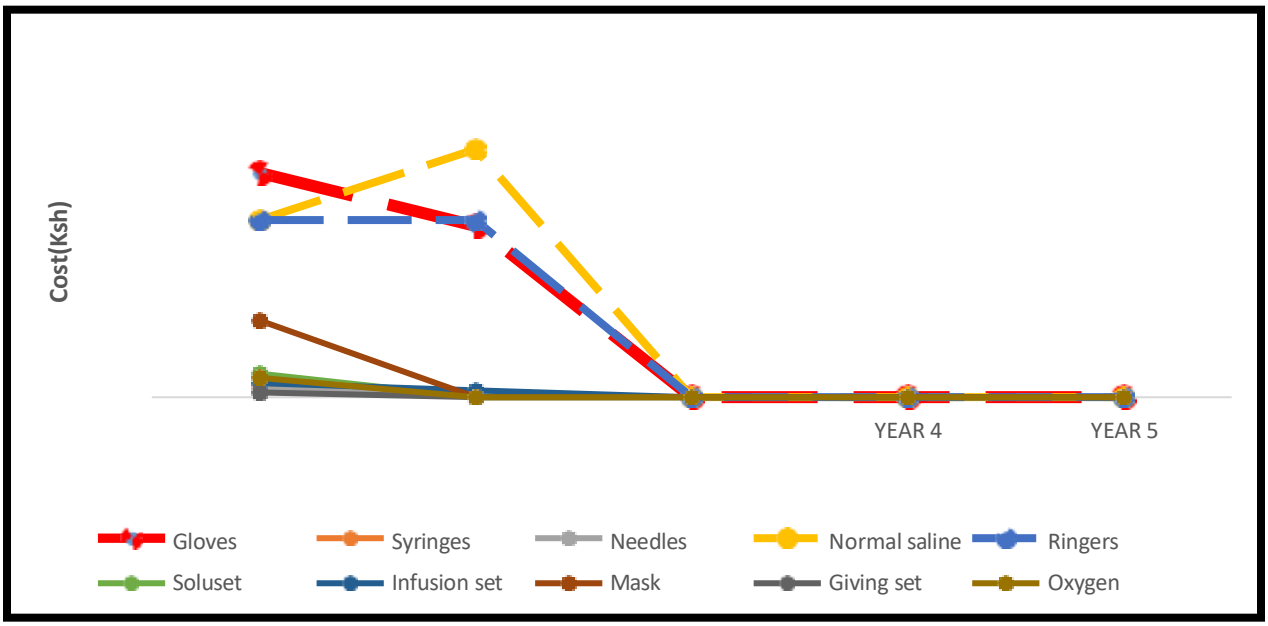


Figure 4.9: Expenditure on Consumables by kidney transplant recipients at Kenyatta National Hospital

4.9 Medical Outcomes

A majority of the KTRs are alive (56,49.1%) compared to those that are deceased (16,14 %). In addition, a large number of KTRs did not experience acute rejection (75,65.8%) compared to those who did (39,34.2%).

4.6 Monthly Expenditure for kidney transplant recipients at Kenyatta National Hospital per patient

The total expenditure incurred in the management of post-kidney transplant patient was the sum of all the cost categories. They included immunosuppressants, drugs to manage hypertension, diabetes, and infections, laboratory tests, consumables and services offered. The total expenditure incurred by kidney recipients per month was calculated as a sum of input presented in Equation 4.1. The monthly expenditure was converted to US dollars at the prevailing rate of 1 dollar to Ksh 102.9.

Equation 4.1 The cost function for computation of yearly costs incurred by post kidney transplant patients

Yearly expenditure = Immunosuppressant's + anti-hypertensives + anti-Diabetes + Antimicrobials + Laboratory tests + Consumables + Services

Table 4. 3 Monthly and total expenditure incurred by patients at Kenyatta National Hospital

	Year 1	Year 2	Year 3	Year 4	Year 5
Immunesuppressants	241,807.58	167,725.18	233,602.26	219,552.3	165,419.44
Hypertension	14,329.615	25,080.45	21,351.98	9802.19	9658.17
Diabetes	12,808.5	18,036.28	23,488.62	4914.8	3271.2
Anti-microbials	24,064.2	3,986.25	5731.6	0	0
Laboratory tests	70,440	49,660	20,920	16,260	20,640
Consumables	6,245	5150	0	0	0
Services	24,890	27,070	2575	0	2370
Total	394,584.9	296,708.2	307,669.5	250,529.3	201,358.8
Expenditure per month per patient	32,882	24,726	25,639	20,877	16,780
Expenditure per patient per month (USD)	320	240	249	203	163

Monthly Expenditure was highest in the first year post-kidney transplant at Ksh 32,882 per month followed by year three at Ksh 25,639. Expenditure decreased gradually from year one to year five in this cohort of patients and this was due to less frequent monitoring using laboratory tests, fewer incidents of post-transplant infections and graft rejection and better management of comorbidities. Figure 4.9 depicts the decline in yearly total expenditure per patient. It declined form Ksh. 394, 585 in the first year to about Ksh. 201,379 in year 5 post-transplant.

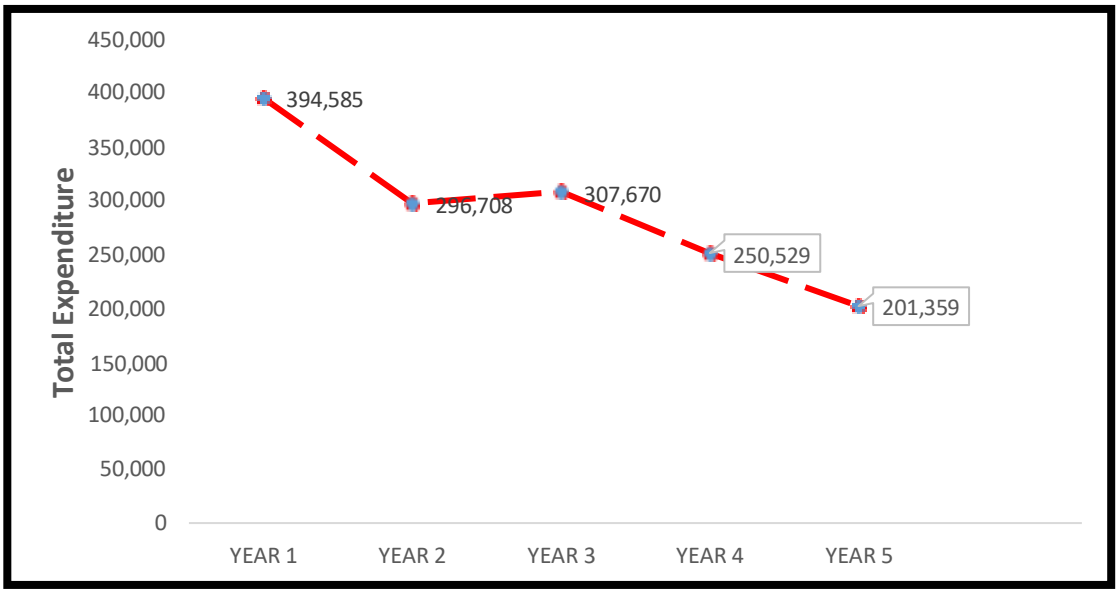


Figure 4.10 Expenditure for Post-transplant recipients at Kenyatta National Hospital over five years

4.7 One-way Sensitivity Analysis for inputs that have most impact on total yearly expenditure

One-way deterministic sensitivity analysis to identify the expenditure categories whose uncertainty had the most impact on the total expenditure incurred. Data sources for the expenditure incurred per month were obtained from a retrospective analysis of kidney transplant patients at the Kenyatta National Hospital renal unit. In order to conduct deterministic one-way sensitivity analysis, all the cost categories were varied by ±50 % of their base values that were presented in Table 4.3. The maximum and minimum costs of the inputs that were used for one-way sensitivity analyses were summarized in Table 4.3

Table 4.4 Minimum and maximum of cost items used for one-way sensitivity analyses for the yearly cost incurred by kidney transplant recipients.

Expenditure	Year one	Year two	Year three
	Minimum, Maximum cost (Ksh)		
Immunosuppressants	2660, 5010	2069, 3699	1855, 4125
Laboratory	3492, 4177	2642, 3125	2888, 3092
Antimicrobials	3718, 3952	2864, 2903	2962, 3018
Services	3714, 3956	2752, 3015	2978, 3003
Anti-hypertensives	3765, 3904	2762, 3005	2886, 3094
Anti-diabetic	3772, 3897	2796, 2971	2876, 3104
Consumables	3804, 3865	2858, 2909	2990, 2990

As presented in Figure 4.10, cost categories whose changes in value had the most impact on the total yearly expenditure were immunosuppressants, laboratory tests, antimicrobial drugs and services offered post-transplant in that order. In particular, the cost of immunosuppressants had a significant notable effect. Consumables with the smallest bar had least impact on the total expenditure.

