# COST UTILITY AND BUDGET IMPACT ANALYSIS OF 5-FLUOROURACIL AND CAPECITABINE BASED REGIMENS FOR MANAGEMENT OF COLORECTAL CANCER AT KENYATTA NATIONAL HOSPITAL

**NANCY JEBET KOECH**

**U51/12212/2018**

Department of Pharmacology and Pharmacognosy

University of Nairobi

***A thesis submitted in partial fulfillment of the requirements for the award of the Degree of Master of Pharmacy in Pharmacoepidemiology and Pharmacovigilance of the University of Nairobi.***

***August, 2022.***

## DECLARATION

This is my original work and has not been presented for examination in this or any other university.

Signature …… …… Date: 22nd/08/2022

Nancy Jebet Koech

**SUPERVISORS:**

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

Signature…… Date…….

**Prof Faith Okalebo, PhD**

Department of Pharmacology and Pharmacognosy

Signature…… Date…… August 25, 2022

**Dr. Elizabeth Owiti, PhD**

School of Economics, University of Nairobi

Signature…… Date…… 25/8/2022

**Dr. David Wata, Mpharm**

Cancer Treatment Centre, Kenyatta National Hospital

# DECLARATION OF ORIGINALITY

**Name of Student**: Nancy Jebet Koech

**Registration Number**: U51/12212/2018

**College**: College of Health Sciences

**Department**: Department of Pharmacy

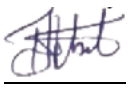
**Unit:** Unit of Pharmacology and Pharmacognosy

**Course Name**: Master of Pharmacy, Pharmacoepidemiology and Pharmacovigilance

**Title of the work:** Cost utility analysis of 5-fluorouracil and capecitabine based regimens for management of colorectal cancer at Kenyatta National Hospital

**DECLARATION**

1. I understand what Plagiarism is and I am aware of the University's policy in this regard.
2. I declare that this thesis is my original work and has not been submitted elsewhere for examination, the award of a degree or publication. Where other people's work or my own work has been used, this has properly been acknowledged and referenced in accordance with the University of Nairobi's requirements.
3. I have not sought or used the services of any professional agencies to produce this work.
4. I have not allowed, and shall not allow anyone to copy my work with the intention of passing it off as his/her own work.
5. I understand that any false claim in respect of this work shall result in disciplinary action, in accordance with the University anti-Plagiarism Policy.

Nancy Jebet Koech 

U51/12212/2018

## DEDICATION

I dedicate this work to my late sister Cynthia Jeruto, whom I lost to colon cancer. I did this for you and for the betterment of patients battling with colon cancer in Kenya.

## ACKNOWLEGDEMENTS

I thank the Almighty God for giving me knowledge and strength through the course of this study. I am grateful to my research supervisors: Prof. Faith Okalebo, Dr. Elizabeth Owiti and Dr. David Wata for the support, guidance, advice and mentorship throughout this study.

I acknowledge the encouragement and support I received from my parents Joel Koech and Leah Koech and my siblings. I am grateful to my colleagues and friends who have been supportive in this journey.

# TABLE OF CONTENTS

DECLARATION ..... i
DECLARATION OF ORIGINALITY ..... ii
DEDICATION ..... iii
ACKNOWLEGDEMENTS ..... iv
TABLE OF CONTENTS ..... v
LIST OF TABLES ..... viii
LIST OF FIGURES ..... ix
LIST OF EQUATIONS ..... ix
ABSTRACT ..... x
LIST OF ABBREVIATIONS AND ACRONYMS ..... xiii
OPERATIONAL DEFINITIONS ..... iiiv
CHAPTER ONE: INTRODUCTION ..... 1
1.1 Background ..... 1
1.2 Study problem ..... 4
1.3 Research question ..... 5
1.4 Objectives ..... 6
1.4.1 Main objective ..... 6
1.4.2 Specific objective ..... 6
1.5 Study justification ..... 6
CHAPTER TWO: LITERATURE REVIEW ..... 8
2.1 Epidemiology of colorectal cancer ..... 8
2.2 Diagnosis and staging of colorectal cancer ..... 9
2. 3 Management of colorectal cancer ..... 11
2.3.1 Principles of Management of Colorectal Cancer ..... 11
2.3.2 Regimens used for the management of colorectal cancer ..... 13
2.3.3 Pharmacology of 5-Fluorouracil and Capecitabine ..... 15
2.4 Efficacy of FOLFOX and XELOX ..... 16
2.5 Safety profile of FOLFOX and XELOX ..... 18

2.6 Colorectal cancer in Kenya ..... 19
2.7 Cost of managing colorectal cancer ..... 21
2.8 Cost effectiveness studies of chemotherapeutic agents used in colorectal cancer ..... 23
2.9 Theoritical and conceptual framework ..... 26
CHAPTER THREE: METHODS ..... 28
3.1 Review of patient records ..... 28
3.1.1 Study design, location and population. ..... 28
3.1.2 Eligibility criteria ..... 29
3.1.4 Sampling procedure and access of patient records ..... 30
3.1.5 Data collection ..... 30
3.1.6 Case definitions ..... 31
3.1.7 Data analysis ..... 32
3.2 Key informant interview ..... 33
3.2.1 Study design and site ..... 33
3.2.2 Sample size for the key informant interview ..... 33
3.2.3 Sampling and eligibility criteria ..... 33
3.2.4 Participant recruitment ..... 34
3.2.5 Data collection ..... 34
3.2.6 Data analysis for the costing data ..... 34
3.3 Cost utility analysis ..... 34
3.3.1 Study design ..... 34
3.3.2 Costing perspective ..... 35
3.3.3 Costing ..... 35
3.3.5 Comparator interventions ..... 36
3.3.6 Data on effectiveness ..... 37
3.3.9 Computation of incremental cost effectiveness ratio (ICER) ..... 37
3.3.10 Modelling ..... 38
3.3.11 Sensitivity analysis ..... 39
3.4 Budget impact analysis ..... 39
3.5 Quality assurance ..... 41
3.6 Data management ..... 41

3.7 Ethical considerations ..... 41
CHAPTER FOUR: RESULTS ..... 43
4.1 Participant recruitment ..... 43
4.2 Characteristics of the study population ..... 44
4.2 The clinical characteristics of the participants in the study population ..... 45
4.3 Therapeutic approaches for management of colorectal cancer ..... 46
**4.4 Comparative analysis of socio-demographic and clinical characteristics of colorectal cancer patients on Fluorouracil and Capecitabine based regimens in KNH** ..... 47
4.5 The predictors of prescribing a given chemotherapeutic regimen ..... 48
4.6 The side effects of the chemotherapeutic regimens ..... 50
4.7 Association between chemotherapy and side effects ..... 50
4.8 The clinical outcomes of the chemotherapeutic regimens ..... 51
4.9 Median survival period ..... 52
4.10 Association between chemotherapeutic regimen and clinical outcomes ..... 52
4.11 The risk factors for mortality in colorectal cancer patients ..... 53
4.12 The predictors for remission in colorectal cancer patients ..... 56
4.13 The predictors for recrudesce in colorectal cancer patients ..... 57
4.14 Cost categories obtained from key informant interviews ..... 59
4.15 Costing analysis of XELOX and FOLFOX ..... 60
4.16 Cost utility analysis of FOLFOX versus XELOX regimens ..... 60
4.17 One way and probabilistic sensitivity analysis for the incremental cost effectiveness of FOLFOX and XELOX ..... 61
4.18 Budget impact analysis ..... 64
CHAPTER FIVE: DISCUSSION, CONCLUSION AND RECOMMENDATIONS ..... 67
5.1 Discussion ..... 67
5.2 Implications for policy ..... 71
5.3 Study Limitations ..... 71
5.4 Conclusion ..... 72
5.5 Recommendations ..... 73
REFERENCES ..... 74
APPENDICES ..... 82

## LIST OF TABLES

Table 2. 1 Stages of colorectal cancer ..... 10
Table 2. 2 NCCN guidelines for the management of Colon cancer ..... 12
Table 2. 3 Adjuvant chemotherapy regimens and their administration ..... 14
Table 2. 4 Findings from RCTs on the efficacy of FOLFOX and XELOX ..... 17
Table 2. 5 Incidence of the major adverse events induced by chemotherapy regimens in management of colorectal cancer..... 19
Table 2. 6 Summary of colorectal cancer findings in Kenya..... 21
Table 2. 7 The findings of cost effectiveness studies of FOLFOX and XELOX ..... 25

Table 3. 1 Health related quality of life of colorectal cancer states 37

Table 3. 2 Input parameters used in the model ..... 40

Table 4. 1 The socio-demographic characteristics of the study population 44

Table 4. 2 The clinical characteristics of the patients in the study population ..... 45
Table 4. 3 Therapeutic approaches for management of colorectal cancer..... 46
Table 4. 4 Comparative analysis of socio-demographic of colorectal cancer patients on Fluorouracil and Capecitabine based regimens in KNH..... 47
Table 4. 5 Comparative analysis of the clinical characteristics of colorectal cancer patients on Fluorouracil and Capecitabine based regimens in KNH..... 48
Table 4. 6 Summary of logistic regression for the predictors of prescribing capecitabine ..... 49
Table 4. 7 Association between chemotherapy and side effects..... 51
Table 4. 8 Median survival period by chemotherapeutic regimen..... 52
Table 4. 9Association between chemotherapeutic regimen and clinical outcomes for early stage disease ..... 53
Table 4. 10 The Cox proportional regression model for risk factors of mortality in the entire cohort ..... 54
Table 4. 11 The crude Cox proportional regression model for risk factors mortality stratified by disease stage..... 55
Table 4. 12 Adjusted Cox proportional regression model for risk factors for mortality stratified by disease stage..... 55
Table 4. 13 The logistic regression model for remission stratified by disease stage..... 57
Table 4. 14 Propensity adjusted logistic regression model for remission stratified by disease stage ..... 57
Table 4. 15 Logistic regression model for recrudesce stratified by disease stage ..... 58

Table 4. 16 Base case cost and ranges for the cost parameters..... 59
Table 4. 17 Results of the cost utility analysis of FOLFOX versus XELOX..... 61
Table 4. 18 Budget impact results for XELOX vs FOLFOX ..... 64

## LIST OF FIGURES

Figure 1. 1 Region-Specific Incidence Age-Standardized Rates by Sex for colon cancer in 2018.9

Figure 2. 1 Region-Specific Incidence Age-Standardized Rates by Sex for colon cancer in 2018.9
Figure 2. 2 Conceptual framework of the direct costs for the management of colorectal cancer 27

Figure 3. 1 The transition matrix of a stage II or III CRC patient on FOLFOX..... 38

Figure 4. 1 Side effects experienced by patients on chemotherapy..... 50
Figure 4. 2 Clinical outcomes of chemotherapeutic regimens..... 51
Figure 4. 3 Comparison of Kaplan-Meier survival curves by chemotherapy type..... 56
Figure 4. 4 Tornado diagram showing the most sensitive variables to the ICER..... 62
Figure 4. 5 The cost-effectiveness plane of FOLFOX and XELOX ..... 63
Figure 4. 6 The cost-effectiveness acceptability curve of FOLFOX and XELOX..... 64

## LIST OF EQUATIONS

Equation 2.1 Transition probabilities formula..... 26
Equation 3.1 Conchrane formula for sample size computation..... 29
Equation 3.2 Computation of personnel costs ..... 36
Equation 3.3 Formula for computing the incremental cost effectiveness ratio (Paulden, 2020).. 37

# ABSTRACT

## Background

Colorectal cancer (CRC) is the third most common cancer globally and it is the fourth leading cause of cancer-related mortality. Management of CRC has progressively improved over the years, with a number of treatment options available. The cost of managing CRC poses a financial burden to the patients and the society due to the high costs involved. Cost effectiveness studies for capecitabine based and 5-fluorouracil based regimens have been conducted in other parts of the world, however applicability of this data in Africa is limited given the variation in economic status, treatment patterns and advances in technology. In Kenya, Kenyatta National Hospital as the largest national referral hospital and serves a high number of cancer patients with a challenge of limited bed capacity. In addition, the National Hospital Insurance Fund covers only part of the oncology care for cancer patients. Therefore, it is important to establish the most cost-effective regimen for the management of CRC.

## Objectives

The main objective of the study was to compare the cost effectiveness of 5-fluorouracil and capecitabine based regimens for management of colorectal cancer in Kenyatta National Hospital. In addition, a budget impact analysis of the adoption of capecitabine based regimen was conducted.

## Methods

A mixed study design was used. The study was divided into four parts. The first part was a descriptive cross sectional study that was conducted in the oncology wards at Kenyatta National Hospital to establish the cost of managing colorectal cancer and its complications. For this study, the study population was patients diagnosed with colorectal cancer and admitted in Kenyatta National hospital between January 2014 and December 2019.

The second part of the study was a key informant interview that was carried out amongst the administrative officers in charge of billing and procurement to collect information on cost of procuring drugs and other resources used for management of colorectal and its complications.

The third part of the study was a cost utility analysis which is one of the four designs accepted in Pharmacoeconomics. A markov decision model was developed using a theoretical cohort of colorectal cancer patients. Markov modelling was done to estimate long-term costs and benefits of 5-Fluorouracil compared to capecitabine based regimens for the management of colorectal cancer. The study was conducted from a provider perspective with a time horizon of 5 years. Effectiveness data was derived from literature. Lastly a budget impact analysis was conducted to assess the cost impact of the adoption of capecitabine based regimen on the budget at Kenyatta National Hospital.

Descriptive and exploratory data analysis was performed using STATA version 13 software; for data obtained from retrospective review of patients' files and chart review. The level of significance was set at 0.05. The quantitative data on costs was tabulated and summarized in MS Excel spreadsheet. The R version 3.6.0, "*heemod*" package was used for costing, probabilistic and sensitivity analysis.

**Results**

The demographic and clinical characteristics of the participants showed that, majority of the participants were male (55.4%) and the elderly (>55years) (51.0%). Most participants were diagnosed with late stage disease (62.3%). Majority of the patients were on 5-FU regimens (67.2%). Neutropenia was the most common occurring side effect. Metastasis was the most common outcome (28.9%) while mortality was at 24.1%. The determinants for prescribing capecitabine regimen were presence of metastasis, patients who received radiotherapy and those who underwent any chemotherapy switch ($p<0.001$).

FOLFOX was the most expensive regimen(Ksh. 577,270) compared to XELOX (Ksh.207,486). XELOX was found to be the most cost effective regimen with an incremental cost effectiveness ratio (ICER) of Ksh.-38632.74 per quality adjusted life years (QALY) gained. The ICER was negative for XELOX due to the lower cost and more QALY gained.

The results show that the use of XELOX for managing colorectal cancer is cost saving each year. The impact of adopting XELOX on the KNH annual budget and medicines budget over 5 years ranged between 2.27% to 2.90%.

## Conclusion

FOLFOX is the mainstay therapy for CRC management in KNH; it is however more expensive compared to XELOX. XELOX is the most cost effective regimen as compared to FOLFOX from the provider perspective and should be considered as a drug of choice in the management of colorectal cancer in Kenya.