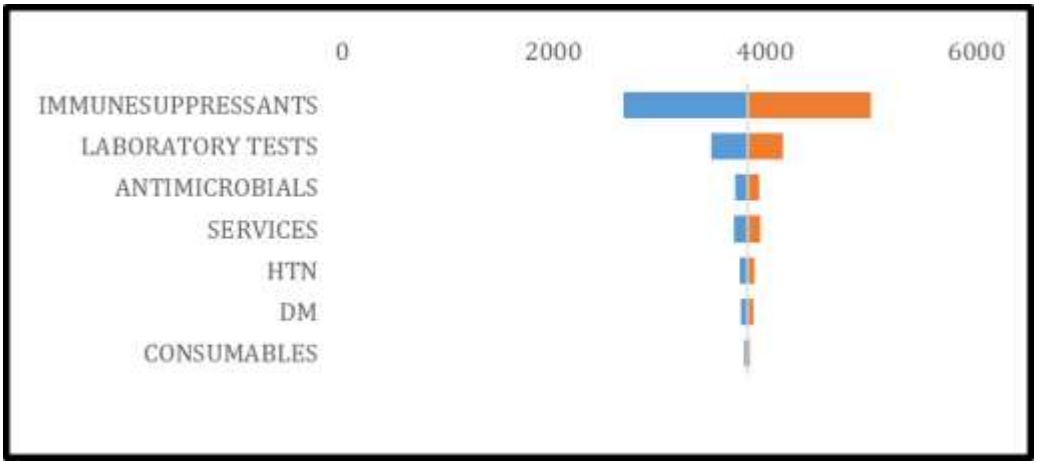


Figure 4.11: Tornado chart for one-way deterministic sensitivity analyses on total yearly expenditure Year One Post-kidney transplant

Figure 4.11 summarizes the effect of uncertainty in the costs of inputs on the total yearly expenditure Year Two and Three post-kidney transplant. The pattern observed in Year one was repeated in year two and three.

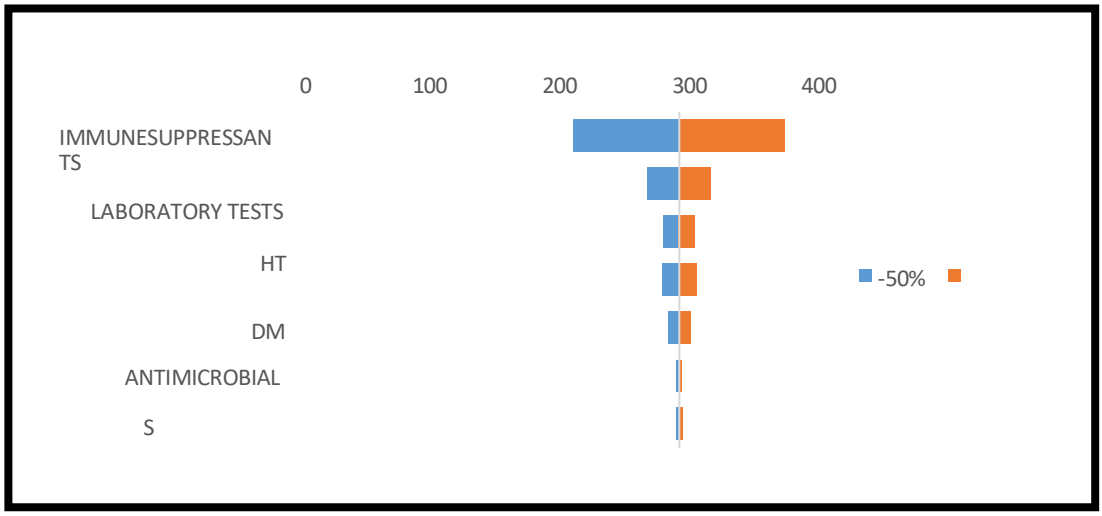


Figure 4.12: Tornado charts for one-way deterministic sensitivity analyses on total yearly expenditure Year two and three Post-kidney transplant. A notable difference however was that in year 3 varying the costs of antihypertensive and anti-diabetic drugs had a greater impact on year expenditure than laboratory tests.

4.8 Budget Impact Analysis

To determine the incremental impact of introducing post-transplant care into the budget of KNH, budget impact analysis was done as presented. Currently, the number of post-transplant patients at the renal unit is 200 and this number was increased by 20 new recipients yearly for a period of five years. The projected expenditure and increase in the annual medicine budget was calculated using the cost function below.

Expenditure = Cost of post-kidney transplant care per year* Number of projected

4.8.2 Projected increase in the Kenyatta National Hospital Medicine Budget

In year one following kidney transplant, the projected expenditure to be incurred in providing care is at the highest at ksh 86,808,700 followed by year three at ksh 79,994,200. Expenditure was lowest in the fifth year post kidney transplant at Ksh 60,407,700. The expenditure trend indicates that as the number of transplant recipients increase there is a general decrease in expenditure from year one to year five post-kidney transplant. This trend could be attributed to the fact that immediately post-transplantation, care involves a rigorous regimen of maintenance immunesuppressants, management of comorbidities, acute rejection and opportunistic infections, frequent scheduling of laboratory and radio-imaging studies.

Year	Expenditure per member per year	Projected number of KTR	Projected expenditure per year	Projected medicine budget
		200		**533,000,000**
2021	394,585	220	86,808,700	619,808,700
2022	296,708	240	71,209,920	691,018,620
2023	307,670	260	79,994,200	771,012,820
2024	250,529	280	70,148,120	841,160,940
2025	201,359	300	60,407,700	901,568,640

Table 4.5: Projected Table of Uptake and coverage and impact on medicine budget

4.8.3 Projected increase in the Kenyatta National Hospital Budget

Following kidney transplant, the annual medicine and hospital budgets increased by Ksh 369,568,640 and Ksh 3,824,569,720 from the baseline expenditure from year one to year five respectively. This translated to an average increase from the baseline of 69.3 % and 26.7 %. The greatest impact on the hospital budget was experienced in year four and five with a 5.1 % increase per year.

Year	Annual Medicine budget (Ksh 533M)	Annual budget (Ksh 14.3B)	Increase in annual hospital budget
2021	619,808,700	14,919,808,700	4.3 %
2022	691,018,620	15,610,827,320	4.6 %
2023	771,012,820	16,381,840,140	4.9 %
2024	841,160,940	17,223,001,080	5.1 %
2025	901,568,640	18,124,569,720	5.1 %
Increment	369,568,640	3,824,569,720	

Table 4.6: Projected Table of Uptake and coverage and impact on the hospital budget

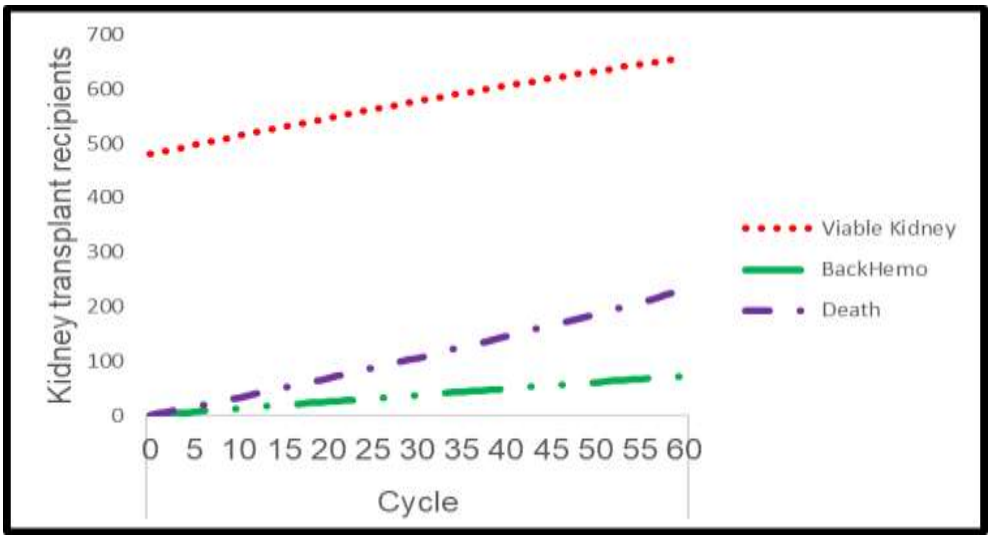
4.12.3 Projected increase in National Health Insurance Outpatient Budget

To determine the five-year projected impact of including post-transplant expenditure into the NHIF budget, we conducted a budget impact analysis on 480 post-kidney recipients in Kenya. The R code that was used to compute the costs associated with each health state is presented in Appendix five and the actual costs are presented in Appendix eight. The costs were not discounted and were obtained for a total of 60 months (5 years) post-transplant. Table 4.8 shows that expenditure will increase from Ksh 175,729,217 million year one to Ksh 275,508,106 million in year five indicating an increment of Ksh 99,778,889 million shillings.

Cycle	Year 1	Year 2	Year 3	Year 4	Year 5
1	13,556,211	15,849,562	17,979,724	20,064,585	22,069,645
2	13,811,202	16,014,726	18,156,776	20,234,836	22,233,020
3	14,015,209	16,213,149	18,333,195	20,404,479	22,395,814
4	14,181,386	16,377,871	18,508,974	20,573,511	22,558,026
5	14,385,278	16,558,810	18,698,854	20,741,928	22,719,652
6	14,551,636	16,739,211	18,858,904	20,922,998	22,892,803
7	14,754,460	16,935,176	19,033,101	21,077,176	23,041,377
8	14,920,597	17,098,718	19,206,689	21,244,049	23,201,516
9	15,122,279	17,277,878	19,379,667	21,410,335	23,361,094
10	15,288,106	17,456,537	19,552,030	21,576,036	23,520,112
11	15,488,675	17,650,228	19,737,806	21,741,154	23,678,572
12	15,654,178	17,812,694	19,895,191	21,905,690	23,836,475
Total	**175,729,217**	**201,984,560**	**227,340,911**	**251,896,777**	**275,508,106**

Table 4.7: Projected Five-year expenditure of Kidney Transplant Recipients in Kenya

We ran the model using a cohort of 480 post-kidney transplant recipients in Kenya. The cohort began the model immediately post-kidney transplant and ran successfully for a period of five years. Progressively results from the cohort simulation model showed that the number of kidney recipients in the viable kidney state increased from 480 to 658 followed by death state at 230 patients and hemodialysis state at 72 patients in five years. The results from this model show indicate that the risk of dying after five years' post-kidney transplant is high at 23.9 %. The distribution of KTRs is shown in Figure 4.14



KEY: *Viable kidney state; patients who have undergone a kidney transplant, BackHemo state; A patient whose graft has failed and returned to Hemodialysis and Death state; Loss of life due to kidney complications or other causes*

Figure 4.13: Five-year Cohort simulation of kidney transplant recipients at Kenyatta National Hospital

To determine the impact of including expenditure for all KTRs into the NHIF Benefit package, the yearly expenditures were added to the outpatient budget. The incremental change over a five-year period for NHIF outpatient budget was Ksh 1,132,459,571 representing a 23% change from their baseline expenditure (2020).

Year	Expenditure per year (Ksh)	NHIF Outpatient expenditure (2020)
		4,935,312,210
2021	175,729,217	5,111,041,427
2022	201,984,560	5,313,025,987
2023	227,340,911	5,540,366,898
2024	251,896,777	5,792,263,675
2025	275,508,106	6,067,771,781

Table 4.8: Projected impact in the NHIF Outpatient expenditure budget

CHAPTER FIVE: DISCUSSION

In this study, we utilized clinic records from the renal unit and general hospital records of Kenyatta National Hospital to determine direct healthcare costs incurred after kidney transplant. As far as we know, this is the first study in Kenya and East Africa to attempt to assess care after kidney transplant. Our findings revealed that the three main categories whose expenditure contributed significantly to the total cost of post-kidney transplant care were immunesuppressants, laboratory investigations and services. Our findings replicate those of a study done in Europe to assess the economic burden post-transplant events which demonstrated that the costs of pharmaceuticals and laboratory diagnostics were key drivers of cost in the post-transplant period. (Chamberlain *et al.*, 2014). These findings are in contrast to those by (Łabuś et all., 2019, who found that in the outpatient setting, laboratory investigations and monitoring of immunosuppressant levels were the main cost drivers. Therefore, efforts should be undertaken to subsidize immunosuppressant and laboratory costs at least for the first three years' post-transplantation in order to guarantee survival of the graft and minimize rejection.

Findings from our study showed a male dominance in those receiving transplants with a mean age of the patients being 46 years (SD=11.7). This demographic profile of transplant recipients is comparable across Europe and a gender disparity in favor of men has been observed in studies of access to renal transplantation. The predominant age group was between 41 to 50 years. The most common comorbidity was found to be hypertension (113, 99.1%), bacterial infection (109, 95.7%) and diabetes mellitus (33, 29%). These results are in concurrence with those of (Allan and Wagude, 2012) in the study of cardiovascular risk factors among renal transplant recipients at KNH who found that hypertension (87, 95.6%) and dysglycemia (45, 49.5%) were most prevalent. The burden of hypertension in particular may be explained by its high prevalence pre-transplant, possibly the adverse effects of immunosuppressants and most of the study participants were in the 41 to 50- year category.

A majority of the transplant recipients are on a cyclosporin regimen (51.8 %). This finding could partly explain why cyclosporin expenditure accounted a large proportion of overall expenditure from year one to five post- transplant. Expenditure on tacrolimus was fairly constant throughout the years. Our findings were in concurrence with that done by (Arogundade, 2013) which found that calcineurin based regimen was used in 95.8 % (137) of transplant recipients. In addition, cyclosporin when compared to tacrolimus is associated with reduced incidences of neurotoxicity, gastrointestinal side effects, new onset diabetes and metabolic syndrome. (Johnson *et al.*, 2012). These results explain why expenditure for therapeutic drug monitoring for cyclosporin and tacrolimus were highest among laboratory tests and had a gradual decline from year one to five.

We demonstrated that expenditure was highest in the first year post-kidney transplant at a cost of Ksh 32,882 per patient per month (PPPM) followed by year three at Ksh 25,639 (PPPM) and the trend decreased gradually from year one to year five. This finding could be explained by the rigorous and frequent graft monitoring, introduction of maintenance regimen of immunosuppressants and provision of nursing care post-transplant. Studies done in Europe showed that expenditure varied from approximately €33,600 per transplant patient in Czech Republic, Netherlands €77,500, UK: €39,865, Spain €64,066 and Italy €70,496. (Chamberlain *et al.*, 2014). This shows that although post-kidney care in Kenya seems to be affordable, caution should be exercised not to extrapolate these findings due to differences in study populations, cost of living and methodologies and these studies were conducted in high income countries.

Our findings from the Markov modelling of health states associated with post-kidney transplant show that generally care after kidney transplant is significantly affordable compared to hemodialysis. The model results in Appendix two show that expenditure incurred decreased gradually from year one to year three where it remained constant till year five. In the long term, our findings confirm that economically kidney transplantation and care afterwards is justified compared to chronic dialysis. On the contrary, expenditure associated with hemodialysis remained at a constant rate of Ksh 48,000 throughout the five-year period.

This figure could be higher with inclusion of non-healthcare related costs which were not the within the scope of this study and ultimately these patients would need a transplant at some point. Therefore, this gap in policy and care after transplantation needs to be addressed by enactment of laws and operationalization of policies that cover immunosuppression medicines at least the first three years' post-transplant.

In addition, in the years following kidney transplant, the annual medicine and hospital budget would increase by Ksh 369,568,640 and Ksh 3,824,569,720 from year one to year five respectively. This translated to an increase of 69.3 % and 26.7 % from the baseline. Even though this study primarily focused on the first five years' post-transplant, our results were in concurrence with those of the economic burden for the transplant center where the associated costs systematically decreased, even in the period of 25 years. (Łabuś and Fliszkiewicz, 2019).

In the budget impact analysis for all the kidney transplant recipients in Kenya, we have demonstrated that the incremental expenditure change over a five-year period for NHIF outpatient budget was Ksh 1,132,459,571 representing a 23% change from their baseline expenditure (2020). We propose that post-kidney transplant care be incorporated into the NHIF benefit package since this amount is reasonable considering the important role of post-transplant care, to ease access and the financial burden associated with out of pocket expenditure.

5.1 Study Limitations and Strengths

In Kenya and the Sub Saharan region, renal transplantation is gaining momentum as a treatment modality for end stage kidney disease. However, there is limited available literature on short term and long terms costs associated with care after transplantation. The use of a mixed design method that enabled us to retrospectively identify and quantify resources used in post-kidney transplant care and Markov modeling to cost health states.

This study relied on data which had been collected retrospectively on patient files. The calculated sample size was not achieved due to missing patient files because most of these records have been at the unit for almost a decade. Secondly, the records present had a paucity of information especially in the years four and five post-kidney transplant. In addition, we relied on Kenyatta National hospital tender prices for valuation of resources and services offered. Tender prices compared to market prices are usually subsidized for public institutions. For these reasons, it was not possible to authoritatively estimate expenditures in these years and make inferences. However, all attempts were made to locate the missing records from the health records department of Kenyatta National Hospital.

CHAPTER SIX: CONCLUSION AND RECOMMENDATIONS

6.1 Conclusion

Our results demonstrate that the main expenditure drivers after kidney transplantation were immunesuppressants, laboratory investigations and services offered to KTRs. The first year post-kidney transplant is associated with the greatest expenditure of approximately Ksh 32,882 per patient per month. This amount is 2.4 times Kenya's monthly minimum wage of Ksh 13,572. Immunosuppressive medicines and laboratory investigations in particular were a major contributor to the yearly total expenditure signifying their important role in post-transplant care. We recommend that these costs can be comfortable borne and factored into the National Hospital Insurance Fund benefit package. From the perspective of the transplant center, we demonstrated that the incremental impact on the annual medicines and hospital budgets over a five-year period would be minimal and thus affordable.

6.2 Recommendations for policy and practice

1. We recommend that the KNH Renal unit adopt an electronic file record system. This would assist in maintaining the quality of records and create a database for future research purposes.
2. We recommend that the cost of immunosuppressants could be made affordable for patients by entering into long term agreements for discounts and price reductions with manufacturers and distributors. This will promote access, availability and affordability to the patients.
3. We recommend that the NHIF includes immunosuppressant medications and laboratory investigations into the Benefit package coverage to provide financial protection and enable access to these life-saving medicines.
4. Parallel importation of generic immunosuppressants with comparable efficacy to reduce immunosuppressant expenditure burden.
5. Enactment and operationalization of Kenya National Blood Transfusion and Organ Transplantation Bill to facilitate timely identification of potential donors and to address ethical issues hindering donation.