## LIST OF ABBREVIATIONS AND ACRONYMS

| | |
|---|---|
| 5FU | 5-Fluorouracil |
| CER | Cost Effectiveness Ratio |
| CRC | Colorectal cancer |
| DFS | Disease Free Survival |
| FA | Folinic Acid |
| FOLFIRI | 5-Fluorouracil, Folinic acid and Irinotecan |
| FOLFOX | 5-Fluorouracil, Folinic acid and Oxaliplatin |
| ICER | Incremental Cost Effectiveness Ratio |
| KNH | Kenyatta National Hospital |
| NHIF | National Health Insurance Fund |
| OS | Overall Survival |
| PFS | Progression Free Survival |
| QALYs | Quality adjusted life years |
| XELOX | Capecitabine and Oxaliplatin |
| XELIRI | Capecitabine and Irinotecan |
| ESMO | European Society for Medical Oncology |
| AJCC | American Joint Committee on Cancer |
| AUCC | International Union Against Cancer |

## OPERATIONAL DEFINITIONS

| | |
|---|---|
| Adjuvant chemotherapy | Therapy administered postoperatively to eliminate microscopic metastases and increase the chance of long-term disease-free survival and cure |
| Average cost effectiveness ratio | Ratio of the cost to benefit of an intervention without reference to a comparator |
| Budget Impact Analysis an economic | Assessment that estimates the financial consequences of adopting a new intervention. |
| Disability adjusted life years | The measure of the overall disease burden, expressed in the number of years lost due to ill health, disability or early death |
| Disease free survival | The length of time after primary treatment for a cancer ends that the patient survives without any signs or symptoms of that cancer |
| Hazard ratio | A measure of how often a particular event happens in one group compared to how often it happens in another group, over time |
| Incremental cost effectiveness ratio | the ratio of the difference in costs to the difference in effectiveness between two interventions |
| Overall survival | The length of time from either the date of diagnosis or the start of treatment for a disease, such as cancer, that patients diagnosed with the disease are still alive |

| | |
|---|---|
| Progression free survival | The length of time during and after the treatment of a disease, such as cancer, that a patient lives with the disease but it does not get worse |
| Time horizon | The length of time over which costs and clinical outcomes are evaluate |

# CHAPTER ONE: INTRODUCTION

## 1.1 Background

Colorectal cancer (CRC) is the third most common cancer globally and is the fourth leading cause of cancer-related deaths. According to World Health Organization 2018 Statistics, colorectal cancer accounts for 1.8 million new cases and almost 861,000 deaths. However, the incidence and mortality has been increasing in low and middle income countries while it is decreasing in high income countries (Arnold et al., 2017). In Sub-Saharan Africa colorectal cancer is the fifth most common cancer (Olaleye and Ekrikpo, 2017). GLOBOCAN 2018 reported the incidence of CRC in Kenya is 9.3 per 100,000 in 2018. A study done in Kenya between 2004 and 2017 indicates the incidence of CRC has increased over the years (Parker et al., 2018). The increase in the number of cases of colorectal cancer is attributed to the risk factors such as smoking, heavy alcohol intake, fatty diet with low fiber intake, genetic factors, age, sex and the lack of physical activity (Granados-Romero et al., 2017).

The management of colorectal cancer has progressively improved over the years and it involves surgical resection, chemotherapy and radiotherapy. The Global Action Plan for the Prevention and Control of non-communicable diseases (NCDs) 2013–2020, recommends surgery with or without chemotherapy and radiotherapy for the treatment of colorectal cancer stages I and II (Ralaidovy et al., 2018). The chemotherapeutic regimen available for management of colorectal cancer include the 5-fluorouracil based regimens, FOLFOX (5FU+folinic acid + oxaliplatin) or FOLFIRI (5FU+ folinic acid+ irinotecan); and the capecitabine based regimen XELOX (capecitabine+ oxaliplatin) or XELIRI (capecitabine+irinotecan). In Kenyatta National Hospital (KNH), both the 5-fluorouracil based regimen (FOLFOX) and the capecitabine based regimen (XELOX) are used. These regimens significantly improve the overall survival of colorectal cancer patients (Shiroiwa et al., 2009).

Management of colorectal cancer poses a public health and socioeconomic burden to the patient, health care system and the society due to the high costs of treatment, productivity losses, morbidity and mortality. The economic burden of CRC and its management is determined by both demand and supply side factors. Demand factors are mainly patient characteristics including socioeconomic status (wealth, ability to pay and the level of education), patient age, the health seeking behavior such as presentation for screening and diagnosis and the choice of oncologic therapy. Cancer treatment takes time, in addition to treatment costs; patients incur travel costs (from various parts of the country to Nairobi) and accommodation costs during the treatment period. The supply factors on the other hand include availability of skilled human resource for health, diagnostic commodities and equipment and treatment commodities. The main costs components of cancer management include the medicines, medical procedures and diagnosis, cost of hospitalization and outpatient clinic visits (Stefan, 2015). Misdiagnosis is a major problem that results in diagnosis of the disease in advanced stage as cancer screening is not done routinely in Kenya. This often results increased costs of treatment and chance of patients dying, thus leading to loss of productivity for both the patient and the caregivers. In Kenya, the cost of care and management of cancer is covered partly by the National Hospital Insurance Fund (NHIF), private insurance and by the patients' out-of-pocket payment. Patients suffer from both the direct costs and the indirect costs of managing CRC which renders them and their families bankrupt (Vanderpuye, 2014). The misdiagnosis, distance to hospital and ability to pay lead to delays in seeking medical care, noncompliance and poor clinical outcomes (Vanderpuye, 2014). These increases inequality in access to cancer treatment among the poor and derails the Government of Kenya's vision of universal health coverage and achieving Sustainable Development Goal (SDG) 3 of leaving no one behind.

Economic evaluation of any health intervention is vital due to resource constrains, competing interest within the health sector, opportunity cost of offering various health interventions, need for prioritization and value for money considerations.

Cost effectiveness studies for management of cancers are important as they help the physicians choose the most cost-effective regimen for management of the patient. Analysis of the Surveillance, Epidemiology and End Results (SEER) database shows that breast, colorectal,

lymphoma, lung, and prostate cancers are the most expensive cancers in terms of total healthcare cost (Mariotto et al., 2011).

Quality adjusted life year (QALY) is a measurement tool for health effectiveness used by decision makers to set priorities for competing healthcare interventions or programs. QALY is obtained by multiplying the duration spent in a given health state by the health related quality of life (HRQoL) associated with the health state. Various studies and systematic reviews have been conducted to obtain the HRQoL of the different health states of colorectal cancer (Lee et al., 2017).

Randomized control studies conducted using XELOX and FOLFOX indicated that both have similar efficacy as well as the overall survival rates (Cassidy et al., 2011). The adverse events are similar other than XELOX causing hand-foot syndrome and grade 3 diarrhea, whereas FOLFOX causes neutropenia (Cassidy et al., 2011).

Cost effectiveness studies done on the management of CRC in other parts of the world show that the capecitabine based regimen (XELOX) was more cost effective compared to 5-fluorouracil based regimen (FOLFOX) which was found to be more costly (Shiroiwa et al., 2009; Płaczek et al., 2017). The application of these studies in Africa is limited given the difference in economic status, variation in treatment patterns and advances in technology.

In high income countries chemo ports and infusion pumps have been adopted for administration of the intravenous FOLFOX regimen. This is of great importance as the patients do not require admission but the regimen can be administered continuously and does not interfere with the patient's activities. This is a challenge in low-middle income countries because of the high costs of the chemo ports and infusion pumps. This therefore necessitates the need for admission of patients in order to administer the FOLFOX regimen; hence the increased costs of admission as well as the challenge of high patient numbers and limited bed capacity.

In Kenya, the increasing burden of non-communicable diseases including cancers and socioeconomic inequalities in access to health services made the Government of Kenya to put in place legislation and policies that guide health service provision to the citizens. Some of the major health related policies includes the constitution.

The Constitution of Kenya 2010 emphasizes the right to socioeconomic rights including right to health, hence even cancer patients have a right to health. The Government of Kenya has put in place the National Guidelines for the Management of Cancers 2013 and the National Cancer control strategy 2017-2022.

Among the Government's Big 4 Agenda is Universal health coverage (UHC); which aims to improve access to quality health care for all including cancer patients without catastrophic health expenditure. Thus the need to review the package for cancer patients by increasing NHIF coverage to reduce catastrophic health expenditure.

The Government of Kenya adopted of global health policies including Sustainable Development Goals (SGDs). Among the goals of SGD 3 on ensuring healthy lives and promoting well-being for all are; reduce premature mortality due to NCDs, achieving universal health coverage including financial risk protection and increase healthcare financing. The Government of Kenya therefore has the mandate of promoting and providing affordable health care services for cancer patients in order to reduce mortalities due to cancer. This study intends to assess the cost effectiveness of chemotherapeutic regimens (5-fluorouracil and capecitabine based) for the management of colorectal cancer in Kenya.

### 1.2 Study problem

There has been a rise in the incidence and mortality of non-communicable diseases in Africa. Of the global cancer mortalities, low- and middle-income countries including Africa accounts for 65% of the cancer mortalities and 75% of premature deaths due to cancer (Dent et al., 2017). Colorectal cancer is highly prevalent in Kenya, with an age standardized incidence rate (ASR) of 9.3 per 100,000 in 2018 according to GLOBOCAN. The alarming increase in the prevalence of CRC necessitates the need for more resources and getting the right treatment interventions. Given the resource constraints and competing interests there is need for prioritization. Currently CRC is being managed using two regimens, 5-fluorouracil based (FOLFOX) and capecitabine based (XELOX) regimen at Kenyatta National Hospital in Kenya. The capecitabine based regimen (XELOX) is an oral treatment, given in an outpatient clinic; no admission is required. FOLFOX on the other hand is given as an intravenous infusion in an inpatient setting. There is

need to assess the impact of hospitalization costs on the overall assessment of the cost effectiveness of the two regimens in the local context.

Clinical trial evidence shows that the two regimens are equally effective (Schmoll et al., 2015). There has been no comparative cost utility analysis that compares the two regimens in Africa. Therefore, there is lack of evidence on cost-effectiveness to support adoption of capecitabine based regimen for routine management of colorectal cancer in Africa and in Kenya.

Failure to adopt capecitabine based regimen as first line therapy has probably led to unnecessary hospitalization and the resultant increase in costs. The delays in treatment due to long waiting time by patients to receive treatment given the limited bed capacity and the high number of patients seeking treatment at KNH. The delays leads to poor outcomes including advanced disease stage hence increased cost of treatment and risk of mortality. This study seeks to compare the costs and benefits of fluorouracil (FOLFOX) and capecitabine based (XELOX) regimens. The findings of the study will inform the formulary committee on the optimal regimen that minimizes cost and maintains good health outcomes.

### 1.3 Research question

The research questions were:

1. What are the clinical characteristics and outcomes of CRC patients on 5-fluorouracil (5FU) and capecitabine based regimens at KNH?
2. What is the difference in the cost of managing colorectal cancer with 5-fluorouracil (5FU) compared to capecitabine based regimens at KNH?
3. Which is the most cost-effective intervention?
4. What is the budget impact of adopting the most cost effective intervention?

## 1.4 Objectives

### 1.4.1 Main objective

The main objective of the study was to assess the cost effectiveness of 5-fluorouracil based regimens against capecitabine based regimens for the management of colorectal cancer in Kenyatta National Hospital.

### 1.4.2 Specific objective

The specific objectives of this study were to:

1. compare the clinical effectiveness of 5-fluorouracil (5FU) and to capecitabine based regimens at KNH
2. estimate the cost of 5-fluorouracil and capecitabine based regimens in the management of colorectal cancer at KNH
3. identify the most cost effective regimens
4. conduct a budget impact analysis of the adoption of capecitabine based regimen.

## 1.5 Study justification

The study sought to provide evidence of the cost implications of using the two regimens and to support decision making process by clinicians and policy makers. The findings of this study will inform future policies on the decision of the best right treatment option managing colorectal cancer in the Kenya. Given the low socio-economic status of the patients and the limited bed capacity, the findings of this study are critical. The patients will benefit from the results of this study as they will be treated with a regimen that is cost effective thus reducing the out-of-pocket expenditure and catastrophic health expenditure to the household. In addition, it will ensure availability of information to the patients hence promoting patient centered approach as the patients will be aware of the alternative chemotherapy available. The Government of Kenya

through the Ministry of Health and NHIF may use the results of the study to review the healthcare financing for oncology treatment and setting levels of NHIF reimbursements.

# CHAPTER TWO: LITERATURE REVIEW

## 2.1 Epidemiology of colorectal cancer

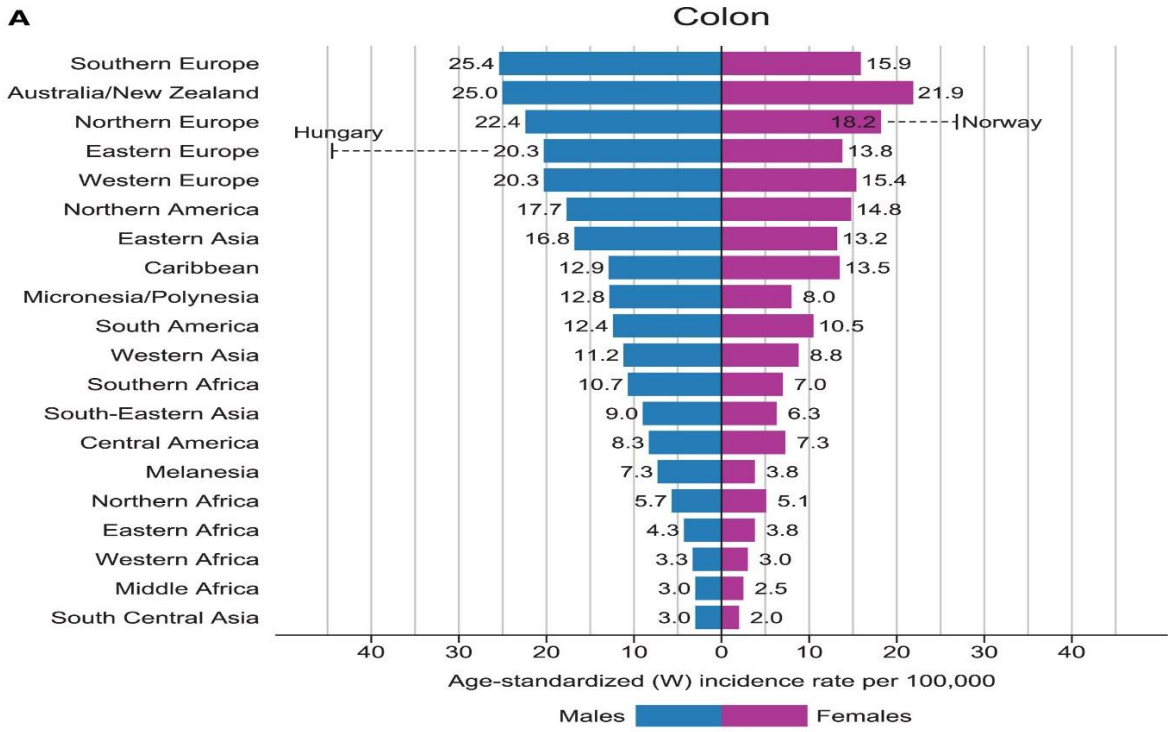
There is a global rise in the incidence and mortality of cancer. GLOBOCAN 2018 statistics indicates that colorectal cancer is the fourth most common cancer worldwide with an incidence of 1.8 million (10.2%) and mortality of 881000 (9.2%) of all cancers reported (Bray et al., 2018). Studies have shown that countries undergoing rapid economic and societal change have a high incidence of CRC. Colorectal cancer is frequently observed in high and middle income countries as opposed to low and income countries (Arnold et al., 2017) . Figure 2.1 presents the incidence rates in selected countries.

However, this observation may be attributed to the limited epidemiological data available in Sub-Saharan Africa; hence the perception that colorectal cancer is rare in low income countries (Katsidzira et al., 2017). The GLOBOCAN 2018 report estimates the annual new cases of CRC in Eastern Africa is 17,125 with a mortality of 12,201. The incidence by sex is 780,000 in males and 770,000 in females (Bray et al., 2018). A systematic analysis conducted in Sub-Saharan Africa (SSA), showed a higher incidence of CRC among males as compared to females with a peak at above 75 years of age (Graham et al., 2012a).

Globally the incidence and mortality rates of CRC vary widely across human development index. This is attributed to the risk factors for CRC in the different socioeconomic status. The modifiable risk factors for CRC include obesity, alcohol consumption, smoking, lack of physical activity and poor diet (high consumption of processed food, red meats and low consumption of food rich in fiber) (Kolligs, 2016; Arnold et al., 2017) . The non-modifiable risk factors for CRC include advanced age (>50 years), colorectal polyps, family history of colorectal cancer, familial adenomatous polyposis (FAP), inflammatory bowel disease and hereditary non-polyposis colorectal cancer (Schaeybroeck; Peterson, 2015).

The primary preventive strategy for CRC involves increased consumption of whole grains and fruits and vegetables, increased physical activity, and weight reduction. To detect CRC at early stages, reduced treatment costs and risk of premature mortality, screening for colorectal cancer is

recommended (Stintzing, 2014 ; Laiyemo et al., 2016). According to the Cancer Statistics 2018, Countries that adopted the screening programs detects CRC at earlier stages (Cancer Statistics 2018). However, the screening programs should be accompanied by treatment plans for patients diagnosed with CRC.




Source: GLOBOCAN 2018

***Figure 2. 1 Region-Specific Incidence Age-Standardized Rates by Sex for colon cancer in 2018.***

**2.2 Diagnosis and staging of colorectal cancer**

Colorectal cancer develops gradually and the importance of screening is underestimated. The symptoms include altered bowel habits, blood per rectum, fatigue, anemia, weight loss and obstruction. Liver metastases are common and usually occur in 5% of patients with CRC. The imaging tools available for staging CRC are magnetic resonance imaging, computed tomography scan and positron emission tomography. Intraoperative ultrasound is a sensitive method for evaluating liver metastases. The stage of colorectal cancer can be determined either clinically, microscopically or pathologically. Surgical resection specimen is used to determine the local

extent of the disease using the pathological staging information. This information is used to determine the appropriateness of the postoperative adjuvant chemotherapy. In addition, pathologic staging in colon and rectal cancer aids in understanding the spectrum of disease presentation, treatment interventions, and outcomes in clinical trials ( Compton and Greene, 2004; Gress et al., 2017).