6.3 Recommendations for future research

1. Further research should be conducted to evaluate the impact of non-adherence to immunesuppressants on graft survival and quality of life for kidney transplant recipients.
2. Research on the potential cost savings to be made after kidney transplantation compared to dialysis.
3. In addition, studies on the impact of non-healthcare related costs should be done to reveal the financial burden on transplant recipients.

REFERENCES

1. Adamu, B. *et al.* (2012) 'Commercial kidney transplantation : Trends , outcomes and challenges — A single-centre experience', 11(2). doi: 10.4103/1596-3519.93527.
2. Afaneh, C. *et al.* (2011) 'Induction Therapy : A Modern Review of Kidney Transplantation Agents', pp. 1–7. doi: 10.4172/2161-0991.S4-001.
3. Allan, J. and Wagude, A. (2012) 'CARDIOVASCULAR RISK FACTORS IN RENAL TRANSPLANT RECIPIENTS ATTENDING NEPHROLOGY CLINICS IN NAIROBI , KENYA A dissertation submitted in part fulfillment for the degree of Master of Medicine in Internal Medicine , University of Nairobi By'.
4. Alloway, R. R. *et al.* (2019) 'Rabbit anti - thymocyte globulin for the prevention of acute rejection in kidney transplantation', (February), pp. 1–10. doi: 10.1111/ajt.15342.
5. Arbagy, A. R. El *et al.* (2015) 'Recent advances in immunosuppression for kidney transplantation', pp. 272–281. doi: 10.4103/1110-2098.163862.
6. Arogundade, F. A. (2013a) 'Kidney transplantation in a low-resource setting : Nigeria experience'. Elsevier Masson SAS, pp. 241–245. doi: 10.1038/kisup.2013.23.
7. Arogundade, F. A. (2013b) 'Kidney transplantation in a low-resource setting: Nigeria experience', *Kidney International Supplements*. Elsevier Masson SAS, 3(2), pp. 241–245. doi: 10.1038/kisup.2013.23.
8. Article, R. (2017) 'Managing kidney transplant recipients in primary care', 30(6). doi: 10.1097/01.JAA.0000513351.60771.d1.
9. Atlani, M., Sharma, R. K. and Gupta, A. (2013) 'of Kidney Diseases and Transplantation Original Article Basiliximab Induction in Renal Transplantation : Long-Term Outcome', 24(3), pp. 473–479.
10. Azzi, J. R. *et al.* (2019) 'Calcineurin Inhibitors: 40 Years Later, Can't Live Without …'. doi: 10.4049/jimmunol.1390055.
11. Baker, R. J. *et al.* (2017) 'Renal association clinical practice guideline in post-operative care in the kidney transplant recipient'. BMC Nephrology, pp. 1–41. doi: 10.1186/s12882-017-0553-2.
12. Bakr, M. A., Nagib, A. M. and Donia, A. F. (2014) 'Induction Immunosuppressive Therapy in Kidney Transplantation Induction Immunosuppressive Therapy in Kidney

Transplantation', (March). doi: 10.6002/ect.25Liver.L58.

13. Barnieh, L. *et al.* (2011) 'A Description of the Costs of Living and Standard Criteria Deceased Donor Kidney Transplantation', pp. 478–488. doi: 10.1111/j.1600-6143.2010.03425.x.
14. Briggs, A. and Sculpher, M. (1998) 'An Introduction to Markov Modelling for Economic Evaluation', 13(4), pp. 397–409.
15. Chamberlain, G. *et al.* (2014) 'The Economic Burden of Post-transplant Events in Renal Transplant Recipients in Europe', 97(8), pp. 854–861. doi: 10.1097/01.TP.0000438205.04348.69.
16. Githinji, M. E. (2014) 'Running head: POST RENAL TRANSPLANT PATIENTS' & ALLOGRAFT SURVIVAL 1 Post renal transplant patients' and allograft survival at Kenyatta National Hospital Renal Unit: A four Year Retrospective Cohort Study'.
17. Hardinger, K. L., Brennan, D. C. and Klein, C. L. (2013) 'Selection of induction therapy in kidney transplantation', 26(Table 2), pp. 662–672. doi: 10.1111/tri.12043.
18. Helmuth, M. E. *et al.* (2019) 'Article Secular Trends in the Cost of Immunosuppressants after Solid Organ Transplantation in the United States', pp. 421–430. doi: 10.2215/CJN.10590918.
19. Hill, N. R. *et al.* (2016) 'Global Prevalence of Chronic Kidney Disease – A Systematic Review and Meta-Analysis', pp. 1–18. doi: 10.5061/dryad.3s7rd.Funding.
20. Human, T. and Cost, F. (no date) 'Chronic Kidney Disease in England : The Human and'.
21. Johnson, E., Bartman, B. and Briesacher, B. (2012) 'Effective health care program', *Agency for Healthcare Research and Quality (AHRQ)*, (90), pp. 1–24. Available at: http://www.effectivehealthcare.ahrq.gov/ehc/products/442/1086/Decide32_IncidentUserDesign_FinalReport_20120515.pdf.
22. Josephson, M. A. (2011) 'Monitoring and Managing Graft Health in the Kidney Transplant Recipient', 6. doi: 10.2215/CJN.01230211.
23. Kalluri, H. V. and Hardinger, K. L. (2012) 'World Journal of Transplantation', 2(4), pp. 51–68. doi: 10.5500/wjt.v2.i4.51.
24. Kaze, A. D. *et al.* (2018) 'Burden of chronic kidney disease on the African continent : a systematic review and meta-analysis'. BMC Nephrology, pp. 1–11.
25. Łabuś, A. and Fliszkiewicz, M. (2019) 'Costs of Long-Term Post-Transplantation Care in

Kidney Transplant Recipients', pp. 252–259. doi: 10.12659/AOT.914661.

26. Liu, J. *et al.* (2017) 'Efficacy and Safety of Everolimus for Maintenance Immunosuppression of Kidney Transplantation : A Meta-Analysis of Randomized Controlled Trials'. doi: 10.1371/journal.pone.0170246.
27. Luyckx, V. A. and Stanifer, J. W. (2018) '& practice The global burden of kidney disease and the sustainable development goals', (November 2017), pp. 414–422.
28. Muntean, A. and Lucan, M. (2013) 'IMMUNOSUPPRESSION IN KIDNEY TRANSPLANTATION kidney transplantation', 86(3), pp. 177–180.
29. Naik, M. R. G., Glander, P. and Budde, K. (2011) 'Optimization of Therapy with Mycophenolic Acid After Kidney Transplantation', pp. 3–12.
30. Pascual, J. *et al.* (2017) 'Special article Recommendations for the use of everolimus in de novo kidney transplantation : False beliefs , myths and realities ☆', 7(3), pp. 253–266.
31. Pedroso, J. A. and Citterio, F. (2015) 'Cyclosporine Therapy for Kidney Transplant : What is New for an Old-Fashioned Therapy ?', 5(5). doi: 10.4172/2161-0495.1000272.
32. Peter Maritim, Ahmed Twahir, and Mogamat Razeen Davids, Global Dialysis Perspective: Kenya, Kidney360,
33. Publish Ahead of Print, 2022, 10.34067/KID.0006662021
34. Rangaswami, J. *et al.* (2019) 'Cardiovascular disease in the kidney transplant recipient : epidemiology , diagnosis and management strategies', (April), pp. 760–773. doi: 10.1093/ndt/gfz053.
35. Review, C. E. (no date) 'Calcineurin Inhibitors for Renal Transplant', (166).
36. Rodrigue, J. R., Schold, J. D. and Morrissey, P. (no date) 'Direct and Indirect Costs Following Living Kidney Donation : Findings From the KDOC Study'. doi: 10.1111/ajt.13591.
37. Russ, G. R. (2013) 'Optimising the use of mTOR inhibitors in renal transplantation', 2(Suppl 1), pp. 1–7.
38. Salamzadeh, J. *et al.* (2014) 'Costs of Treatment after Renal Transplantation : Is it Worth to Pay More ?', 13(November 2013), pp. 271–278.
39. Sandelowski, M. (1995) 'Focus on Qualitative Methods Sample Size in Qualitative', pp. 179–183.
40. Schaefer, H. M. (2012) 'Long-Term Management of the Kidney Transplant Recipient',

2372, pp. 205–211. doi: 10.1159/000334158.

41. Snyder, K. A. M. and Bremerton, N. H. (2016) ‘Primary Care of the Solid Organ Transplant Recipient’.
42. Sonnenberg, F. A. *et al.* (1993) ‘Medical Decision Making Markov Models in Medical Decision Making : A Practical Guide’. doi: 10.1177/0272989X9301300409.
43. Stanifer, J. W. *et al.* (2016) ‘NDT Perspectives Chronic kidney disease in low- and middle-income countries’, (February), pp. 868–874. doi: 10.1093/ndt/gfv466.
44. Taylor, P. *et al.* (no date) ‘The safety of calcineurin inhibitors for kidney- transplant patients The safety of calcineurin inhibitors for kidney-transplant patients’, (September 2015). doi: 10.1517/14740338.2015.1083974.
45. Vassalotti, J. A. *et al.* (2016) ‘Practical Approach to Detection and Management of Chronic Kidney Disease for the Primary Care Clinician’, *The American Journal of Medicine*. Elsevier Inc, 129(2), pp. 153-162.e7. doi: 10.1016/j.amjmed.2015.08.025.
46. Webster, A. C. *et al.* (2017) ‘Seminar Chronic kidney disease’, *The Lancet*. Elsevier Ltd, 389(10075), pp. 1238–1252. doi: 10.1016/S0140-6736(16)32064-5.
47. Wouters, O. J. *et al.* (2015) ‘management and models of care’, *Nature Publishing Group*. Nature Publishing Group, 11(8), pp. 491–502. doi: 10.1038/nrneph.2015.85.

APPENDICES

Appendix 1: DATA COLLECTION FORM

BIO-DATA

Study number: Date filled:

Date of transplant:

Gender: Male Female

Weight: Height: BMI:

1. IMMUNESUPPRESSANT MEDICATION

Drug	Unit	Frequency	Quantity used	Unit cost	Total cost
Tacrolimus 0.5 mg	Tabs				
Tacrolimus 1 mg	Tabs				
Tacrolimus 5 mg	Tabs				
Ciclosporin 25 mg	Caps				
Ciclosporin 100mg	Caps				
Mycophenolate sodium 180 mg	Tabs				
Mycophenolate sodium 360 mg	Tabs				
Mycophenolate mofetil 250 mg	Tabs				
Mycophenolate mofetil 500 mg	Tabs				
Azathioprine 50 mg	Tabs				
Everolimus					
Sirolimus					

Basiliximab 20mg	Vial				

2. DRUGS USED TO MANAGE COMORBIDITIES

a) HYPERTENSION

Drug	Unit	Frequency	Quantity used	Unit cost	Total cost
Amlodipine besilate 5mg	Tabs				
Amlodipine besilate 10 mg	Tabs				
Nifedipine 20 mg	Tabs				
Diltiazem					
Felodipine					
Enalapril 2.5 mg	Tab				
Enalapril 5 mg	Tab				
Enalapril 10 mg	Tab				
Losartan potassium 50 mg	Tab				
Furosemide 40 mg	Tabs				
Furosemide 10 mg/ml, 2ml	Ampoule				
Indapamide 2.5 mg	Tabs				
Metolazone 5 mg	Tabs				
Spironolactone 25 mg	Tabs				
Spironolactone 100 mg	Tabs				

Atenolol 50 mg	Tabs				
Nebivolol					
Metoprolol 50 mg	Tabs				
Metoprolol 100 mg	Tabs				
Metoprolol tartrate 1 mg/ml, 5ml	Ampoule				
Carvedilol 3.125 mg	Tabs				
Carvedilol 6.25 mg	Tabs				
Carvedilol 12.5 mg	Tabs				
Carvedilol 25 mg	Tabs				
Hydralazine 25 mg	Tabs				
Hydralazine 20 mg/ml	Inj				
Methyldopa 250 mg	Tabs				
Methyldopa 500 mg	Tabs				
Clonidine 100 mcg	Tabs				
Clonidine 300 mcg	Tabs				

b) ANEMIA

Drug	Unit	Frequency	Quantity used	Unit cost	Total cost
Recombinant Human erythropoietin 2000 iu	Inj				
Iron tablets	Tabs				
Vitamin B complex	Tabs				

c) DYSLIPIDEMIA

Drug	Unit	Frequency	Quantity used	Unit cost	Total cost
Atorvastatin 10 mg	Tabs				
Atorvastatin 20 mg	Tabs				
Atorvastatin 40 mg	Tabs				
Rosuvastatin					
Fluvastatin					

d) DIABETES MELLITUS

Drug	Unit	Frequency	Quantity used	Unit cost	Total cost
Metformin 500mg	Tabs				
Metformin 850 mg	Tabs				
Metformin 1 g	Tabs				
Sitagliptin					
Glibenclamide 5mg	Tabs				
Vildagliptin					

e) OPPORTUNISTIC INFECTIONS

Drug	Unit	Frequency	Quantity used	Unit cost	Total cost
Zinacef 750 mg	**Vial**				
Tazocin 4.5g	Vial				
Sevelamar HCL 800mg	Tabs				
Pantoprazole 20 mg	Tabs				
Pantoprazole 40 mg	Vial				
Valganciclovir					
Opsite spray canister	Canister				

f) REJECTION

Drug	Unit	Frequency	Quantity used	Unit cost	Total cost
Prednisolone 5 mg	Tabs				
Methylprednisolone 500 mg	Vial				

3. CONSUMABLES

Item	Frequency	Unit cost	Total cost
Giving set			
Transfusion set			
Alcohol swabs			

4. ROUTINE LABORATORY INVESTIGATIONS

Test name	Frequency	Unit cost	Total cost (Ksh)
Liver function test			
Urinalysis			
Microalbumin			
Lipid profile			
Complete blood count			
Creatinine			
Therapeutic drug monitoring			
Random blood glucose			

Urea & Electrolytes			

Appendix 2A: Informed Consent for Key Informant Interview

Title of the study: ASSESSMENT OF THE COST AND BUDGET IMPACT ANAYLSIS OF POST KIDNEY TRANSPLANT CARE AT KENYATTA NATIONALHOSPITAL

Institution: Department of Pharmacology and Pharmacognosy, School of Pharmacy, University of Nairobi, P.O BOX 30197-00400, Nairobi

Investigator: Bernard Kamau Njuguna, P.O BOX 30197-00400, Nairobi; Mobile No. 0721368486

Supervisors:

Prof F.A. Okalebo

Department of Pharmacology and Pharmacognosy

Dr. Peter Karimi

Department of Pharmaceutics & Pharmacy Practice

Dr S.K. Wahome

Kenyatta National Hospital

INTRODUCTION

This study seeks to assess the cost and budget impact analysis of post kidney transplant care from the perspective of a health provider such as Kenyatta National Hospital. Although NHIF pays up to a maximum of Ksh 500,000 for a kidney transplant, for both local and overseas transplants while dialysis is offered at a maximum of ksh 9,500 per session twice weekly, it does not fund post-kidney transplant care. Consequently, many healthcare providers in Kenya have lamented about this cost and resultant impact of non-adherence.

PURPOSE OF THE STUDY

The purpose of this study is to evaluate the costs incurred in the post-transplant period from a provider perspective. I therefore request you to participate in this study and the followingprinciples apply to participants involved in medical research.

1. Your agreement to participate in this study is voluntary
2. You may withdraw from this study at any time without giving a reason
3. Please feel free to ask any questions pertaining the study

PROCEDURE

I will engage you on the costs involved in the provision of immunesuppressants, laboratory investigations, drugs to manage adverse events and comorbidities. All the information provided will be handled with confidentiality and will be used only for this study.

RISKS

To the best of my knowledge there will be no risks involved in this study

BENEFITS

The findings of this study will be useful in informing policy on the cost of post-kidney transplant care.

CONTACTS

Please feel free to contact me or my academic department at the University of Nairobi using the contacts provided.

I request you to sign the consent form attached.

Appendix 2B: Consent form

ASSESSMENT OF THE COST AND BUDGET IMPACT ANAYLSIS OF POST KIDNEY TRANSPLANT CARE AT KENYATTA NATIONAL HOSPITAL

I, the undersigned, willingly agree to participate in this study, the nature and purpose of which have been fully explained to me by the supervisor. I understand that the information gathered will be used for the purpose of this study only and maximum confidentiality will be maintained.

Respondent……

Sign…… Date……

Witness (Research assistant) ……..

Sign…… Date……

Investigators' statement

I, the undersigned have explained to the participant in a language he/she understands, the procedures to be followed, risks and benefits involved.

Investigator ……

Sign …… Date……..

APPENDIX 3: KNH-UoN ERC Approval Letter

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

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

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

KENYATTA NATIONAL HOSPITAL APPROVED 25 MAR 2020 KNH/UoN-ERC P.O. BOX 20723 - 00202 NAIROBI

Ref: KNH-ERC/A/108

25th March 2020

Bernard Kamau Njuguna
Reg. No. U51/12328/2018
Dept. of Pharmacology and Pharmacognosy
School of Pharmacy
College of Health Sciences
University of Nairobi

Dear Bernard,

RESEARCH PROPOSAL – ASSESSMENT OF THE COST AND BUDGET IMPACT ANALYSIS OF POST-KIDNEY TRANSPLANT CARE AT KENYATTA NATIONAL HOSPITAL (P953/11/2019)

This is to inform you that the KNH- UoN Ethics & Research Committee (KNH- UoN ERC) has reviewed and **approved** your above research proposal. The approval period is 25th March 2020 – 24th March 2021.