The stage of disease is determines prognosis, survival and the treatment of the patient (Kolligs, 2016b). Colorectal cancer classification is based on tumor invasion, local invasion depth (T), the lymph node involvement (N) and the presence of distant metastases (M). Table 2.1 gives the staging of colorectal cancer according to American Joint Committee on Cancer (AJCC) and International Union Against Cancer (UICC) (Amin et al., 2017b).

***Table 2. 1 Stages of colorectal cancer***

| Stage | Sub-stage | Tumor invasion depth | Lymph node involvement | Metastasis |
|---|---|---|---|---|
| **0** | - | Tis (*in situ*) | None | None |
| **I** | - | T1-2 (submucosa to muscularis propria) | None | None |
| **II** | A | 3 (muscularis propria) | None | None |
| | B | 4a (visceral peritoneum) | | |
| | C | 4b (adhering to other organs) | | |
| **III** | A | 1-2 (submucosa to muscularis propria) | N1/N1c (1-3 nodes) | None |
| | | 1 (*in situ*) | N2a (4-6 nodes) | |
| | B | 3-4a (muscularis propria and visceral peritoneum) | NI/N1c (1-3 nodes) | |
| | | 2-3 (muscularis propria to the colorectal fat tissue | N2a (4-6 nodes) | |
| | | 1-2 (submucosa to muscularis propria) | N2b (≥ 7 nodes) | |
| | C | 4a (visceral peritoneum) | N2a (4-6 nodes) | |
| | | 3-4a (muscularis propria to visceral peritoneum) | N2b (≥ 7 nodes) | |
| | | 4b (adhering to other organs) | N1-2 (1-7 nodes) | |
| **IV** | A | Any T | Any N | M1a (metastases to one organ) |
| | B | | | M1b (more than one organ) |
| | C | | | M1c (peritoneal metastases) |

**T-tumor stage, N-nodal stage, M-metastasis**
**Source: (Amin et al., 2017; Compton and Greene, 2004).**

The tumor, node, metastasis (TNM) staging system of the International Union Against Cancer (UICC) and the American Joint Committee on Cancer (AJCC) is the standard for colorectal cancer staging in the latest 8th edition of the cancer staging manual (Amin et al., 2017; Compton and Greene, 2004).

## 2. 3 Management of colorectal cancer

### 2.3.1 Principles of Management of Colorectal Cancer

Management of colorectal cancer is complex and it depends on histopathological results obtained following surgical inspection and determining the spread of the tumor. The stage of the cancer, the patient's performance status and the molecular makeup of the tumor determines the choice of treatment for the management colorectal cancer.

The treatment options include surgery, chemotherapy, targeted therapy, immunotherapy and radiation therapy. According to the NCCN guidelines, for early stage CRC (stage 0 or stage I), the treatment of choice is surgery with no additional treatment. Patients in stage IIA and IIB may undergo surgical resection followed by close observation or receive adjuvant chemotherapy. Stage III patients undergo surgery followed by adjuvant chemotherapy. The patients are then followed up for over five years from the initial treatment to assess for recurrence of the cancer and to determine the overall survival ((Venook, 2019).

Stage IV disease presents with metastases and hence its treatment is complex and is based on the metastases location and resectability. Neoadjuvant chemotherapy is administered first followed by colonoscopy and resection of the metastases; adjuvant chemotherapy is administered and the metastatic disease resected. Patients with advanced unresectable primary tumor undergo palliative care (Venook, 2019). Table 2.2 is a summary of the NCCN treatment guidelines for colon cancer.

*Table 2. 2 NCCN guidelines for the management of Colon cancer*

**Stage I**

Surgical resection

**Stage II**

1) Low risk; surgical resection
2) High risk; surgical resection plus adjuvant chemotherapy (CAPEOX or FOLFOX; Other options include: Capecitabine or 5-FU/LV)

**Stage III**

1) Surgical resection
2) Adjuvant therapy as follows:

Low risk; CAPEOX (3 months) or FOLFOX (3–6 months) Other options include: Capecitabine (6 months) or 5-FU (6 months)

High risk; CAPEOX (3–6 months) or FOLFOX (6 months) and other options include Capecitabine (6 months) or 5-FU (6 months).

**Stage IV**

**a) Resectable disease**

Staged colectomy with lung or liver resection and/or local therapy or Neoadjuvant therapy (for 2–3 months) CAPEOX or FOLFOX or FOLFIRI followed by synchronous colectomy and resection of metastases or Colectomy, followed by chemotherapy and staged resection of metastatic disease.

Adjuvant therapy; FOLFOX or CAPEOX or 5-FU/leucovorin or Capecitabine (total 6months perioperative treatment preferred)

**b) Unresectable disease**

Primary treatment; (FOLFIRI or irinotecan) ± (bevacizumab or ziv-afliberceptor ramucirumab) or (FOLFIRI or irinotecan) ± (cetuximab or panitumumab) or ([Nivolumab ± ipilimumab] or pembrolizumab) or (Irinotecan + [cetuximab or panitumumab] + vemurafenib The disease is then evaluated every two months if it remains unresectable systemic therapy is continued; if resectable consider adjuvant therapy. Six months preoperative treatment is preferred. After resection continue with systemic therapy with or without biologic therapy.

**Source:( "Colon_Cancer_rev0819.pdf," n.d.) (Venook, 2019)**

### 2.3.2 Regimens used for the management of colorectal cancer

There are several chemotherapeutic regimens available for treatment of colon and rectal cancer. The common agents used in combination include; fluorouracil/leucovorin, capecitabine, oxaliplatin, irinotecan, and bevacizumab. The combinations available are include the capecitabine based, capecitabine plus oxaliplatin (XELOX), capecitabine plus irinotecan (XELIRI) and capecitabine plus oxaliplatin with bevacizumab. The 5-FU based combinations include fluorouracil with leucovorin (5-FU/LV), 5-FU/LV plus oxaliplatin (FOLFOX), fluorouracil/leucovorin plus irinotecan (FOLFIRI), 5-FU/LV with bevacizumab and 5-FU/LV plus irinotecan with bevacizumab (Geng et al., 2017).

Recently targeted agents have been incorporated in the management of metastatic CRC. These agents include; antiangiogenic (VEGF) inhibitors such as aflibercept, bevacizumab, regorafenib and ramucirumab: Epithelial growth factor receptor (EGFR) inhibitors include cetuximab and panitumumab (Geng et al., 2017).

Adjuvant chemotherapy is administered to destroy any residual microscopic metastatic disease after surgical resection and to reduce tumor recurrence. These regimens and their administration protocols are summarized in Table 2.3.

*Table 2. 3 Adjuvant chemotherapy regimens and their administration*

| | |
|---|---|
| **5-Fluorouracil based regimens** | |
| **5-FU/leucovorin** | Leucovorin (LV) 500mg/m2 given as a 2-hour infusion and repeated weekly for 6 weeks, plus 500mg/m2 IV bolus of 5-FU administered 1 hour after the start of LV and repeated weekly for 6 weeks. The cycle is repeated every 8 weeks for 4 cycles. |
| **FOLFOX 4** | Day 1: 85 mg/m$^2$ IV Oxaliplatin over 2 hours plus 200 mg/m$^2$ IV LV as a 2 hours' infusion before 400 mg/m$^2$ IV bolus of 5FU, after which a 600 mg/m$^2$ IV continuous infusion is given over 22 hours on day 1 and 2. Repeat the cycle after every two weeks |
| **FOLFOX6** | Day 1: 85 mg/m$^2$ of IV Oxaliplatin, 400 mg/m$^2$ IV LV over 2 hours and 400 mg/m$^2$ IV bolus of 5FU after which 2400mg/m$^2$ IV continuous infusion of 5FU is administered for 46 hours on day 1 and 2. Repeat the cycle after every two weeks. |
| **FOLFIRI** | Irinotecan 180 mg/m$^2$ as a 90-min infusion on day 1 and LV 200 mg/m2 as a 2-h infusion during irinotecan, immediately followed by a bolus dose of 5-FU 400 mg/m$^2$ and a 46-h continuous infusion of 2,400 mg/m$^2$. |
| **Capecitabine based regimens** | |
| **Capecitabine** | Days 1–14: Capecitabine 1,000-1,250mg/m2 orally twice daily. Repeat cycle every 3 weeks for 24 weeks. |
| **CapeOx/XELOX** | Day 1: Oxaliplatin 130mg/m2 IV over 2 hours; for day 1–14: Capecitabine 1,000mg/m$^2$ orally twice daily. Repeat cycle every 3 weeks for 24 weeks. |
| **XELIRI** | Day 1:250 mg/m$^2$ of Irinotecan then capecitabine 1000 mg/m$^2$ twice daily from day 2-15, every 21 days. |

**Source:( "Colon_Cancer_rev0819.pdf," n.d.) (Venook, 2019)**

### 2.3.3 Pharmacology of 5-Fluorouracil and Capecitabine

Both 5-FU and capecitabine are fluoropyrimidines, they act by causing nucleotide pool imbalance and induce thymidylate deficiency thus leading to impaired DNA replication, transcription, repair and cell death (Derissen et al., 2016a).

Fluorouracil is a prototype of fluoropyrimidine (FP), which is administered intravenously and is activated intracellularly by ribosylation and sequential phosphorylation. Three fluorinated nucleotides are formed and intergrated into the DNA, replacing thymidine leading to inhibition of DNA replication and cell death. The primary active metabolite, fluorodeoxyuridine monophosphate (FdUMP) inhibits thymidylate synthase (TS). TS inhibition prevents conversion of deoxyuridine monophosphate (dUMP) to deoxythymidine monophosphate (dTMP), consequently causing impaired DNA synthesis and arresting S phase of the cell cycle. Alternate enzymatic pathways leads to creation of 5-fluorouridine triphosphate (5-FUTP), 5-fluorodeoxy triphosphate (5-FdUTP) and other 5-FU metabolites; they form nucleotides that are taken up into the DNA and cause abnormal production of proteins and cell death (Derissen et al., 2016; Hammond et al., 2016).

Although 5FU infusion is administered intravenously, modern chemotherapy involves the use of implantable port systems and disposable infusion pumps which have been developed and have become widely acceptable. They are easy to handle, safe and are well-tolerated alternative to hospitalization for the infusion of chemotherapy (Inoue and Kusunoki, 2014). They are, however, used mainly in the high-income countries and have not been adopted widely in low income countries.

Capecitabine is an oral fluoropyrimidine carbamate that mimics continuous 5-FU infusion and undergoes metabolic conversion in vivo to yield fluorouracil by thymidylate phosphorylase (TP), cytidine deaminase and carboxylesterase which are found in high concentrations in tumor cells. Hence activation occurs at the tumor site (Derissen et al., 2016b). Though orally administered, it functions similarly to 5-FU infusion; a consistent amount of drug is administered to cancer cells over time (Hammond et al., 2016). Since it is given orally, it does not require intravenous drug preparation and administration and associated clinic visits and admission. It is used in

combination with other therapeutic agents in management of colorectal, gastric and breast cancer.

### 2.4 Efficacy of FOLFOX and XELOX

Fluoropyrimidines are the mainstay chemotherapy for both early and advanced CRC. The use of XELOX and FOLFOX in adjuvant and metastatic colorectal cancer chemotherapy have showed no statistically significance difference in the overall survival (OS) and the progression free survival (PFS) (Crawford et al., 2017).

In a meta-analysis to assess the risk of recurrence of colon cancer on adjuvant chemotherapy; the five-year disease-free survival (DFS) for stage II patients who underwent surgery without adjuvant chemotherapy was 81.4% while for those on adjuvant chemotherapy, the five-year DFS was 79.3%. For stage III patients without chemotherapy, the DFS was 49.0% and for those treated adjuvant chemotherapy it was 63.6% (Böckelman et al., 2015a). These results showed decreased the risk of death by use of adjuvant chemotherapy.

Guo et al. in a meta-analysis of XELOX vs FOLFOX, found out that the difference in progression free survival, overall survival and overall response rate was not statistically significant ($p=0.63$,$p=0.56$ and $p=0.16$ respectively) (Guo et al., 2016a). Table 2.4 gives a summary of the efficacy data from the meta-analysis.

In an RCT to compare the adjuvant therapy for stage III colon cancer, XELOX caused a 20% reduction in the relative risk of any adverse event compared to FU/FA after 74 months follow up. The superior efficacy of XELOX was maintained after every year of follow-up (Schmoll et al., 2015). The relative risk of death was reduced by 13% in the XELOX group compared to FU/FA after 5 years follow up. For stage III colon cancer a 17% decrease in the relative risk of death was observed ($p=0.04$). The XELOX group had a longer relapse free survival (RFS) than the FU/FA group ($p= 0.002$) (Schmoll et al., 2015).

*Table 2. 4 Findings from RCTs on the efficacy of FOLFOX and XELOX*

| Study | Regimen | Sample size | Overall survival (OS)(months) | Progression free survival (PFS)(months) | Hazard ratio (95% CI) |
|---|---|---|---|---|---|
| **FOCA trial (Martoni et al., 2006)** | XELOX | 62 | NA | 9 | NA |
| | FOLFOX | 52 | | 7 | |
| **AIO trial (Porschen et al., 2007)** | XELOX | 241 | 16.8 | 7.1 | 1.12(0.92-1.38) |
| | FOLFOX | 233 | 18.8 | 8 | |
| **TTD study (Díaz-Rubio et al., 2007)** | XELOX | 171 | 18.1 | 8.9 | 1.22(0.90-1.60) |
| | FOLFOX | 171 | 20.8 | 9.5 | |
| **Comella et al., 2009** | XELOX | 158 | 16 | 4.9 | 1.01(0.74-1.38) |
| | FOLFOX | 164 | 17.1 | 4.7 | |
| **NO16966 trial (Cassidy et al., 2008** | XELOX | 1017 | 19.8 | 8 | 0.99(0.88-1.12) |
| | FOLFOX | 1017 | 19.6 | 8.5 | |
| **Rothenberg et al., 2008** | XELOX | 313 | 11.9 | 4.7 | 1.02(0.86-1.21) |
| | FOLFOX | 314 | 12.5 | 4.8 | |
| **Ducreux et al., 2011a** | XELOX | 156 | 19.9 | 8.9 | 1.02(0.81-1.30) |
| | FOLFOX | 150 | 20.5 | 9.3 | |

Ducreux et al., 2011 showed that XELOX is non-inferior compared to FOLFOX-6 as the first line treatment in the management of metastatic CRC (mCRC); the non-inferiority margin was 15%. The overall survival was 20.1 months for XELOX and 18.9 months for FOLFOX.

In a study in Chinese population, capecitabine showed high efficacy in patients with mCRC both as a single drug or in combination therapy. It was also well tolerated with few adverse effects (Xu et al., 2014).

**2.5 Safety profile of FOLFOX and XELOX**

The most common adverse effects associated with capecitabine include diarrhea, hand -and -foot syndrome, nausea, vomiting, stomatitis and fatigue (Lacovelli et al., 2014). FOLFOX on the other hand is associated with neutropenia, nausea, vomiting, diarrhea, fatigue, mucositis, abdominal pain and neuropathy (Schmoll et al., 2014a).

Generally, XELOX and FOLFOX show a similar profile of adverse events. The common toxicities include gastrointestinal (nausea, vomiting, diarrhea and stomatitis) and neurosensory toxicities (peripheral neuropathy and paresthesia) (Cassidy et al., 2011). Significant differences have been reported in the incidence of dose limiting toxicities ($p=0.006$), hand- foot syndrome ($p<0.0001$), diarrhea ($p<0.0001$) and thrombocytopenia ($p=0.0005$) with the use of XELOX as compared to FOLFOX (Guo et al., 2016a). Hand-foot syndrome is usually mild with symptoms of numbness, tingling, erythema, and discomfort of hands/feet; this may progress into a higher grade leading to ulceration, blistering, and severe pain of the hands/feet. Neutropenia and mucositis however show a higher incidence with the use of FOLFOX. The difference in the incidences of grade 3 and 4 toxicities, such as nausea, vomiting and anemia between the two regimens was not statistically significant (Loree et al., 2018a). However, Crawford found that there is no significant difference in the incidence of most of the adverse events between FOLFOX and XELOX, except a higher incidence of hand-foot syndrome in patients treated with XELOX ($p = 0.0007$).