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. 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 Director, CS, KNH
The Chairperson, KNH- UoN ERC
The Assistant Director, Health Information, KNH
The Dean, School of Pharmacy, UoN
The Chair, Dept. of Pharmacology and Pharmacognosy, UoN
Supervisors: Prof. Faith A. Okalebo (Dept. of Pharmacology and Pharmacognosy, UoN),
Dr. Peter N. Karimi (Dept. of Pharmaceutics and Pharmacy Practice, UoN),
Dr. S.K. Wahome (KNH)

APPENDIX 4: Time varying transition probabilities for the Markov model

Cycle	Viable kidney to Dialysis	Dying when on Dialysis	Dying with Viable kidney
1	0.007515303	0.011385531	0.011766357
2	0.002922616	0.006810753	0.010203179
3	0.002211138	0.006102049	0.009362873
4	0.001847215	0.005739546	0.008812313
5	0.00161649	0.00550972	0.008413801
6	0.001453586	0.005347451	0.008107212
7	0.001330748	0.005225092	0.007861376
8	0.001233896	0.005128619	0.007658253
9	0.001155026	0.005050056	0.007486555
10	0.001089204	0.004984491	0.0073388
11	0.001033203	0.004928708	0.007209801
12	0.000984812	0.004880505	0.00709583
13	0.000942457	0.004838316	0.006994128
14	0.000904987	0.004800992	0.0069026
15	0.000871533	0.004767668	0.006819625
16	0.00084143	0.004737682	0.006743925
17	0.000814155	0.004710515	0.006674475
18	0.000789296	0.004685752	0.006610444
19	0.000766516	0.004663061	0.006551148
20	0.000745543	0.00464217	0.00649602
21	0.000726152	0.004622854	0.006444585
22	0.000708153	0.004604926	0.006396438
23	0.00069139	0.004588228	0.006351239
24	0.000675727	0.004572626	0.00630869
25	0.000661051	0.004558007	0.006268539
26	0.000647262	0.004544272	0.006230564
27	0.000634274	0.004531335	0.00619457
28	0.000622015	0.004519123	0.006160389
29	0.000610417	0.004507571	0.006127869
30	0.000599425	0.004496622	0.006096879
31	0.000588988	0.004486225	0.006067298
32	0.000579061	0.004476337	0.006039021
33	0.000569603	0.004466916	0.006011954
34	0.00056058	0.004457928	0.00598601
35	0.000551958	0.00444934	0.005961112

36	0.000543711	0.004441125	0.005937191
37	0.00053581	0.004433255	0.005914182
38	0.000528233	0.004425708	0.005892029
39	0.000520959	0.004418462	0.005870678
40	0.000513968	0.004411497	0.005850081
41	0.000507241	0.004404797	0.005830194
42	0.000500764	0.004398345	0.005810975
43	0.000494521	0.004392126	0.005792389
44	0.000488498	0.004386127	0.005774399
45	0.000482682	0.004380334	0.005756974
46	0.000477063	0.004374737	0.005740085
47	0.00047163	0.004369325	0.005723704
48	0.000466372	0.004364087	0.005707805
49	0.00046128	0.004359016	0.005692365
50	0.000456346	0.004354101	0.005677362
51	0.000451562	0.004349336	0.005662774
52	0.000446921	0.004344712	0.005648583
53	0.000442415	0.004340224	0.005634772
54	0.000438038	0.004335864	0.005621321
55	0.000433785	0.004331627	0.005608217
56	0.000429649	0.004327508	0.005595444
57	0.000425625	0.0043235	0.005582988
58	0.000421709	0.004319598	0.005570835
59	0.000417895	0.004315799	0.005558975
60	0.000414179	0.004312098	0.005558975