Oxaliplatin in the two regimens is responsible for the increased incidence of peripheral neuropathy; this greatly affects the quality of life. Discontinuation of oxaliplatin is recommended after 3 months of therapy for patients who experience neurotoxicity (Guo et al., 2016a). Table 2.5 summarizes the incidences of adverse events of the chemotherapeutic regimens (Schmoll et al., 2014a).

***Table 2. 5 Incidence of the major adverse events induced by chemotherapy regimens in management of colorectal cancer***

| Regimen | Incidences of adverse events (%) | | | Study |
|---|---|---|---|---|
| | **Neutropenia** | **Grade 3 diarrhea** | **Hand and foot syndrome** | |
| XELOX | - | 17.0 | - | (Iacovelli et al., 2014) |
| FOLFOX | - | 12.9 | - | |
| XELOX | <1 | 20 | 31 | (J Cassidy et al., 2011a) |
| FOLFOX | 5 | 11 | 11 | |
| XELOX | 5 | 15 | 12 | (Schmoll et al., 2014a) |
| FOLFOX | 24 | 12 | <1 | |
| XELOX | 8.6 | 31.8[a] | 19.9 | (Loree et al., 2018b) |
| FOLFOX | 25.9 | 9.0[a] | 2.1 | |

**a- General diarrhea**

For XELOX, reducing the duration of adjuvant chemotherapy to 3 months prevents 26% of patients from ever experiencing a dose limiting toxicities (Loree et al., 2018a), and the dose reduction does not affect clinical outcomes (Mamo et al., 2016) and higher dose reduction of XELOX compared to FOLFOX enables treatment completion with fewer toxicities (Gao et al., 2013).

Capecitabine is taken orally while oxaliplatin is administered every 3 weeks; XELOX therefore requires fewer planned visits clinics than the FOLFOX regimens. Hence XELOX is more patient friendly compared to FOLFOX.

Though XELOX and FOLFOX exhibit similar curative effects, different patients respond and benefit differently from the treatments. For patients with anemia, bleeding tendency, gastrointestinal dysfunction; FOLFOX is recommended whereas those with diabetes, immuno-deficiencies, or old age are put on XELOX (Guo et al., 2016a).

## 2.6 Colorectal cancer in Kenya

The incidence of colorectal cancer in rural Kenya from increased from age-standardized rate of 2.0 per 100,000 for the 1998-2002 to 9.6 per 100,000 in 2013-2017 but the Nairobi Cancer Registry reported the incidence of CRC to be 12.9 per 100,000 in 2008-2012 (Parker et al.,

2019). The increased incidence is attributed to increase in the diagnostic facilities, improved health seeking behavior by patients, availability of specialist consultation services and life style changes (Parker et al., 2019). The age group that is largely affected by colorectal cancer in Kenya is 41-50 years with a prevalence of 25.9% while those below 40 years the prevalence is 17.6% (Saidi et al., 2011a). The study assessing the clinical outcomes of CRC showed a 37.5% overall survival of CRC and 29.4% mortality rate. The most commonly use chemotherapeutic regimens are FOLFOX at 29.2% and XELOX at 7.9% (Saidi et al., 2011a) Table 2.6 summarizes the data on CRC in Kenya.

Patients' perception on the management of CRC in KNH is influenced mainly by their social economic status, monthly income, the duration of diagnosis and the treatment modalities received. Inadequate bed space, chemotherapeutic drugs and radiotherapy machines are the major health care system factors affecting the attitude of patients towards treatment (Chitah et al., 2018).

The factors affecting access to cancer testing and treatment in Kenya include: high cost of testing and treatment, availability of specialized healthcare is limited, long distances to access diagnostic and treatment services, poor acceptability and uptake of oncology services, lack of decentralized diagnostic and treatment facilities and lack of better cancer policy development and implementation (Makau-Barasa et al., 2018).

In addition there is inequality in access to treatment by location of residence, socio economic status, age, level of education and formal employment status. Individuals residing in urban areas have high availability of modern healthcare amenities offering oncology services. Those with an average age, high level of education, formal employment and the rich have better access to oncology treatment both in the public and private facilities (Ilinca et al., 2019).

A study conducted to assess the direct cost of cancer treatment in Kenya showed that the cost of cancer therapy varied with the cancer type. The average cost of chemotherapy alone was KES 138,207 (USD 1364.3); surgery being KES 128,207 (1265.6), and radiotherapy KES 119,036 (1175.1). Patients who received a combination of all three spent KES 333,462 (3291.8) per patient during the year (Omondi et al., 2018).

*Table 2. 6 Summary of colorectal cancer findings in Kenya*

| Health state | Incidence | Reference | Timeframe |
|---|---|---|---|
| **Colorectal cancer** | 9.6/100,000 | (Parker et al., 2019) | 2013-2017 |
| | 12.9/100,000 | | 2008-2012 |
| **Recurrence** | 37.5% | | |
| **Mortality** | 29.4% | | |
| **Chemotherapeutic regimens** | | (Saidi et al., 2011a) | 15.9 months follow up (2005-2009) |
| **FOLFOX** | 29.2% | | |
| **XELOX** | 7.9% | | |
| **5FU/LV** | 52.2% | | |

The Government of Kenya through the NHIF and private insurance plays a critical role in financing healthcare including cancer care. NHIF as the national health payer in Kenya has provided an oncology cover package for its members. This includes; the radiotherapy cover that is capped at Ksh.70,000 for 20 session each at Ksh.3,500. Chemotherapy is provided at covers up to Ksh.25,000 for first line chemotherapy sessions while for second and third line the cover is up to 150,000. The chemotherapy cover is capped at 600,000, covering up to 6 cycles. The reimbursement rates for magnetic resonance imaging (MRI), computerized tomography (CT) and ultrasound (U/S) are Ksh.15,000, 8,000 and 3000 respectively. For surgical procedures, a graduated price per procedure and the reimbursement rate is based on contract and provider type.

### 2.7 Cost of managing colorectal cancer

Cancer is an economic burden across society; not only does cancer take an enormous toil on the health of patients and survivors but it also has a financial impact. Cancer care for patients entails high costs for both metastatic and non-metastatic disease (Mar et al., 2017). The cost of

management of CRC can be viewed from different perspectives, which include those of the health service or provider, employers, patients and their family and society. Patients suffer from both the direct costs and the indirect costs which causes bankruptcy (Vanderpuye, 2014). Indirect costs can lead to delays in seeking medical attention, noncompliance and poor clinical outcomes because of the out-of-pocket payments required for treatment (Vanderpuye, 2014).

Cancer treatment has an impact in both the productivity cost both for the patient and the care giver. Patient productivity loss is associated with disease progression, side effects, treatment-associated cognitive impairment, long sick leaves and high probability of not returning to work. The caregiver related productivity is affected negatively because of increased involvement in household activities and time spent on hospital-related activities, such as treatment, appointments, and adverse effects. Hospital acquired infections can result in prolonged hospitalization and increased risk of mortality hence increased the cost of cancer treatment and care (Kamal et al., 2017). In African countries such as Kenya, the social national insurance funds cover only part of the cancer treatment and the rest of the costs are met by patients.

The health service costs include hospitalization, diagnosis, surgery, radiotherapy, chemotherapy, emergencies and outpatient visits. Costs of managing colorectal cancer vary with the stage of the cancer. The Ireland National Cancer Registry estimated the overall health service cost of managing colorectal cancer is €39,607, with €35,918 accounting for treatment while €1,634 and €2,055 for diagnosis and follow up respectively (Tilson et al., 2012; Hanly et al., 2015).

Productivity loss (employer costs) resulting from colorectal cancer arises as a result of absenteeism, disability, ongoing reduced working hours or permanent workforce departure. Premature mortality results in life years lost. A study conducted in Ireland found the average lost productivity cost per person is €303,338 per person; that was18% greater for males (€331,554) than females (€279,990). The main cost determinants are age, wages and gender, pension age and length of illness (Hanly et al., 2013b).

From the patient's perspective, the time and travel costs incurred in the CRC management amounted to €11,055, with time related cost amounting to 96% of the total cost. These costs however vary more with the stage and site of the cancer (Hanly et al., 2013a). Hanly in his study found substantial informal care costs are incurred during diagnosis and the early treatment

period. The average hospital-related costs borne per caregiver was €5,085, the domestic-related costs were €7,895 while the out of pocket costs were €1,499. The other costs for patients and their families include emotional costs which can be severe. The caregivers and patients may also experience anxiety, fear, anger and depression (Ó Céilleachair et al., 2012). The age of the patient and cancer stage during diagnosis are the major determinants of the choice of treatment and the associated cost. The treatment of the later stages of colorectal is achieved at a high financial cost. New targeted chemotherapeutic agents also account for the escalating cost of treating CRC. The economic burden of managing colorectal cancer should be taken into account in making healthcare decisions (Ananda et al., 2016).

### 2.8 Cost effectiveness studies of chemotherapeutic agents used in colorectal cancer

As the cost of managing cancer escalates at an alarming rate, it is critical for the oncology community to embrace interventions that provide value to the patients and the society. In colorectal cancer new highly priced molecules have emerged over the years; however the use of these targeted molecules in Africa is still a challenge due to limited resources available (Shankaran, 2015). In the WHO-CHOICE cost-effectiveness study, treatment of early colorectal cancer, using surgery with or without radiotherapy and chemotherapy is cost effective with an ICER of I$ 217 per healthy life years (HLY) gained in eastern sub-Saharan Africa and I$ 238 per HLY gained in southeast Asia. Utilization of the regional data is important in making decisions based on region-based costs, health system capacity and epidemiologic profile (Ralaidovy et al., 2018).

The treatment of colorectal cancer involves the use of several adjuvant chemotherapeutic regimens. Cost-effectiveness studies in addition to clinical trials, are important in selection of the optimal treatment regimen (Shankaran, 2015). Adjuvant chemotherapy FOLFOX and XELOX remain the mainstay interventions in colorectal cancer management in Africa. Several studies have been conducted to assess the cost effectiveness of adjuvant therapy; the findings of these studies are summarized in Table 2.7.

Shiroiwa et al., 2009 found out that in the UK health care setting, XELOX was superior to FOLFOX in terms of cost and QALYs gained; it decreased treatment costs by 7600 Euros (8643 USD).

In Poland, FOLFOX was found to be both more expensive and more cost-effective compared to XELOX in treatment of advanced stage III and IV colorectal cancer. The majority of the cost was attributed to hospitalization costs for the FOLFOX group and the medication costs for the XELOX group (Płaczek et al., 2017).

In China, XELOX was found to be more clinically beneficial over other adjuvant treatments and is a more affordable option. The ICER over FOLFOX was $15016.33 (Wen et al., 2014).

In Thailand, the cost utility analysis conducted from the provider and societal viewpoint showed that 5-FU/LV was the cheaper and less effective adjuvant chemotherapy for rectal cancer. Capecitabine was the most expensive with higher effectiveness than 5-FU plus LV and 5-FU CI. Use of capecitabine however, reduced the direct non-medical costs that burden patients and families (Katanyoo et al., 2018).

Amy and Chu review of cost effectiveness analysis studies of adjuvant chemotherapy showed that capecitabine-based regimens are less costly and more effective than 5–fluorouracil-based regimens (Soni and Chu, 2015).

In Africa no study has been done to determine the cost-effective regimen in colorectal cancer treatment. To fill-in the information gap, this study sought to compare the use of XELOX and FOLFOX for treatment of patients in early and late colorectal cancer stages in Kenya. The results will provide decision makers a more comprehensive view of treatment-related costs, the benefits of the two regimens and the budget impact of adoption of the most cost-effective regimen.

*Table 2. 7 The findings of cost effectiveness studies of FOLFOX and XELOX*

| Chemotherapy regimen | Total cost | QALY | Cost/effect | ICER | Threshold/ QALY | Reference |
|---|---|---|---|---|---|---|
| FOLFOX | $34416.92 | 3.89 | $8948.28 | $15016.33 | $17815.4 | China (Wen et al., 2014) |
| XELOX | $30466.45 | 3.79 | $8047.30 | | $17815.4 | |
| FOLFOX | $40,218 | 0.20-2.50 | $55,000. | $26,260 | | USA (Toumazis et al., 2017) |
| XELOX | $13.1-209.8 | 0.18-3.44 | | | | |
| FOLFOX | 21300 Euros | | | 3000 Euros | | UK (Shiroiwa et al., 2009) |
| XELOX | 18300 Euros | | | | | |
| FOLFOX | 33,879.13 PLN | | | 46,183.47 /QALY | | Poland (Płaczek et al., 2017) |
| XELOX | 20,023.96 PLN | | | | | |
| 5FU/LV | $4,513 | 3.00 | | | | Thailand (Katanyoo et al., 2018) Provider's view |
| Capecitabine | $5,948 | 3.26 | | $5,586/QALY | | |
| 5-FU Continuous | $5,343 | 3.09 | | $9,840/QALY comparator | | |
| 5FU/LV | $6,551 | 3.00 | | | | Thailand (Katanyoo et al., 2018) Societal perspective |
| Capecitabine | $7,450 | 3.26 | | $3504 /QALY | | |
| 5-FU Continuous | $7,206 | 3.09 | | $7778 /QALY | | |

## 2.9 Theoritical and conceptual framework

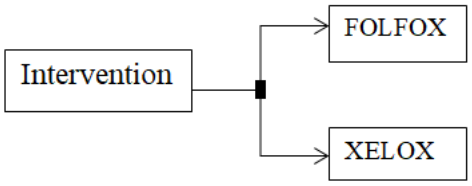
A markov model was used to represent stochastic processes that evolved over time. Markov model is an important tool in economic evaluation used to predict future costs and outcomes. In this study the health states; remission, recurrence, metastasis and death are the recurrent events. The markov chain principle that computes the transition probabilities of events occurring was used. The principle uses transition matrix to predict the occurrence of recurrent health states. The transition matrix was obtained from the prevalence or incidence of events or can be estimated if data is not available in literature. Transition probability is obtained from equation 2.1 (Briggs and Sculpher, 1998).

***Equation 2.1 Transition probabilities formula***

$$tp_1=1-(1-tp_t)^{1/t}$$

$tp_1$is the yearly transition probability and $tp_t$ is the overall probability over time period t.

Cohort simulation approach of the markov model was used, where a hypothetical cohort was assumed to start therapy in 2020 and the future prognosis will be simulated. This was because data collection was conducted in 2020 hence simulation was done prospectively starting the same year. Two groups of patients were assessed in the study; patients on 5FU based (FOLFOX) and those on capecitabine based regimen (XELOX).




The markov cycle is the time period the patient transit from one state to another. The five-year time horizon of the study was divided into 6 months cycles. The life expectancy and mortalities were the expected results of the simulation and were compared across the two arms.

Utility is a measure of the quality of life that is associated with a give health state. The utility value ranges on a scale of zero to one, with a weight of 0 being attached to death and 1 to wellness/alive. The model will be run over the 6-monthly cycle for the five-year time horizon and the sum of the weights will give an average of the average expected life expectancy of the patient. This is then multiplied by the length of the cycle in years to give life expectancy in years.

The key cost determinants for the management of colorectal cancer in Kenya are the cost of chemotherapeutic drugs, hospitalization, personnel costs, laboratory costs and the costs of managing adverse events. The overall cost as a function of these drivers is summarized in Figure 2.2. This study focused on these direct medical costs from a health care provider perspective. The study attempted to determine the overall costs of management of CRC and compared these costs for the 5FU and capecitabine based regimens to determine the most cost-effective regimen.

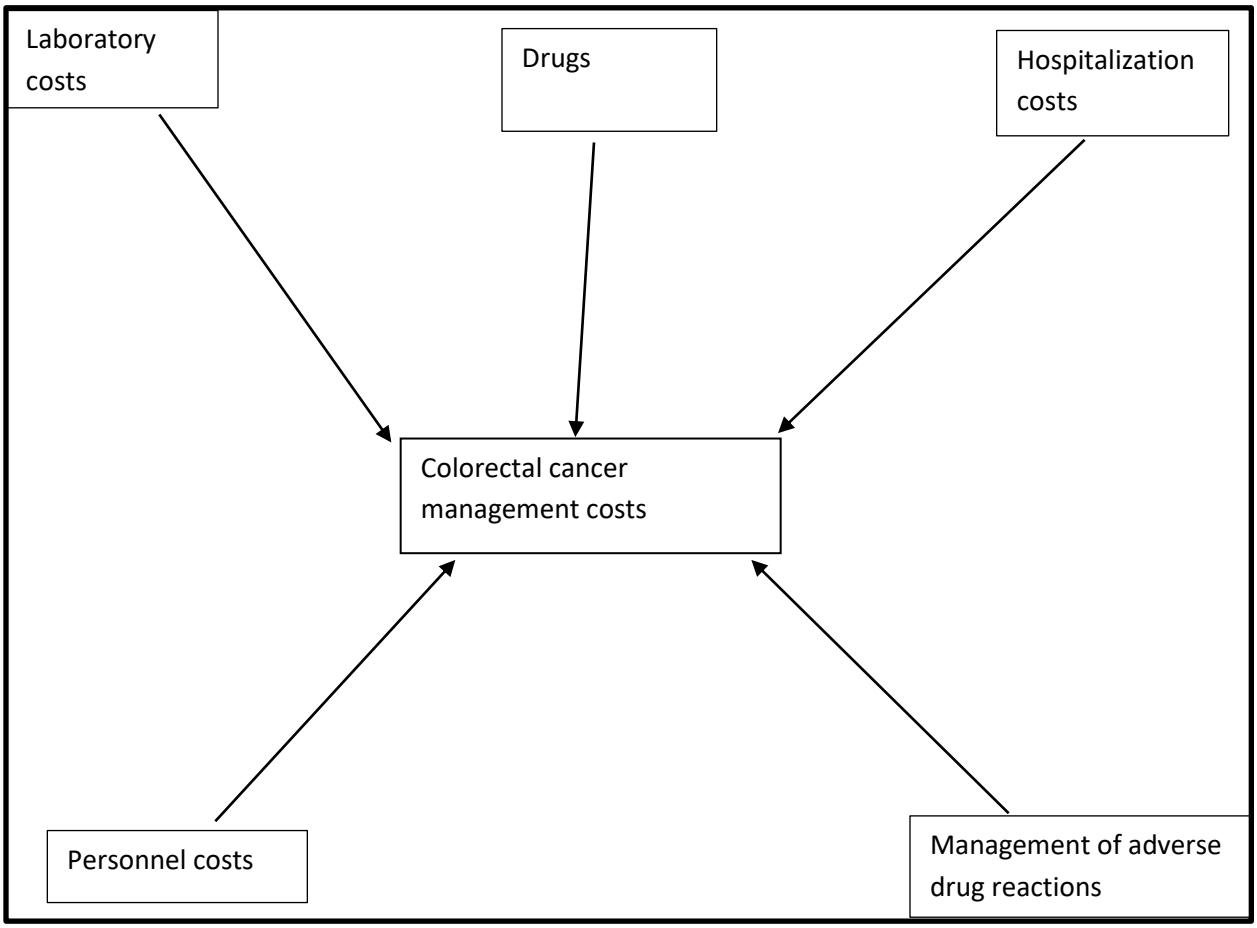



***Figure 2. 2 Conceptual framework of the direct costs for the management of colorectal cancer***

# CHAPTER THREE: METHODS

The methods of the study were divided into four major parts; the review of patient files to obtain data incidence of health states (recurrence, metastasis, remission, side effect (neutropenia, hand and foot syndrome and diarrhea and death) and quantities of drugs consumed by colorectal cancer patients; key informant interview to obtain data on personnel and treatment costs; the cost utility; and the budget impact analysis.

In order to do the costing study effectively a chart review was done for the purpose of identifying the resources that are used for managing patients with colorectal cancer. These resources included drugs, laboratory investigations, days of hospitalization and radiological investigations or tests. This information was obtained from patient files. From the tests the quantities for each resource input was estimated.

The key informant interview was conducted amongst staff at a managerial position in the billing and procurement department. The objective of the key informant interview is to obtain prices that were used in the costing exercise.

The data obtained from the retrospective chart review and key informant interview was used to compute the total cost for management of the various health states. These computed costs were used in the third part of the study which is a cost utility analysis which requires cost data.

## 3.1 Review of patient records

### 3.1.1 Study design, location and population.

The study design was a mixed method study, as both it involved both quantitative (Descriptive cross section study) and qualitative (key informant interviews) methods.

A hospital based descriptive cross sectional study was conducted to estimate the costs of colorectal cancer treatment through review of patient files who were admitted between1$^{st}$ January 2014 to 31$^{st}$ December 2019. The study was carried out at the cancer treatment centre in Kenyatta National Hospital (KNH), Kenya. It is the largest teaching and referral hospital in East Africa. The average annual number of colorectal cancer patients seen in KNH annually is

approximately 300; the patients are admitted in the oncology wards (Ground Floor C (GFC) and Ground Floor D (GFD)) as well as in Medical Ward 8. The target population of the study was colorectal cancer patients in Kenya.

### 3.1.2 Eligibility criteria

#### 3.1.2.1 Inclusion criteria

Colorectal cancer patients registered with the KNH cancer treatment center were included in the study if they met the following criteria:

1) Adult patients aged 18 years
2) Documented diagnosis of CRC stage I,II,III and IV
3) Their records were available
4) Received and completed treatment cycle between 2014 and 2019.

#### 3.1.2.2 Exclusion criteria

The patients were excluded from if they were:

1) Aged less than 18 years.
2) records are not available
3) Seen earlier or later than 2014 and 2019 respectively.

### 3.1.3 Sample size determination

The Cochrane formula (Charan and Biswas, 2013) was used to calculate the sample size of the study (Equation 3.1). This formula was selected because the design is a descriptive cross sectional hospital-based study aimed at computing prevalence.

***Equation 3.1 Cochrane formula for sample size computation***

$$N = \frac{z^2\big(P(1-P)\big)}{d^2}$$

Where:

N = Sample size

Z = standard normal deviate at the desired level of confidence (95%) is 1.96

P = Proportion of the population with the hand and foot syndrome (31%).

d = Degree of precision; will be taken to be 0.05

The incidence of hand and foot syndrome was considered for sample size calculation as it is the outcome with the least incidence of occurrence from literature. A survey of local literature was done on the incidence of hand and foot syndrome in Kenya and no data was found. For the purpose of computing sample size, an incidence of 31% obtained from a randomized control trial to compare XELOX and FOLFOX was used (Cassidy et al., 2011). The minimal sample size of 329 was obtained. The sample size was inflated by 10% to adjust for incomplete records results in a sample size of 358. Cochrane adjustment for a finite population was not conducted in order to improve the precision of the estimates.

### 3.1.4 Sampling procedure and access of patient records

Permission to access records was obtained from the KNH Research and Programs department and the Head of Health Information Department after receipt of ethical approval. At least 10 records were requested daily and perused for eligibility using a checklist in Appendix 1. Systematic random sampling approach was used where all patient records that met the inclusion criteria were included in the study until the desired sample size was reached. This approach was selected because the average colorectal cancer cases encountered in KNH is approximately 300 annually and therefore the sampling frame was obtained and the systematic random sampling applied.

### 3.1.5 Data collection

Data was extracted from the patient medical records using the data collection form in Appendix 2. Data was collected between from April 2020 to June 2020. The data on demographics, diagnostics and treatment the patient received was collected. In addition, data on the following

outcomes was obtained; recrudescence, remission, metastasis, hand and foot syndrome, neutropenia, grade 3 and 4 diarrhea and mortality.

### 3.1.6 Case definitions

**Recrudescence** is the return of a disease or the signs and symptoms of a disease after a period of improvement.

**Remission** is defined as a decrease in or disappearance of signs and symptoms of cancer. In partial remission, some, but not all, signs and symptoms of cancer have disappeared. In complete remission, all signs and symptoms of cancer have disappeared, although cancer still may be in the body.

**Metastasis** is defined as when cancer cells break away from a tumor in the colon or rectum and spread to other parts of the body through the bloodstream or lymphatic system. Metastatic colorectal cancer can occur in the lungs, liver or any other organ.

**Hand and foot syndrome**

In this study hand and foot syndrome was defined as any of the following;

1) A documented history of redness, swelling, or pain on the palms of the hands and/or the soles of the feet
2) A documented history of cracking, flaking, or peeling skin
3) A written diagnosis of hand and foot syndrome

**Neutropenia**

Neutropenia in this study was defined as any of the following;

1) A reduction in neutrophils below normal counts, usually occurring within 7 to 12 days following cancer chemotherapy. With an absolute neutrophil count (ANC) of less than 500 cells per microliter following cytotoxic chemotherapy, or by an ANC expected to decrease to less than 500 cells per microliter within 48 hours
2) A written diagnosis of neutropenia

**Grade 3 and 4 diarrheas**

In this study grade 3 diarrhea was defined as any of the following;

1) An increase of ≥ 7 stools per day over baseline;
2) incontinence;
3) severe increase in ostomy output compared with baseline;
4) written diagnosis of grade 3 diarrhea.

Grade 4 diarrhea was defined has diarrhea with life threatening consequences such as hemodynamic consequences or a written diagnosis of grade 4 diarrhea.

### 3.1.7 Data analysis

Data analysis was done in three phases; descriptive, exploratory and regression data analysis.

For descriptive data analysis, Shapiro-wilk test was performed to determine if continuous variables are normally distributed or not. Continuous variables that are normally distributed were summarized as a mean and standard deviation of mean. Continuous variables that were not normally distributed were summarized as median, interquartile range or range. Categorical variables were summarized as counts and percentages.

Exploratory data analysis was performed to determine if there were any significant correlations between continuous variables and associations between categorical variables. The relationship between continuous variables was examined using scatter plots and correlation analysis using Spearman's and Pearson's correlation tests.

The relationship between linear and categorical variables was examined by comparing the measures of central tendency across the levels of the main outcome (mortality). The inferential tests that were used included; unpaired two sample t test for normally distributed numeric variables and Wilcoxon rank sum tests for numeric variables that are not normally distributed. For categorical variables, Pearson's chi square and Fischer's exact inferential tests will be used.

Cox regression analysis was performed to determine the predictor variables for mortality. Logistic regression analysis for the outcomes: recrudesce, remission and metastasis was done. Model building was done using the forward stepwise building approach.

The descriptive and exploratory data analysis was done using STATA version 13 software. The level of significance was set at 0.05.

### 3.2 Key informant interview

The key informant interview was done to determine the costs.

#### 3.2.1 Study design and site

The study design for the key informant interview was a cross sectional mixed methods study. The study was conducted at Kenyatta National Hospital (KNH) in Nairobi. The objective of the key informant interview was to obtain prices to be used in the costing analysis. The study population was key personnel involved in billing and procurement.

#### 3.2.2 Sample size for the key informant interview

The principles for sampling in qualitative studies was used to estimate sample size (Vasileiou et al., 2018). The principles state that for key informant interviews, the minimum sample size is four. The key informants included one informant from each department involved in cancer care at the cancer treatment center. The departments targeted included; the pharmacy, oncology, billing and procurement. The principle of saturation was used to determine the final sample size. When no additional information was obtained from interviewing more subjects, sampling terminated.

#### 3.2.3 Sampling and eligibility criteria

Purposive sampling was conducted for the key informant interviews. Participants who met the following eligibility criteria were included as informants;

a) Personnel involved in billing and procurement especially of drugs and laboratory tests.

b) Had worked for the organization for at least two years
c) Gave informed consent to participate in the study

Anyone who did not meet these criteria were excluded from participating

### 3.2.4 Participant recruitment

A letter of introduction was obtained from the School of Pharmacy, University of Nairobi and a letter of ethical approval from the University of Nairobi/Kenyatta National Hospital Ethics Review Committee (UON/KNH-ERC) was given to the head of the KNH administration as well as the departmental heads for permission to interview the key informants. An interview appointment with the identified informants was booked at their convenience through either a personal visit or a telephone call.

### 3.2.5 Data collection

The purpose and the intended uses of information obtained from the interview were explained and the key informant persons signed the informed consent from the key informant interview in Appendices 3 and 4.

The oral key informant interview was conducted by the investigator; while a research assistant recorded the proceedings of the interview. An interview guide in Appendix 5 was used. The written and recorded information from the interviews was transcribed within 24 hours of the interview.

### 3.2.6 Data analysis for the costing data

A summary interview sheet was prepared at the end of every interview in order to reduce the cost information to tabulated costs. The quantitative data on costs were tabulated and summarized in a Microsoft Excel $^{TM}$ spreadsheet.

## 3.3 Cost utility analysis

### 3.3.1 Study design

A comparative cost utility study was used to compare the cost and effectiveness of 5-FU and capecitabine based regimens in the management of colorectal cancer. This study design was selected because it allows a formal comparison of costs against effectiveness. The measure of effectiveness used was the utility. In addition, budget impact analysis was conducted.

### 3.3.2 Costing perspective

The study was conducted from the healthcare provider perspective which in this case was Kenyatta National Hospital. The time horizon of the study was five years. This time horizon was selected because modeling beyond that time would not be realistic in the absence of empirical data and in addition, most government funding is usually projected expenditure of 5 years for planning purposes.

### 3.3.3 Costing

A micro-ingredient costing approach was used whereby the cost data of the items was obtained from key resource persons and the data from patient file reviews. The costing was divided into four steps; the first step entailed identification of critical cost items. The cost categories included chemotherapy and pre-medications, hospitalization, surgery, radiotherapy, laboratory investigation, management of neutropenia and personnel costs. Only direct medical costs were considered given that the study was conducted from the provider's perspective.

The second step in costing entailed quantification of amounts consumed of each cost item. The amount of drug was based on optimal treatment approach as specified in the National Comprehensive Cancer Network (NCCN) treatment guidelines (Venook, 2019) and the actual quantities of drugs consumed was obtained from the review patient medical records.

The third aspect of costing was determination of unit costs, which entailed attaching a price to the items. The KNH items and services costs were obtained from the health management information system. The market price was used instead of hospital charges as the costs of drugs in KNH tend to be lower because of the open tender system, consumption of large quantities (bulk buying), and discounts because of perceived added marketing value for a company when their products are stocked in KNH.

The total costs were obtained by multiplying the amounts of each input and its market value. The costs were presented in Kenyan shillings (Ksh.)

### 3.3.4 Personnel costs

The number and the type of personnel required for the medical care of an early colorectal cancer patient in the cancer treatment center was obtained from key informant interview. The Kenyan Government salaries for these staff were used to compute the personnel cost. The estimated salaries were obtained from salary explorer website (Health and Medical Average Salaries in Kenya 2020). Data from review of patients' files indicated an average admission period of 4 days for chemotherapy administration. The personnel responsible for the care of these patients that were considered included: an oncologist, medical officer, pharmacist, pharmaceutical technologist and a registered nurse. The capacity of the cancer ward was assumed to be 30 patients in a day. The personnel worked for 8 hours daily for 25 days in a month. The salaries were converted into per minute salary and the approximate time spent by each cadre to see the patients in during the chemotherapy administration session was determined. The total personnel expenditure was determined by multiplying the per min salary by the time commitment of the personnel in minutes as shown in Equation 3.2.

***Equation 3.2 Computation of personnel costs***

Personnel cost = {monthly salary/ (25*8*60)}*personnel time commitment during treatment

### 3.3.5 Comparator interventions

The interventions considered in the study were XELOX and FOLFOX; FOLFOX was considered as the standard of care while XELOX the comparator intervention. According to the NCCN and ESMO guidelines being used at KNH, the XELOX regimen is a 3-week treatment for 8 cycles, including a 2-h intravenous infusion of oxaliplatin (130 mg/m2 ) on day 1 and oral capecitabine (1000 mg/m2 ) twice a day from day 1 to day 14. FOLFOX consists of 2 hours intravenous infusions of oxaliplatin (85 mg/m2 ) and leucovorin 200 mg/m2 on day 1, followed by a bolus of 400 mg/m2 of 5-FU and a 22 hours infusion of 5-FU 600 mg/m2 lasting 22 hours every 14 days, for 12 cycles (Venook, 2019). FOLFIRI and XELIRI are considered second line treatment choice for patients with metastasis and recurrent disease.

### 3.3.6 Data on effectiveness

Effectiveness data was obtained from systematic reviews and meta-analyses from literature (Pandor et al., 2006; André et al., 2015; Jeong and Cairns, 2016). Quality adjusted life years (QALYs) were obtained by multiplying the utility by the years lived in a given state. Parameter estimates, standard deviations, and data sources for the base case utilities are shown in Table 3.1. Given the lack of Kenyan data on the health-related quality for colorectal cancer patients, sensitivity analysis was conducted to assess the robustness of the assumption that the data from these studies can be extrapolated to the Kenyan context.