APPENDIX 5: The R code for computation of Expenditure for the Markov model

```
data<- read.csv("C:/Users/Bernard/Desktop/MPharm Epivigil/Thesis/Thesis
Corrections/Modified Thesis/New folder/Thesis drafts/New/RemadeHeemod.csv")

DeathHemo = flexsurv::flexsurvreg(survival::Surv(EndMonth, DiedHemo) ~ 1, dist = "weibull",
data = data)
Death_viable_kidney = flexsurv::flexsurvreg(survival::Surv(EndMonth, DiedVaible) ~ 1, dist =
"weibull", data = data)
BackHemoRegress=flexsurv::flexsurvreg(survival::Surv(EndMonth, BackHemo) ~ 1, dist =
"weibull", data = data)

##GRAPHING
DeathHemoA = survfit((EndMonth, DiedHemo) ~ 1, data = data)
ggsurvplot(DeathHemoA,data=data, risk.table=TRUE)

Death_viable_kidney = flexsurv::flexsurvreg(survival::Surv(EndMonth, DiedVaible) ~ 1, dist =
"weibull", data = data)

BackHemoRegress=flexsurv::flexsurvreg(survival::Surv(EndMonth, BackHemo) ~ 1, dist =
"weibull", data = data)

#Generating the conditional probabilities of surviving to
X = eval_surv(DeathHemo, time=1:60)
Y = eval_surv(Death_viable_kidney, time=1:60)
Z = eval_surv(BackHemoRegress, time=1:60)

#Y= calc_prob_from_surv(X)- calculates transition probs from #condProbs

param <- define_parameters(
   age = 46)

#Decided to be gender neutral
#Decided not to factor in an age increase because the mortality rates are in 4
# to 5 year wide categories and thethis is equivalent to cycle lenght
##There were difficulties in retrieving the mortality rates for Kenya using the #Heemod package.
Therefore the latest age specific mortality rate for Kenya #(not gender specific) was retrieved for
the following age-groups:
#https://apps.who.int/gho/data/view.main.60850?lang=en



#This is the probability of dying in one year.
```

```
#15 to 19 years: 0.006581245
#45 to 49 years: 0.045803721
#65 to 69 years: 0.1441905626

#The probability of dying at 35 to 39 years was: 0.023913
#Convert to monthly all cause probability to dying
# 15 to 19 years
rescale_prob(p = 0.006581245, to = 1/12)
# 45 to 49 years
mr=rescale_prob(p = 0.045803721, to = 1/12)
# 65 to 69 years
rescale_prob(p = 0.1441905626, to = 1/12)

  #Age related mortality rate
param <- modify(param, mr = 0.003899534)

##Mortality rates – dying directly with an alive viable kidney
#eval_surv: Generate either survival probabilities or conditional #probabilities of event for each
model cycle.#output is a numeric #vector

N=rep(mr,60)
#death with viable kindey
TprobViableKidney = calc_prob_from_surv(Y)

TprobViableKidney = c(TprobViableKidney,0.001665937)

comboTransViableDeath = combine_probs(
N, TprobViableKidney)

#death from Hemodialysis
TprobDeathHemo = calc_prob_from_surv(X)
comboTransHemoDeath= combine_probs(N, TProbDeathHemo)
comboTransHemoDeath

##Transition probability  to back to hemodialysis

TProbVaibleHemo <- calc_prob_from_surv(Z)
as.vector(TProbVaibleHemo)
TProbVaibleHemo

TProbVaibleHemo=c(TProbVaibleHemo,  0.001677000)



#The transition probabilities
```

```
comboTransViableDeath
comboTransHemoDeath
TProbVaibleHemo

mat_base <- define_transition(
state_names = c(v_Viable_Kidney, v_Hemodialysis, "Death"),
C, TProbVaibleHemo , comboTransViableDeath,
0, C, comboTransHemoDeath,
0, 0, 1)
mat_base
#plot(mat_base)

#Create a tunnel state - EXPANDED MATRIX
## Number of tunnels for each state
n_t=60
n_tunnel_size <- n_t
## Names for tunnel states of Viable  Kidney  state
v_ViableKidney_tunnel <- paste("V1_", seq(1, n_tunnel_size), "Month", sep = "")
## Names for tunnel states of Hemodialysis  state
v_Hemodialysis_tunnel <- paste("Hemo_", seq(1, n_tunnel_size), "Month", sep = "")
v_names_states_tunnels <- c(v_ViableKidney_tunnel , v_Hemodialysis_tunnel , "Death") # state
names

#Next get the length
n_states_tunnels <- length(v_names_states_tunnels) # number of states
n_states_tunnels

## Initialize first cycle of Markov trace accounting for the tunnels
##This is expected number of people at the start of the cycle
## There will be beginning hemodialysis, all other states will have none
##In the first tunnel with viable kidney, there are current 457 who have a transplant, I spread
these over 60 months evenly ie. 8 each month post-transplant. I want the first state to have 10
people and the other states none, 457 will be at month 15

already_KTP <-rep(8,60) #Total is 480
length(already_KTP)

v_s_init_tunnels = c(already_KTP, rep(0,61))
length(v_s_init_tunnels)

#Initialize the matrix
m_P <- matrix(0,  nrow = n_states_tunnels, ncol = n_states_tunnels,
dimnames = list(v_names_states_tunnels, v_names_states_tunnels))

# From Viable kidney to hemodialysis
```

```
#The transition probabilities
comboTransViableDeath
comboTransHemoDeath

V_tprob_Viable_Hemo1 = TProbVaibleHemo
#To ensure the length of the vector is equal to the length of the #expanded matrix
diff=n_states_tunnels- n_tunnel_size
V_tprob_Viable_Hemo1a = c(V_tprob_Viable_Hemo1, rep(0, diff))
V_tprob_Viable_Hemo1a
m_P[, "Hemo_1Month"]<- V_tprob_Viable_Hemo1a

#All transitions to Death
V_p_viable_to_death <- comboTransViableDeath
V_p_Hemo_to_death <- comboTransHemoDeath
V_p_death <- c(V_p_viable_to_death , V_p_Hemo_to_death, 1)
m_P[, "Death" ]<- V_p_death

#C is 1 minus the sum of rows - tunnels involving viable kidney
for (i in 1:59)  {(m_P[i,i+1]  = 1-sum(m_P[i,]))}

#C is 1 minus the sum of rows – tunnels involving hemodialysis
for (i in 61:119) {(m_P[i,i+1]  = 1-sum(m_P[i,]))}
#m_P

#ADDING A PROVISION OF THE LAST TUNNEL IN A GIVEN STATE
sss = sum(m_P[60,])
sss
m_P[60, 60]=1-sss
ttt=sum(m_P[120,])
m_P[120,120]=(1-ttt)

#check row total for m_P (transition matrix is 1)
V_RowTotal_MP = apply(m_P, 1, sum)
V_RowTotal_MP

#COSTS

#COST OF MANAGING COMORBIDITIES
ProbHypertension = 0.9912
CostMonthlyHypertension      = 1200
ExpectedCostHypertension = ProbHypertension * CostMonthlyHypertension

ProbDiabetes = 0.2895
CostMonthlyDiabetes = 1200
ExpectedCostDiabetes = ProbDiabetes * CostMonthlyDiabetes
```

```
ProbDyslipidemia = 0.2895
CostMonthlyDyslipidemia = 1200
ExpectedCostDyslipidemia = ProbDyslipidemia * CostMonthlyDyslipidemia

ProbabAnemia = 0.1053
CostAnemiaMonthly=5000
ExpectedCostMonthlyAnemia= CostAnemiaMonthly * ProbabAnemia

ExpectedCostcomorbidities = ExpectedCostDiabetes + ExpectedCostDyslipidemia  +
ExpectedCostHypertension + ExpectedCostMonthlyAnemia

v_Cost_comorbidities = rep(ExpectedCostcomorbidities,60)

Immuno_induction = 22400

p_cyclo = 0.518
monthly_costCyclo = 29204.4
Immuno_mainten_Cyclo = p_cyclo * monthly_costCyclo

p_tacrolimus = 0.328
monthly_costTacro = 17058.6
Immuno_mainten_Tacro = p_tacrolimus * monthly_costTacro

p_OtherRegimen = 0.154
monthly_costOtherRegimen = 15000
Immuno_mainten_OtherRegimen = p_OtherRegimen * monthly_costOtherRegimen
ExpectedMonthlyImmuno = Immuno_mainten_OtherRegimen + Immuno_mainten_Tacro +
Immuno_mainten_Cyclo


v_immunotherapy_viable = c((Immuno_induction+ ExpectedMonthlyImmuno),
rep(ExpectedMonthlyImmuno,59))
v_immunotherapy_viable

TDMCostPerTest = 2500

TDMFirstYear<- c(rep(c(TDMCostPerTest,0),6), TDMCostPerTest)
TDMFirstYear
v_cost_viable_TDMTest1= c(TDMFirstYear,rep(0,47))
v_cost_viable_TDMTest15<-c(rep(0,14), TDMCostPerTest, rep(0,45))
v_cost_viable_TDMTest19<-c(rep(0,18), TDMCostPerTest, rep(0,41))
```

```
v_cost_viable_TDMTest23<-c(rep(0,22), TDMCostPerTest, rep(0,37))

v_cost_viable_TDMTest29<-c(rep(0,28), TDMCostPerTest, rep(0,31))

v_cost_viable_TDMTest35<-c(rep(0,34), TDMCostPerTest, rep(0,25))

v_cost_viable_TDMTest42<-c(rep(0,41), TDMCostPerTest, rep(0,18))

v_cost_viable_TDMTest54<-c(rep(0,53), TDMCostPerTest, rep(0,6))

v_cost_viable_TDMTest <- (v_cost_viable_TDMTest1 + v_cost_viable_TDMTest15 +
v_cost_viable_TDMTest19 + v_cost_viable_TDMTest23 + v_cost_viable_TDMTest29 +
v_cost_viable_TDMTest35 + v_cost_viable_TDMTest42 + v_cost_viable_TDMTest54)
v_cost_viable_TDMTest

LabCostYearOne= c(rep(3078,12), rep(0,48))
LabCostYearTwo= c(rep(0,12), rep(2472,12), rep(0,36))
LabCostYearThree =c(rep(0,24), rep(743,12), rep(0,24))
LabcostYearFourFive=c(rep(0,36), rep(480,24))
LabCost60months= LabCostYearOne+LabCostYearTwo+ LabCostYearThree+
LabcostYearFourFive
LabCost60months

pricexray = 183
priceUltraSound =208
MonthlyRadiological= pricexray + priceUltraSound
v_radiological_cost= rep(MonthlyRadiological,60)

##total costs viable kidney

V_costs_totalviableKidney = v_radiological_cost + LabCost60months+
v_cost_viable_TDMTest + v_immunotherapy_viable + v_Cost_comorbidities
V_costs_totalviableKidney

#COST HEMODIALYSIS

CostSession=10000
NumberSessions=8
ExtractionSurgery=200000
monthylyCostHemodialysis = CostSession * NumberSessions
monthylyCostHemodialysis
vector_BackHemo = c((ExtractionSurgery+monthylyCostHemodialysis)
, rep(monthylyCostHemodialysis,59))
length(vector_ExctractionSurgery)
```

```
####COSTING VECTOR THAT WILL BE USED FOR ANALYSIS

ALLcostsVector = c(V_costs_totalviableKidney, vector_BackHemo, 0)
length(ALLcostsVector)

#Only those with viable kidney
CostOnlyViableKidney = c(V_costs_totalviableKidney, rep (0, 61))
length(CostOnlyViableKidney)

#CostOnlyImmunoSupressants
CostOnlyImmunoSupressants = c((v_cost_viable_TDMTest + v_immunotherapy_viable), rep(0,
61))

##RUNNING THE MODEL – BUDGET IMPACT ANALYSIS WITH
#Number receiving transplant monthly in Kenya is 4
v_n_enter= c(4, rep(0,120))
length(n_enter)
m_n_enter=rbind(v_n_enter)
dim(m_n_enter)

#Cohort trace matrix – change in population over time

m_M <- matrix(NA,
nrow = (n_t + 1), ncol = n_states_tunnels,
dimnames = list(0:n_t, v_names_states_tunnels))
# Store the initial state vector in the first row of the cohort #trace
m_M[1, ] <-v_s_init_tunnels

#the run with people entering
for (j in 1:n_t){
m_M[j+1,] <- (m_M[j,] + m_n_enter)%*% m_P}

#Convert the costs vectors to matrices

dim(m_M)
##m_M is a 61 X 121 matrix
##The length of the cost vector is 121
### 61 X 121  matrix  %*% 121 X 1  = 1 X 61

####ALL COSTS IF THEY GO BACK TO HEMODIALYSIS – INCLUDES EXTRACTION
M_ALLcosts = as.matrix(ALLcostsVector, nrows=121)
dim(M_ALLcosts)
```

```
M_ALLcosts
AllcostsEachCycle = m_M %*% ALLcostsVector
AllcostsEachCycle

m_ViableKidneycosts = as.matrix(CostOnlyViableKidney
, nrows=121)
ViableKidneyCostsEachCycle = m_M %*% m_ViableKidneycosts
ViableKidneyCostsEachCycle

m_ViableKidneycosts = as.matrix(CostOnlyViableKidney
, nrows=121)
ViableKidneyCostsEachCycle = m_M %*% m_ViableKidneycosts
ViableKidneyCostsEachCycle

m_CostImmunosuppressants = as.matrix(CostOnlyImmunoSupressants
, nrows=121)
ImmunosuppressantCostsEachCycle = m_M %*% m_CostImmunosuppressants
ImmunosuppressantCostsEachCycle

#NEXT STEPS
m_n_t=as.matrix(1:61, nrows=61)

##Summarize people in the trace cohort

M_trace_ViableKidney=m_M[,1:60]
M_trace_HemoDialysis=m_M[,61:120]
M_trace_Death = m_M[,121]

V_rowsum_trace_ViableKidney = apply(M_trace_ViableKidney, 1, sum)
V_rowsum_trace_HemoDialysis = apply(M_trace_HemoDialysis, 1, sum)
Matrix_people = cbind(m_n_t, V_rowsum_trace_ViableKidney,
V_rowsum_trace_HemoDialysis, M_trace_Death)

#Testing if all numbers of people is realistic
rowSumPeople = apply(Matrix_people,1, sum)
rowSumPeople

##Concantrate the matrices on costs
M_Costs_all= cbind(m_n_t, ImmunosuppressantCostsEachCycle,
ViableKidneyCostsEachCycle, AllcostsEachCycle)

##Transfer to Word
Matrix_people
```

```
M_Costs_all

##DrawGraphs
#Convert the matrix to a dataframe
df_Matrix_people = as.data.frame(Matrix_people, names=c("Month", "Viable Kidney",
"Hemodialysis", "Death"))
vvvv= apply(Matrix_people,1, sum)

p2 <- ggplot(df_Matrix_people) +
geom_point(aes(x = df_Matrix_people[,1], y = df_Matrix_people[, 2], colour="red")) +
geom_point(aes(x = df_Matrix_people[,1], y = df_Matrix_people[, 3]), colour="blue") +
geom_point(aes(x = df_Matrix_people[,1], y = df_Matrix_people[, 4]), colour="green")+
labs(
   title = "Predicted Outcomes",
   subtitle = "(Months, Post Kidney Transplant)",
   caption = "Cohort Markov Model",
   x = "Months Post Transplant",
   y = "Number of individuals"
 )

p2 + theme_classic()

ggplot(df_Matrix_people, aes(x = df_Matrix_people[,1], y = df_Matrix_people[, 2])) +
geom_line()

Matrix_people
M_Costs_all
```

APPENDIX 6: Time dependent costs of Hemodialysis and Living with a viable kidney (KNH)

	Viable Kidney and all Medications and Services	TDM and Immunotherapy	Hemodialysis and all medications and services	Hemodialysis
1	53812.84	47933.1	53879.74	48000
2	28912.84	23033.1	53879.74	48000
3	31412.84	25533.1	53879.74	48000
4	28912.84	23033.1	53879.74	48000
5	31412.84	25533.1	53879.74	48000
6	28912.84	23033.1	53879.74	48000
7	31412.84	25533.1	53879.74	48000
8	28912.84	23033.1	53879.74	48000
9	31412.84	25533.1	53879.74	48000
10	28912.84	23033.1	53879.74	48000
11	31412.84	25533.1	53879.74	48000
12	28912.84	23033.1	53879.74	48000
13	30806.84	25533.1	53273.74	48000
14	28306.84	23033.1	53273.74	48000
15	30806.84	25533.1	53273.74	48000
16	28306.84	23033.1	53273.74	48000
17	28306.84	23033.1	53273.74	48000
18	28306.84	23033.1	53273.74	48000
19	30806.84	25533.1	53273.74	48000
20	28306.84	23033.1	53273.74	48000
21	28306.84	23033.1	53273.74	48000
22	28306.84	23033.1	53273.74	48000
23	30806.84	25533.1	53273.74	48000
24	28306.84	23033.1	53273.74	48000
25	26577.84	23033.1	51544.74	48000
26	26577.84	23033.1	51544.74	48000
27	26577.84	23033.1	51544.74	48000
28	26577.84	23033.1	51544.74	48000
29	29077.84	25533.1	51544.74	48000
30	26577.84	23033.1	51544.74	48000
31	26577.84	23033.1	51544.74	48000
32	26577.84	23033.1	51544.74	48000

33	26577.84	23033.1	51544.74	48000
34	26577.84	23033.1	51544.74	48000
35	29077.84	25533.1	51544.74	48000
36	26577.84	23033.1	51544.74	48000
37	26314.84	23033.1	51281.74	48000
38	26314.84	23033.1	51281.74	48000
39	26314.84	23033.1	51281.74	48000
40	26314.84	23033.1	51281.74	48000
41	26314.84	23033.1	51281.74	48000
42	28814.84	25533.1	51281.74	48000
43	26314.84	23033.1	51281.74	48000
44	26314.84	23033.1	51281.74	48000
45	26314.84	23033.1	51281.74	48000
46	26314.84	23033.1	51281.74	48000
47	26314.84	23033.1	51281.74	48000
48	26314.84	23033.1	51281.74	48000
49	26314.84	23033.1	51281.74	48000
50	26314.84	23033.1	51281.74	48000
51	26314.84	23033.1	51281.74	48000
52	26314.84	23033.1	51281.74	48000
53	26314.84	23033.1	51281.74	48000
54	28814.84	25533.1	51281.74	48000
55	26314.84	23033.1	51281.74	48000
56	26314.84	23033.1	51281.74	48000
57	26314.84	23033.1	51281.74	48000
58	26314.84	23033.1	51281.74	48000
59	26314.84	23033.1	51281.74	48000
60	26314.84	23033.1	51281.74	48000

APPENDIX 7: Cohort simulation for Kidney transplant recipients in Kenya

Cycle	Viable Kidney	BackHemo	Death
0	480	0	0
1	483.453	1.326734	3.220268
2	486.9171	2.626126	6.456755
3	490.3789	3.911163	9.709905
4	493.8327	5.185709	12.98161
5	497.2751	6.451904	16.27295
6	500.7042	7.711137	19.58462
7	504.1185	8.964399	22.91709
8	507.5169	10.212437	26.2707
9	510.8985	11.45584	29.64568
10	514.2627	12.695087	33.04222
11	517.609	13.930574	36.46046
12	520.9369	15.162639	39.9005
13	524.246	16.391569	43.36241
14	527.5362	17.617613	46.84624
15	530.807	18.840989	50.35201
16	534.0583	20.06189	53.87976
17	537.29	21.280486	57.42949
18	540.5019	22.496926	61.00117
19	543.6938	23.711348	64.59481
20	546.8658	24.92387	68.21038
21	550.0176	26.134601	71.84784
22	553.1492	27.343639	75.50715
23	556.2607	28.551072	79.18827
24	559.3519	29.756977	82.89115
25	562.4228	30.961426	86.61573
26	565.4736	32.164482	90.36196
27	568.504	33.366203	94.12978
28	571.5143	34.56664	97.91911
29	574.5043	35.765839	101.7299
30	577.4741	36.963842	105.562
31	580.4238	38.160683	109.4155
32	583.3535	39.356397	113.2902
33	586.263	40.551011	117.186
34	589.1526	41.74455	121.1028
35	592.0223	42.937036	125.0407
36	594.8721	44.128488	128.9994

37	597.7021	45.31892	132.979
38	600.5125	46.508346	136.9792
39	603.3032	47.696777	141.0001
40	606.0743	48.88422	145.0415
41	608.826	50.070682	149.1033
42	611.5583	51.256167	153.1855
43	614.2714	52.440677	157.2879
44	616.9653	53.624212	161.4105
45	619.6401	54.806771	165.5532
46	622.2959	55.988351	169.7158
47	624.9328	57.168947	173.8982
48	627.551	58.348555	178.1005
49	630.1505	59.527166	182.3224
50	632.7314	60.704773	186.5638
51	635.2939	61.881365	190.8247
52	637.8381	63.056934	195.105
53	640.364	64.231466	199.4045
54	642.8718	65.40495	203.7232
55	645.3616	66.577371	208.061
56	647.8336	67.748715	212.4177
57	650.2878	68.918967	216.7933
58	652.7243	70.088111	221.1876
59	655.1433	71.256128	225.6005
60	657.5449	72.423052	230.0321

APPENDIX 8: Time dependent costs for Kidney transplant recipients in Kenya

Cycle	Immunosuppressant expenditure	Immunosuppressant and dialysis	Post-transplant expenditure
1	11515088	13556211	13556211
2	11392720	13439716	13811202
3	11488997	13542219	14015209
4	11546983	13606705	14181386
5	11642711	13709172	14385278
6	11701028	13774446	14551636
7	11795949	13876532	14754460
8	11854314	13942257	14920597
9	11948334	14043831	15122279
10	12006594	14109831	15288106
11	12099669	14210834	15488675
12	12157730	14277011	15654178
13	12249841	14373292	15849562
14	12307645	14439562	16014726
15	12398792	14539283	16213149
16	12456313	14605484	16377871
17	12530114	14688072	16558810
18	12603430	14770281	16739211
19	12692354	14868205	16935176
20	12748886	14933848	17098718
21	12821059	15015243	17277878
22	12892741	15096266	17456537
23	12979452	15192442	17650228
24	13034913	15257510	17812694
25	13105442	15327252	17979724
26	13175492	15407124	18156776
27	13245058	15486465	18333195
28	13314131	15565267	18508974
29	13397447	15658265	18698854
30	13451072	15721528	18858904
31	13518981	15799028	19033101
32	13586415	15876008	19206689
33	13653371	15952465	19379667
34	13719840	16028393	19552030
35	13799848	16117816	19737806
36	13851588	16178933	19895191

37	13916908	16252140	20064585
38	13981765	16326284	20234836
39	14046159	16399901	20404479
40	14110087	16472987	20573511
41	14173544	16545538	20741928
42	14249797	16630822	20922998
43	14299301	16689292	21077176
44	14361643	16760538	21244049
45	14423541	16831277	21410335
46	14484997	16901511	21576036
47	14546013	16971243	21741154
48	14606591	17040475	21905690
49	14666732	17109207	22069645
50	14726436	17177443	22233020
51	14785706	17245182	22395814
52	14844538	17312424	22558026
53	14902930	17379165	22719652
54	14972995	17457519	22892803
55	15018630	17511384	23041377
56	15075978	17576903	23201516
57	15132915	17641952	23361094
58	15189442	17706534	23520112
59	15245563	17770651	23678572
60	15301281	17834307	23836475