***Table 3. 1 Health related quality of life of colorectal cancer states***

| | | **Remission** | **Recurrence** | **Metastasis** | **References** |
|---|---|---|---|---|---|
| Utility | | 0.92(0.78-0.92) | 0.75(0.64-0.79) | 0.45(0.25-0.68) | (Jeong and Cairns, 2016) |
| Overall survival (years) | XELOX | 4.68 | 4.39 | 1.66 | (Pandor et al., 2006; André et al., 2015) |
| | FOLFOX | 4.24 | 3.76 | 1.71 | |
| QALYs | XELOX | 4.04(3.424-4.039) | 2.76(2.355-2.907) | 0.75(0.415-1.129) | |
| | FOLFOX | 3.90(3.307-3.901) | 2.82(2.406-2.907) | 0.77(0.428-1.163) | |

### 3.3.9 Computation of incremental cost effectiveness ratio (ICER)

From the total costs and the measures of effectiveness, ICER was calculated using the formula in Equation 3.3.

***Equation 3.3 Formula for computing the incremental cost effectiveness ratio (Paulden, 2020).***

ICER= costs of intervention A- costs of intervention B/ effect of A- effect of B

### 3.3.10 Modelling

The model was based on a 55 year old patient with stage II or III colorectal cancer. A base case age of 55 was used because this is the median age of colorectal cancer incidence at KNH. Outcomes considered were effectiveness (utilities and quality-adjusted life-years gained) and direct medical costs, from the provider (KNH) perspective. Patients received regimens of XELOX and FOLFOX as described in the NCCN guidelines. FOLFOX was considered to be the base case. Throughout the model patients could die from other age/sex/risk-related causes.

The discrete Markov model simulated the natural history of a hypothetical cohort of 55-year-old with stage I to III colorectal cancer in KNH. The base case of 55 years was used because this was the mean age of majority of the participants obtained from the cross-sectional descriptive study. Figure 3.1 shows the state diagram model for the Folfox treatment. A 6 month cycle length was used, with a 5-year time horizon. The 'Heemod' package in R software was used for the analysis.

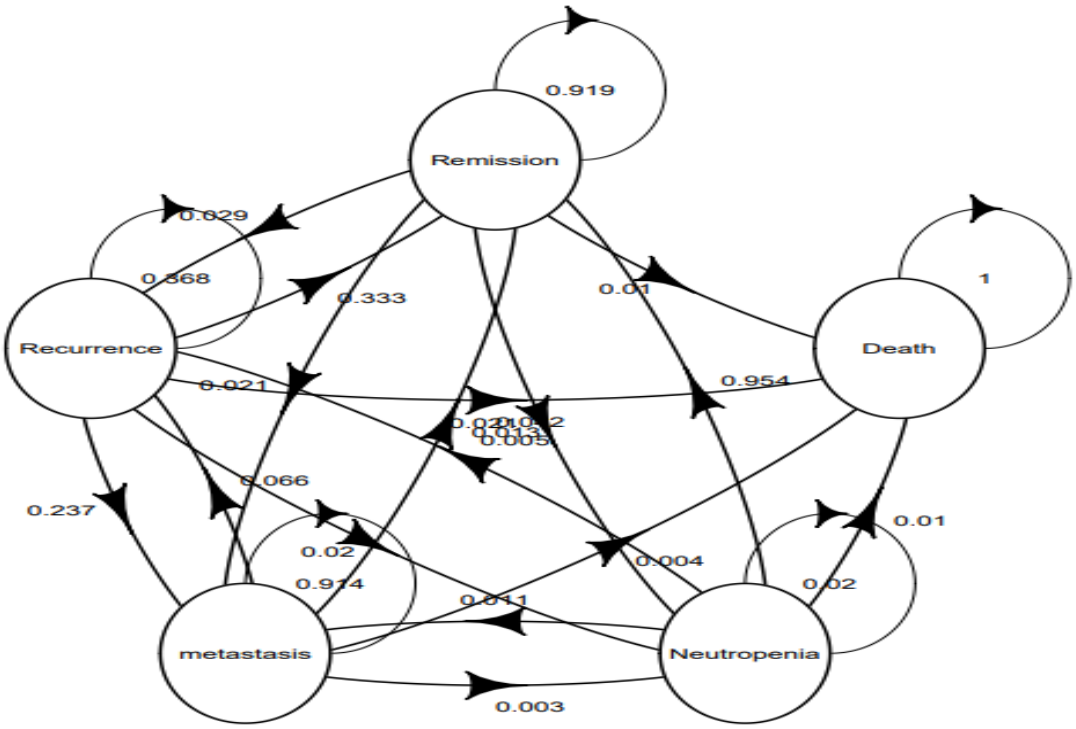



*Figure 3. 1 The state transition diagram for a stage II or III CRC patient on FOLFOX*

Four states were considered in the model; remission, recurrence, metastasis and death. The cycle length of the Markov model was set to 6 months. Base case, standard deviation, and plausible range estimates were determined for each transition probability. Parameter estimates, standard deviations, data sources, and threshold values for the base case transition probabilities are shown in Table 3.2.

### 3.3.11 Sensitivity analysis

Model parameter uncertainty was evaluated using the one way and probabilistic sensitivity analysis. This was done to determine the impact of varying the costs of inputs and changes in effectiveness that can occur given the study population may be systematically different from the population in clinical trials. Probabilistic sensitivity analysis was performed by Monte Carlo simulation 10,000 times to illustrate the probabilities of cost-effectiveness comparing the two regimens. The willingness to pay threshold was set at Kshs. 150,000. The R version 3.6.0, "*heemod*" package was used for costing, probabilistic and sensitivity analysis.

## 3.4 Budget impact analysis

Budget impact analysis was done to estimate the number needed to treat and the cost the provider will incur for treating these individuals yearly. The incremental costs for treating these individuals were obtained from the output of the Markov model.

The estimate of the number of people who need to be treated was obtained using the current prevalence of colorectal cancer and the incidence was used to estimate the total number of people who will be under treatment for the next five years.

The numbers to be treated for each year was multiplied by the incremental costs of treatment for a given year. The final total cost was the impact of taking up the policy on the healthcare provider budget.

*Table 3. 1 Input parameters used in the model*

| Parameter | Base /mean | Range | Distribution | Ref |
|---|---|---|---|---|
| **Utility of remission** | 0.85 | 0.78-0.920 | Normal | Ramsey et al., 2000 |
| **Utility of recurrence** | 0.75 | 0.64-0.790 | Normal | Starling et al., 2007 |
| **Utility of metastasis** | 0.45 | 0.25-0.680 | Normal | Glimelius et al., 1995; Djalalov 2014 |
| **Probability of transition from remission to remission for FU** | 0.831 | 0.731-0.861 | Binomial | André et al., 2015 |
| **Probability of transition from remission to recurrence for FU** | 0.033 | 0.026-0.034 | Binomial | |
| **Probability of transition from remission to metastasis for FU** | 0.027 | 0.024-0.034 | Binomial | |
| **Probability of transition from remission to death for FU** | 0.109 | 0.089-0.211 | Binomial | |
| **Probability of transition from recurrence to remission for FU** | 0.224 | 0.209-0.236 | Binomial | Böckelman et al., 2015b |
| **Probability of transition from recurrence to recurrence for FU** | 0.582 | 0.53-0.619 | Binomial | |
| **Probability of transition from recurrence to metastasis for FU** | 0.032 | 0.028-0.056 | Binomial | |
| **Probability of transition from recurrence to death for FU** | 0.162 | 0.144-0.178 | Binomial | |
| **Probability of transition from metastasis to remission for FU** | 0.170 | 0.156-0.179 | Binomial | Guo et al., 2016b; André et al., 2015 |
| **Probability of transition from recurrence to recurrence for FU** | 0.033 | 0.025-0.041 | Binomial | |
| **Probability of transition from recurrence to metastasis for FU** | 0.542 | 0.420-0.618 | Binomial | |
| **Probability of transition from recurrence to death for FU** | 0.225 | 0.204-0.360 | Binomial | |
| **rr1 (odds ratio for transition from remission to recurrence for XELOX)** | 1 | 0.027-0.04 | Binomial | Cheng et al., 2020 |
| **rr2 (odds ratio for transition from remission to metastasis for XELOX)** | 1.02 | 0.023-0.034 | Binomial | |
| **rr3 (odds ratio for transition from remission to death for XELOX)** | 0.93 | 0.085-0.121 | Binomial | |
| **rr4(odds ratio for transition from recurrence to remission for XELOX)** | 0.95 | 0.155-0.258 | Binomial | Ayvaci et al., 2013 |
| **rr5(odds ratio for transition from recurrence to metastasis for XELOX)** | 1.03 | 0.029-0.039 | Binomial | |
| **rr6 (odds ratio for transition from recurrence to death for XELOX)** | 1.18 | 0.138-0.167 | Binomial | |
| **rr7(odds ratio for transition from metastasis to remission for XELOX)** | 1.007 | 0.146-0.175 | Binomial | Guo et al., 2016b; Hillner et al., 2005 |
| **rr8(odds ratio for transition from metastasis to recurrence for XELOX)** | 1.04 | 0.03-0.04 | Binomial | |
| **rr9(odds ratio for transition from metastasis to death for XELOX)** | 0.87 | 0.184-0.268 | Binomial | |

### 3.5 Quality assurance

The study was peer reviewed by other researchers who have conducted research in this area to ensure the study is credible. Standard health economic evaluation guidelines for the best practices were adhered to, including quality data collection, adherence to ethical practices, analytical methodology and reporting the findings (Drummond et al., 2008). Two research assistants were trained on data collection methods, the level of training was considered sufficient if an inter data collector agreement is 85%. Both verbal and non-verbal communication during the interview was recorded. The data abstraction tool and the interview guide were pretested and the findings used to make necessary adjustments.

### 3.6 Data management

Data from the cost studies and key informant interviews was entered into MS-Excel and MS word document respectively on the same day of data collection. Data cleaning and validation was performed to achieve a clean dataset, which was stored safely with a password protection. Back up files will be stored in external drives and online, these were updated on a daily basis to avoid loss of the data.

The data obtained from the retrospective chart review of patients' files and key informant interviews was coded. Data was accessed only by the principal investigator and only upon request by supervisors.

### 3.7 Ethical considerations

Ethical approval to conduct the study was obtained from the Kenyatta National Hospital and University of Nairobi Ethical review committee (KNH-UON ERC). In addition, permission to conduct the study was sought from the Kenyatta National Hospital (KNH) administration. The letter of approval is appended in the Appendix 6. The information that was obtained during the study was handled with confidentiality and used only for the intended purpose of the study. The review of patients' files was done within the oncology clinic and the records office to ensure confidentiality and safety of patients' records. Study number was used to identify patients and

conceal their identity. Informed consent to participate in the study was sought from the key informants.

# CHAPTER FOUR: RESULTS

## 4.1 Participant recruitment

The records of the registered colorectal cancer patients in KNH were retrieved. Systematic random sampling was used to recruit participants using a sampling frame of registered CRC patients over the five year period. The eligibility list in Appendix 5 was used to determine the eligible participants. A total of 408 files met the eligibility criteria. After data cleaning, the participants' records missing key variables were omitted and a final sample size of 332 participants was used in the analysis. Figure 4.1 shows the consortium diagram for participant recruitment.

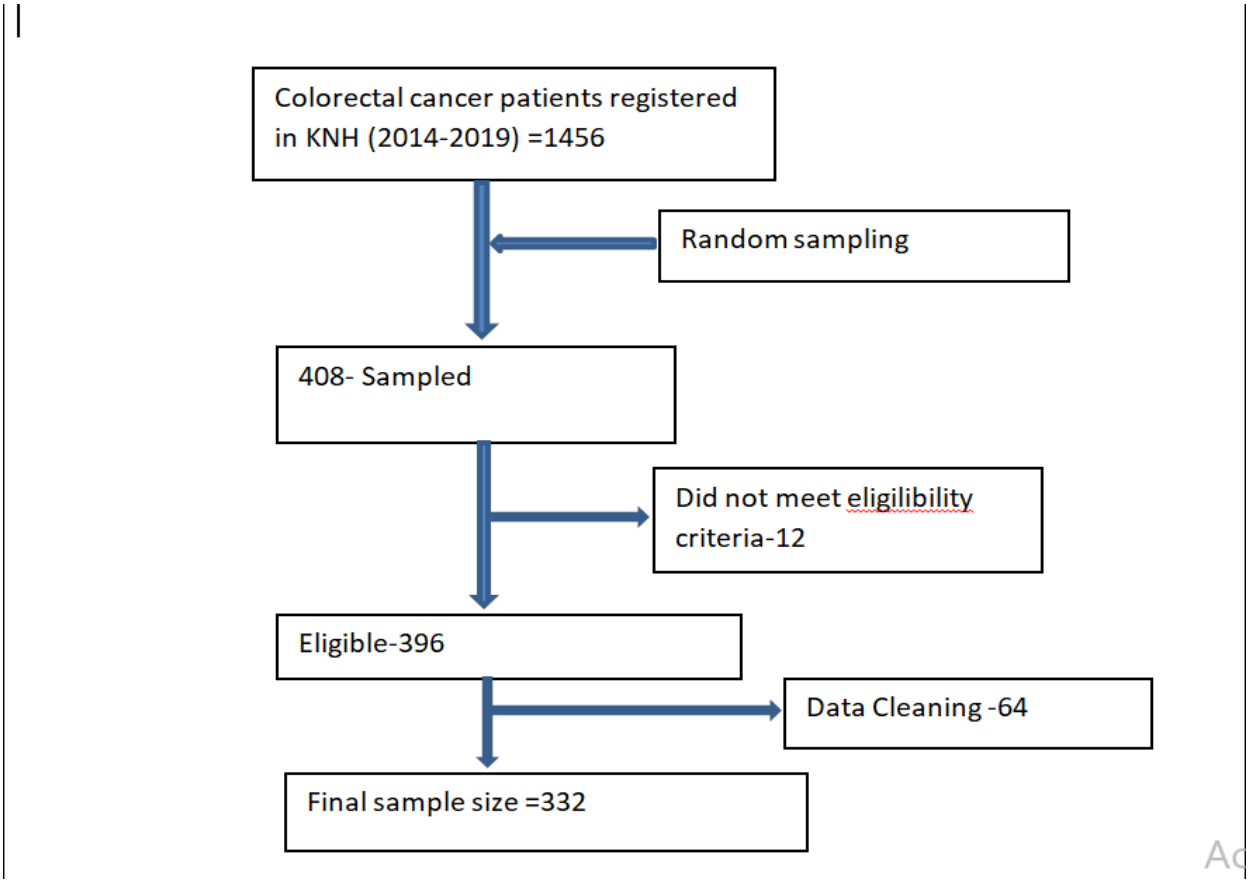



***Figure 4.1 The consortium diagram for participant recruitment of colorectal cancer participants in KNH***

### 4.2 Characteristics of the study population

The baseline characteristics of the participants in the study are depicted in Table 4.1. There were more male participants (55.4%) than females (44.6%). Slightly over half of the participants (51.0%) were the elderly, aged 55 years and above; 10.6% were aged between 18-35 years. The BMI of most patients (57.7%) was within the normal range, 19.1% of the patients were underweight while 4.6% were obese. Majority of the patients (39.8%) had attained secondary level of education; this estimate was affected by missing data on education level.

***Table 4. 1 The socio-demographic characteristics of the study population***

| **Variable** | | **n (%)** |
|---|---|---|
| **Age** | 18-35 | 36 (10.6%) |
| | 35-55 | 131 (38.4%) |
| | >55 | 174 (51.0%) |
| **BMI** | <18.5 | 48 (24.7%) |
| | 18.5<25.0 | 101 (52.1%) |
| | 25.0<30.0 | 36 (18.6%) |
| | ≥30.0 | 9 (4.6%) |
| **Gender** | Male | 184 (55.4%) |
| | Female | 148 (44.6%) |
| **Level of education** | No formal schooling | 4 (1.2%) |
| | Primary | 22 (6.6%) |
| | Secondary | 31 (9.3%) |
| | Tertiary | 21 (6.3%) |
| | Education not stated | 254 (76.5%) |
| | | **Mean(sd)** |
| **Weight** | | 59.282 (11.323) |
| **Height** | | 1.646 (0.079) |

### 4.2 The clinical characteristics of the participants in the study population

The clinical characteristics of the study population are summarized in Table 4.2. Most of the participants (62.3%) were diagnosed at late stage disease (stage III and IV). The rectum was the most common tumor site (45.2%). Metastasis occurred in 35.5% of the patients with the liver being the common site of metastasis (16.3%). Hypertension was the most common comorbidity (8.5%).

***Table 4. 2 The clinical characteristics of the patients in the study population***

| **Variable** | | **n (%)** |
|---|---|---|
| **Early vs. late disease** | Early(1&2) | 125 (37.7%) |
| | Late(3&4) | 207 (62.3%) |
| **Disease stage** | I | 47 (14.2%) |
| | II | 78 (23.5%) |
| | III | 118 (35.5%) |
| | IV | 89 (26.8%) |
| **Tumor site** | Rectum | 150 (45.2%) |
| | Colon | 127 (38.2%) |
| | Colon and rectum | 50 (15.1%) |
| | Anorectal | 5 (1.5%) |
| **Metastasis** | Yes | 118 (35.5%) |
| **Site of Metastasis** | Liver | 54 (16.3%) |
| | Lung | 16 (4.8%) |
| | Skeletal | 3 (0.9%) |
| | Liver and lung | 29 (8.7%) |
| | Other | 5 (1.5%) |
| | Liver, lung and skeletal | 11 (3.3%) |
| **Comorbidities** | Any comorbidity | 64 (19.3%) |
| **Comorbidity type** | Diabetes | 8 (2.4%) |
| | Hypertension | 28 (8.5%) |
| | HIV/AIDS | 7 (2.1%) |
| | Asthma | 2 (0.6%) |
| | Diabetes and hypertension | 15 (4.5%) |
| | Other | 4 (1.2%) |

### 4.3 Therapeutic approaches for management of colorectal cancer

Table 4.3 shows the therapeutic approaches used for the management of colorectal cancer at Kenyatta National Hospital. Majority of the patients (67.2%) were on the 5-fluorouracil based regimens while 32.8% were on the capecitabine regimen. Less than 10% of the patients were on second line treatment with FOLFIRI, XELIRI or FOLFOXIRI. Most of the patients (62.0%) underwent tumor resection and 33.1% received radiotherapy.

***Table 4. 3 Therapeutic approaches for management of colorectal cancer.***

| **Variable** | | **Regimen** | **N (%)** |
|---|---|---|---|
| FU vs Capecitabine | | 5FU-based | 223 (67.2%) |
| | | Capecitabine-based | 109 (32.8%) |
| Chemotherapy regimen | First line therapy | All first line | 302 (91.0%) |
| | | FOLFOX | 196 (59.0%) |
| | | XELOX | 60 (18.1%) |
| | | XELODA | 46 (13.9%) |
| | | All second line | 30 (9.0%) |
| | Second line therapy | FOLFIRI | 20 (6.0%) |
| | | XELIRI | 3 (0.9%) |
| | | FOLFOXIRI | 7 (2.1%) |
| Underwent surgery | | Yes | 189 (62.0%) |
| Received radiotherapy | | Yes | 110 (33.1%) |

### 4.4 Comparative analysis of socio-demographic and clinical characteristics of colorectal cancer patients on Fluorouracil and Capecitabine based regimens in KNH

The patients in the study either received fluorouracil or capecitabine based regimens, the characteristics of these patients are summarized in Table 4.4 and Table 4.5.There was no difference in the distribution of patients in the two treatment regimens by weight (p=0.443), height (p=0.216), gender (p=0.423) and age (p=0.185). Patients who received capecitabine based regimen had a higher level of education as compared to those on 5FU regimen; this finding was statistically significant (p=0.013).

***Table 4. 4 Comparative analysis of socio-demographic of colorectal cancer patients on Fluorouracil and Capecitabine based regimens in KNH***

| **Variable** | | **FU based (n=223)** | **Capecitabine based (n=109)** | **Total** | **P value** |
|---|---|---|---|---|---|
| Age | 18-35 | 21 (9.4%) | 15 (13.8%) | 36 (10.8%) | 0.185 |
| | 35-55 | 95(42.6%) | 36(33.0%) | 131 (39.5%) | |
| | >55 | 107(48.0%) | 58(53.2%) | 165 (49.7%) | |
| Weight | | 59.185(11.216) | 59.411(11.526) | 59.282(11.324) | 0.443 |
| Height(m) | | 1.642(0.084) | 1.651(0.074) | 1.646(0.079) | 0.216 |
| BMI | <18 | 20(19.0%) | 17(19.1%) | 37 | 0.720 |
| | 18-<25 | 58(55.2%) | 54(60.7%) | 112 | |
| | 25-<30 | 22(21.0%) | 14(15.7%) | 36 | |
| | ≥30 | 5(4.8%) | 4(4.5%) | 9 | |
| Gender | Male | 127(57.0%) | 57(52.3%) | 184 | 0.423 |
| | Female | 96(43.0%) | 52(47.7%) | 148 | |
| Level of education | Low (<tertiary) | 52(91.2%) | 14(66.7%) | 66(84.62%) | **0.013** |
| | Tertiary | 5(8.8%) | 7(33.3%) | 12(15.38%) | |

Fluorouracil based regimens were more likely to be given

to patients with advanced disease (p=0.016). The patients on fluorouracil regimen were more likely to have had metastasis (p<0.001). Patients who underwent radiotherapy were more likely to receive capecitabine based regimens (p<0.001). Patients on capecitabine regimen were more likely to have the tumor in the rectum (p=0.022).

***Table 4. 5 Comparative analysis of the clinical characteristics of colorectal cancer patients on Fluorouracil and Capecitabine based regimens in KNH***

| Variable | | FU based (n=223) | Capecitabine based (n=109) | Total | P value |
|---|---|---|---|---|---|
| **Early vs late stage disease** | Early(1&2) | 74(33.2%) | 51(46.8%) | 125 | **0.016** |
| | Late(3&4) | 149(66.8%) | 58(53.2%) | 207 | |
| **Disease stage** | 1 | 29(13.0%) | 18(16.5%) | 47 | **0.002** |
| | 2 | 45(20.2%) | 33(30.3%) | 78 | |
| | 3 | 75(33.6%) | 43(39.4%) | 118 | |
| | 4 | 74(33.2%) | 15(13.8%) | 89 | |
| **Tumor site** | Rectum | 92(41.3%) | 58(53.2%) | 150 | **0.022** |
| | Colon | 97(43.5%) | 30(27.5%) | 127 | |
| | Colon and rectum | 32(14.3%) | 18(16.5%) | 50 | |
| | Anorectal | 2(0.9%) | 3(2.8%) | 5 | |
| **Metastasis** | Yes | 97(43.5%) | 21(19.3%) | 118 | **<0.001** |
| **Comorbidities** | Yes | 40(17.9%) | 24(22.0%) | 64 | 0.376 |
| | No | 183(82.1%) | 85(78.0%) | 268 | |
| **Surgery** | Yes | 132(64.4%) | 57(57.0%) | | 0.212 |
| | No | 73(35.6%) | 43(43.0%) | | |
| **Radiotherapy** | Yes | 52(23.3%) | 58(53.2%) | 222 | **<0.001** |
| | No | 171(76.7%) | 51(46.8%) | 110 | |

**4.5 The predictors of prescribing a given chemotherapeutic regimen**

Prescribing of

capecitabine based regimen was not independent. Patients who needed a chemotherapy switch were most likely to be prescribed for capecitabine.

The predictors for prescribing capecitabine based regimens are summarized in Table 4.6. Patients on capecitabine based regimen were 0.310 less likely to have experienced metastasis ($p<0.001$). The odds of the patients on capecitabine experiencing metastasis were 0.310 compared to those on fluorouracil ($p<0.001$). Patients with advanced disease were 0.565 less likely to be put on capecitabine based regimen compared to those on early stages ($p=0.017$). Patients undergoing radiotherapy were 3.740 times more likely to be put on capecitabine regimen ($p<0.001$). A chemotherapy switch was 2.458 times more like to have occurred to patients who were put on capecitabine based regimen ($p<0.001$).

On performing the forward stepwise model building, the most predictors for prescribing capecitabine regimen were presence of metastasis ($p<0.001$), radiotherapy ($p<0.001$) and any chemotherapy switch ($p<0.001$).

***Table 4. 6 Summary of logistic regression for the predictors of prescribing capecitabine***

| **Predictor variable** | **Unadjusted OR** | **95%C.I** | **P value** | **Adjusted OR** | **95% C.I** | **P value** |
|---|---|---|---|---|---|---|
| **Low level vs Tertiary education** | 5.2 | 1.431,18.900 | 0.012 | - | - | - |
| **Early vs late stage** | 0.565 | 0.353,0,902 | 0.017 | - | - | - |
| **Any metastasis** | 0.310 | 0.180,0.534 | 0.000 | 0.225 | 0.123,0.412 | <0.001 |
| **Radiotherapy** | 3.740 | 2.296,6.091 | 3.740 | 3.828 | 2.257,6.494 | <0.001 |
| **Any chemotherapy switch** | 2.458 | 1.538,3.928 | 0.000 | 2.675 | 1.585,4.512 | <0.001 |
| **Surgery** | 0.733 | 0.450,1.195 | 0.213 | - | - | - |
| **Any comorbidity** | 1.292 | 0.732,2.279 | 0.377 | - | - | - |

### 4.6 The side effects of the chemotherapeutic regimens

Neutropenia was the most common side effect (137, 41.3%). Hand and foot syndrome was the least frequently occurring side effect (17, 5.1%). The side effects experienced by the patients are shown in Figure 4.2.

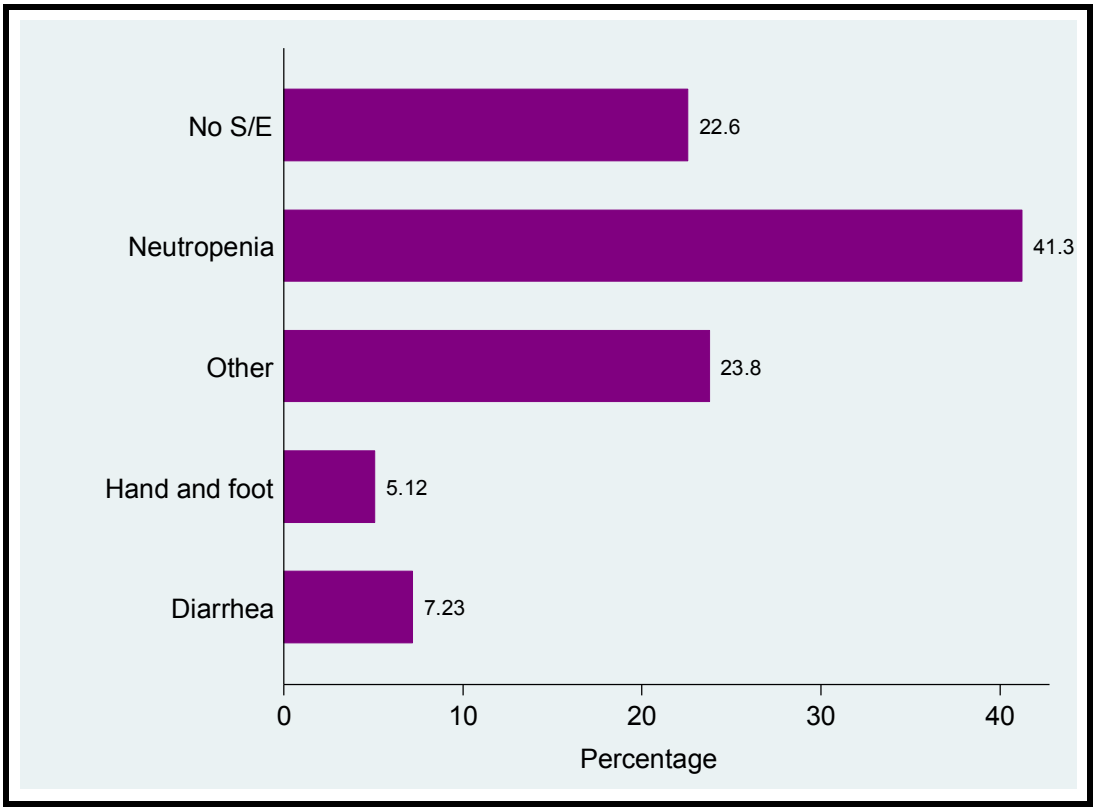



***Figure 4. 2 Side effects experienced by patients on chemotherapy***

### 4.7 Association between chemotherapy and side effects

The relationship between chemotherapy and occurrence of side effects are summarized in Table 4.7. The occurrence of side effects between the fluorouracil and capecitabine based regimens varied significantly ($p<0.001$). Neutropenia was common among the patients on fluorouracil regimens (116, 84.7%). Hand and foot syndrome occurred more in patients on capecitabine (14, 82.4%). Diarrhea was common among the fluorouracil group of patients (16, 66.7%). There was

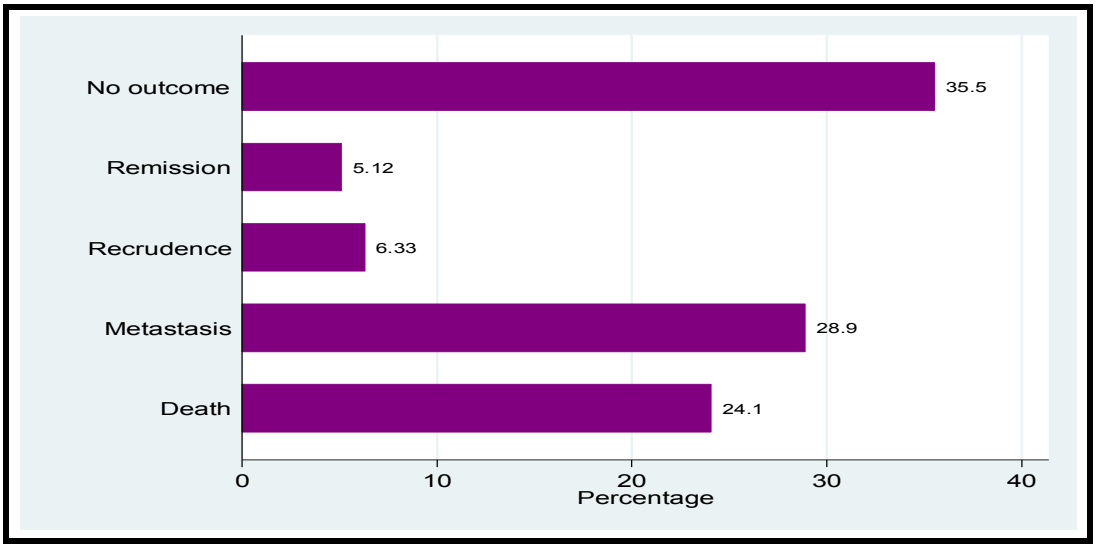
no significant difference in the occurrence of anemia and neuropathy in the two groups ((42, 53.2%) in the fluorouracil and (37, 46.8%) for the capecitabine group).

***Table 4. 7 Association between chemotherapy and side effects***

| **Chemotherapy regimen** | **Side effects** | | | |
|---|---|---|---|---|
| | Neutropenia | Hand and foot | Diarrhea | Others(anemia & neuropathy) |
| **Any FU based** | 116 (84.7%) | 3 (17.7%) | 16 (66.7%) | 42 (53.2%) |
| **Any capecitabine based** | 21 (15.3%) | 14 (82.3%) | 8 (33.3%) | 37 (46.8%) |

### 4.8 The clinical outcomes of the chemotherapeutic regimens

Metastasis was the most common treatment outcome (96, 28.9%). Eighty patients died (24.1%) while seventeen (5.1%) went into remission. Figure 4.3 summarizes the clinical outcomes in CRC patients.




*Key; No outcome-indicates no outcome recorded after completing a full treatment course*

***Figure 4. 3 Clinical outcomes of chemotherapeutic regimens***

### 4.9 Median survival period

A summary of the median survival period by chemotherapeutic regimen are depicted in Table 4.8. The median of the overall survival of patients on 5-FU based regimen was 17 months while those on capecitabine based regimens was 12 months. The difference in these survival period between the two groups was statistically significant ($p<0.001$). This finding was however confounded by indication through chemotherapy switch in these patients. The median survival period for patients on early stage disease was relatively longer for FU patients (19 months).

***Table 4. 8 Median survival period by chemotherapeutic regimen***

| **Chemotherapy** | **Median survival period (months)** | **P value** |
|---|---|---|
| **All stages** | | |
| FU based | 17[13,27.5] | <0.001 |
| Capecitabine based | 12[8,18] | |
| **Early stage disease** | | |
| FU based | 19[14,30] | <0.001 |
| Capecitabine based | 11[9,21] | |
| **Late stage disease** | | |
| FU based | 17[12,27] | <0.001 |
| Capecitabine based | 12[8,17] | |

### 4.10 Association between chemotherapeutic regimen and clinical outcomes

The findings on the association between chemotherapy and clinical outcomes; stratified by disease stage are summarized in Tables 4.9. Ten of the FU-based participants with early stage disease went into remission (13.5%). Mortality and recurrence was relatively similar in both FU and capecitabine groups of patients with early stage disease.

Mortality was high among FU participants with advanced disease (52, 34.9%). Majority of the FU participants with advanced disease experienced metastasis (68, 48.6%). Four participants in the FU group with advanced disease went into remission (2.7%). Incidence of recrudesce was

relatively similar across the two groups of participants with late stage disease ((7, 4.7%) in the FU group and (5, 8.6%) for the capecitabine group).

***Table 4. 9Association between chemotherapeutic regimen and clinical outcomes for early stage disease***

| **Chemotherapy regimen** | **Outcomes** | | | | |
|---|---|---|---|---|---|
| | Remission | Recrudesce | Metastasis | Death | No outcome |
| a. Early stage disease | | | | | |
| **FU based** | 10 (13.5%) | 5 (6.8%) | 8 (10.8%) | 7 (9.5%) | 44 (59.5%) |
| **Capecitabine based** | 3 (5.9%) | 4 (7.8%) | 3 (5.9%) | 6 (11.8%) | 35 (68.6%) |
| b. Late stage disease | | | | | |
| **FU based** | 4 (2.7%) | 7 (4.7%) | 68 (45.6%) | 52 (34.9%) | 18 (12.1%) |
| **Capecitabine based** | 0(0.0%) | 5 (8.6%) | 17 (29.3%) | 15 (25.9%) | 21 (36.2%) |

### 4.11 The risk factors for mortality in colorectal cancer patients

To adjust for confounding by indication, the participants were dichotomized into two groups. Those with a high propensity of receiving FU (with a score >0.25) were coded one while those with high propensity of receiving capecitabine regimen (score<0.25) were coded two. This data was used to adjust for propensity in the regression analysis.

Table 4.11 shows the cox regression model for mortality in CRC patients stratified by disease stage. Surgery reduced the risk of mortality significantly in early stage disease (p=0.009). Chemotherapy switch increased the mortality risk (OR=2.907), this finding was however not significant. On adjusting for propensity score, surgery reduced the risk of mortality. This finding was however not statistically significant.

Cox proportional hazard regression model and a Kaplan-Meier graph were drawn to compare the survival. Table 4.10 is a summary of the predictor variables for mortality in the univariable analysis. CRC patients with advanced disease were 2.955 times more likely to die as to those on early disease stage (p<0.001) Surgery reduced the risk of death by about 55% (p=0.004). CRC

patients who received chemotherapy switch were 2.008 times more likely to die. Metastasis, being on capecitabine regimen and presence of comorbidities increased the risk of death slightly; these findings were however not statistically significant. Survival of colorectal cancer patients was significantly associated with; early vs. late stage disease ($p<0.001$), surgery ($p=0.004$) and any chemotherapy switch ($p=0.003$). On performing multivariable Cox proportional regression model, surgery was found to be the most predictor for survival of colorectal cancer patient ($p=0.021$).

Patients with late stage disease who had received a chemotherapy switch had a 2.196 increased risk of mortality compared to patients; this finding was found to be significant after adjusting for propensity score ($p=0.012$). The findings of the cox regression model on adjusting for propensity are shown in Table 4.12.

***Table 4. 10 The Cox proportional regression model for risk factors of mortality in the entire cohort***

| **Variable** | **HR(95%C.I)** | **P value** | **Adjusted HR(95%C.I)** | **P value** |
|---|---|---|---|---|
| Gender | 1.026(0.660-1.596) | 0.908 | | |
| Age | 0.998(0.981-1.015) | 0.788 | | |
| FU Vs. capecitabine | 1.201(0.725-1.992) | 0.477 | | |
| Education level | 1.734(0.753-3.992) | 0.196 | | |
| Early vs. late stage | 2.955(1.658-5.265) | **0.000** | 1.542(0.801-2.969) | 0.195 |
| Surgery | 0.450(0.262-0.772) | **0.004** | 0.521(0.299-0.906) | **0.021** |
| Radiotherapy | 0.717(0.435-1.183) | 0.193 | | |
| Metastasis | 1.328(0.853-2.066) | 0.209 | | |
| Comorbidities | 1.246(0.744-2.087) | 0.403 | | |
| Any ADR | 0.841(0.491-1.440) | 0.527 | | |
| Any chemo switch | 2.008(1.265-3.185) | **0.003** | 1.533(0.838-2.804) | 0.166 |

***Table 4. 11 The crude Cox proportional regression model for risk factors mortality stratified by disease stage***

| A. Early stage disease | | | B. Late stage disease | |
|---|---|---|---|---|
| **Variable** | **Unadjusted HR(95%C.I)** | **P value** | **Unadjusted HR(95%C.I)** | **P value** |
| Gender | 0.741(0.256,2.143) | 0.580 | 1.137(0.691,1.873) | 0.613 |
| FUvs. Capecitabin | 1.712(0.582,5.036) | 0.329 | 1.208(0.675,2.160) | 0.525 |
| Education level | 2.146(0.186,24.780) | 0.541 | 1.717(0.706,4.178) | 0.233 |
| Surgery | 0.238(0.081,0.702) | **0.009** | 0.681(0.362,1.281) | 0.233 |
| Radiotherapy | 1.489(0.516,4.294) | 0.462 | 0.591(0.331,1.056) | **0.076** |
| Metastasis | - | 1.000 | 0.954(0.585,1.555) | 0.850 |
| Comorbidities | 1.886(0.651,5.461) | 0.242 | 1.614(0.876,2.977) | 0.125 |
| Any ADR | 0.575(0.192,1.716) | 0.321 | 0.813(0.433,1.528) | 0.520 |
| Any chemo switch | 2.907(1.005,8.413) | **0.049** | 1.411(0.844,2.359) | 0.189 |

***Table 4. 12 Adjusted Cox proportional regression model for risk factors for mortality stratified by disease stage***

| A. Early stage disease | | | B. Late stage disease | |
|---|---|---|---|---|
| **Variable** | **HR(95%C.I)** | **P value** | **HR(95%C.I)** | **P value** |
| FUvs. Capecitabin | 0.880 (0.281,2.761) | 0.827 | 1.347 (0.730,2.486) | 0.340 |
| Education level | 1.867 (0.163,21.434) | 0.616 | 2.020 (0.791,5.157) | 0.142 |
| Surgery | 0.356 (0.897,13.132) | **0.071** | 0.676 (0.359, 1.274) | 0.226 |
| Radiotherapy | 0.385 (0.115,1.292) | 0.122 | 0.570 (0.288, 1.129) | **0.107** |
| Metastasis | - | 1.000 | 0.865 (0.513,1.458) | 0.587 |
| Comorbidities | 1.751 (0.604,5.080) | 0.302 | 1.573 (0.850, 2.911) | 0.149 |
| Any ADR | 0.598 (0.200,1.787) | 0.357 | 0.837 (0.444,1.578) | 0.582 |
| Any chemo switch | 1.170 (0.322,4.250) | 0.812 | 2.196 (1.188,4.061) | **0.012** |

Figure 4.4 shows the comparison of Kaplan-Meier survival curves by chemotherapy type. There was no significant difference in the survival of patients on the two chemotherapy groups; 5FU and capecitabine based regimens (p=0.473). From the graph, the probability of survival is zero after close to 50 months for capecitabine while 5FU the patients survived beyond 60 months. This finding may however have been confounded by indication due to chemotherapy switching.

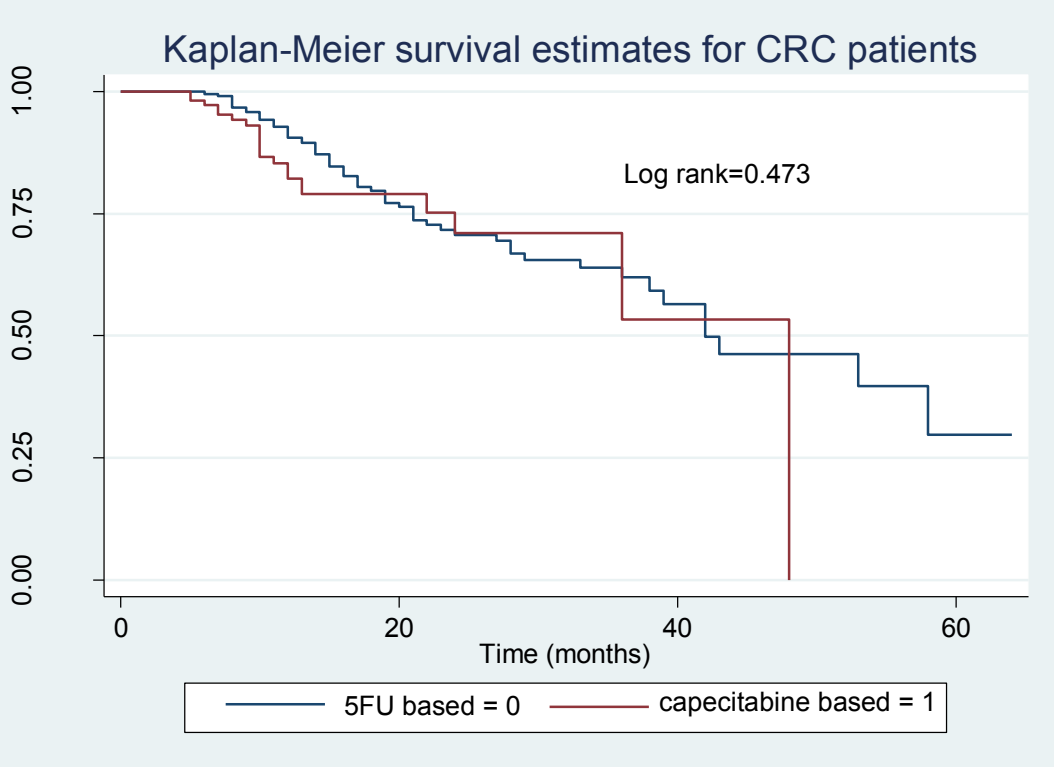



***Figure 4. 4 Comparison of Kaplan-Meier survival curves by chemotherapy type***

### 4.12 The predictors for remission in colorectal cancer patients

Tables 4.13 and 4.14 shows a summary of the predictors for remission obtained from univariable and bivariable regression analysis. Participants on capecitabine regimen were 60% less likely to undergo remission; this finding was however not statistically significant. Early stage participants with comorbidities were 3.964 times more likely to go into remission, this finding was statistically significant after adjusting for propensity (p=0.031).

*Table 4. 13 The logistic regression model for remission stratified by disease stage*

| A. Early stage disease | | | B. Late stage disease | |
|---|---|---|---|---|
| **Variable** | **OR(95%C.I)** | **P value** | **OR(95%C.I)** | **P value** |
| FUvs. Capecitabin | 0.400(0.104,1.533) | 0.181 | - | - |
| Radiotherapy | 0.281 (0.059,1.329) | 0.109 | 0.437 (0.048,3.991) | 0.463 |
| Metastasis | - | - | 0.191 (0.021,1.747) | 0.143 |
| Comorbidities | 2.983 (0.919,9.684) | 0.069 | - | - |
| Tumor site | 1.234 (0.624, 2.444) | 0.547 | 1.084 (0.347,3.392) | 0.889 |
| Any chemo switch | 0.183 (0.023,1.466) | 0.110 | 0.283 (0.031,2.592) | 0.265 |

*Table 4. 14 Propensity adjusted logistic regression model for remission stratified by disease stage*

| A. Early stage disease | | | B. Late stage disease | |
|---|---|---|---|---|
| **Variable** | **OR(95%C.I)** | **P value** | **OR(95%C.I)** | **P value** |
| FUvs. Capecitabine | 0.740 (0.171,3.204) | 0.687 | - | - |
| Radiotherapy | 1.246 (0.100,15.573) | 0.864 | 0.694 (0.051,9.259) | 0.783 |
| Metastasis | - | - | 0.112 (0.011,1.078) | 0.058 |
| Comorbidities | 3.964 (1.135,13.844) | **0.031** | - | - |
| Tumor site | 1.104 (0.464, 2.626) | 0.823 | 0.961 (0.284, 3.257) | 0.949 |
| Any chemo switch | 0.468 (0.039,5.643) | 0.550 | 0.362 (0.026,4.948) | 0.446 |

### 4.13 The predictors for recrudesce in colorectal cancer patients

The univariable and bivariable (adjusted for propensity score) regression analysis for recrudesce are summarized in Tables 4.15. Participants who were diagnosed with early stage disease and later underwent metastasis were 2.29 times more likely to experience recrudesce; this finding was not statistically significant. Late stage disease participants who received a chemotherapy

switch were 4.3 times more likely go into recrudesce (p=0.031). On adjusting for propensity this finding was found not to be statistically significant. After adjusting for propensity score, radiotherapy was found to greatly reduce the risk of recrudesce in late stage participants (OR=0.086, p=0.004).

***Table 4. 15 Logistic regression model for recrudesce stratified by disease stage***

| **A. Early stage disease** | | | **B. Late stage disease** | |
|---|---|---|---|---|
| **Variable** | **OR(95%C.I)** | **P value** | **OR(95%C.I)** | **P value** |
| FU vs. Capecitabine | 1.175 (0.300,4.604) | 0.818 | 1.719 (0.534,5.534) | 0.364 |
| Education level | - | - | 10.500(0.758,145.358) | 0.079 |
| Surgery | 0.585 (0.149,2.307) | 0.444 | 1.617 (0.479,5.465) | 0.439 |
| Radiotherapy | 1.410 (0.359,5.537) | 0.623 | 0.302 (0.065,1.408) | 0.127 |
| Metastasis | 2.292 (0.245,21.427) | 0.467 | 0.472(0.148,1.504) | 0.204 |
| Comorbidities | 0.358 (0.043,2.985) | 0.343 | 0.929 (0.195,4.432) | 0.927 |
| Any chemo switch | 2.100 (0.530,8.317) | 0.291 | 4.306 (1.143,16.221) | **0.031** |
| Tumor site | 0.259 (0.060,1.113) | 0.069 | 1.348 (0.663,2.737) | 0.409 |

### 4.14 Cost categories obtained from key informant interviews

The costs obtained from key informant interviews conducted at KNH were computed to obtain the cost incurred in the full course of chemotherapy treatment (6 months). These total costs categories are presented in Table 4.16. The minimum and maximum costs were estimated based on the market prices and used were used in sensitivity analysis.

***Table 4. 16 Base case cost and ranges for the cost parameters***

| **Description /Costs** | | **Base case (Kshs.)** | **Range for sensitivity analysis** |
|---|---|---|---|
| Chemotherapy | FOLFOX | 137580 | 137580-171975 |
| | XELOX | 180256 | 180256-225320 |
| Surgery | | 63500 | 27000-127000 |
| Radiotherapy | | 3600 | 36000-108000 |
| Pre-medications | FOLFOX | 52728 | 3480-52728 |
| | XELOX | 17360 | 944-17360 |
| Laboratory tests | FOLFOX | 25200 | 25200-31500 |
| | XELOX | 10500 | 10500-15750 |
| Hospitalization | FOLFOX | 52920 | 50000-293400 |
| Personnel costs | FOLFOX | 95984 | 95984-143976 |
| | XELOX | 13196 | 13794-32900 |
| Neutropenia | | 5888 | 5888-17400 |
| CT scan | | 8000 | 8000-25000 |
| Antigen test | | 1000 | 800-3000 |
| Colonoscopy | | 12500 | 8500-20000 |
| Neutropenia Hospitalization | | 10500 | 7500-21000 |
| Second line Chemotherapy | FOLFIRI | 244884 | 195908-293860 |
| | XELIRI | 284096 | 227277-340915 |

### 4.15 Costing analysis of XELOX and FOLFOX

Findings from the total cost of a six course treatment showed that FOLFOX regimen was more expensive (Ksh. 577,270) compared to XELOX (Ksh. 207,486). The main cost items that varied greatly between the two groups are the hospitalization cost, the cost of treating neutropenia, hospitalization cost attributed to neutropenia and the personnel costs. The findings of the cost analysis are summarized in Table 4.17.

***Table 4. 17 The total cost of the treatment regimens for a full course treatment***

| **Cost Item** | **Total cost of a 6 month full course treatment (Ksh.)** | |
|---|---|---|
| | **FOLFOX** | **XELOX** |
| Chemotherapy | 180256 | 137580 |
| Pre-medications | 52728 | 17360 |
| Laboratory tests | 25200 | 10500 |
| Hospitalization | 52920 | 0 |
| Personnel costs | 95984 | 13196 |
| Neutropenia management | 60058 | 7066 |
| Neutropenia Hospitalization | 107100 | 12600 |
| Hand and foot syndrome management | 3024 | 9184 |
| **Total cost (Ksh.)** | **577,270** | **207,486** |

### 4.16 Cost utility analysis of FOLFOX versus XELOX regimens

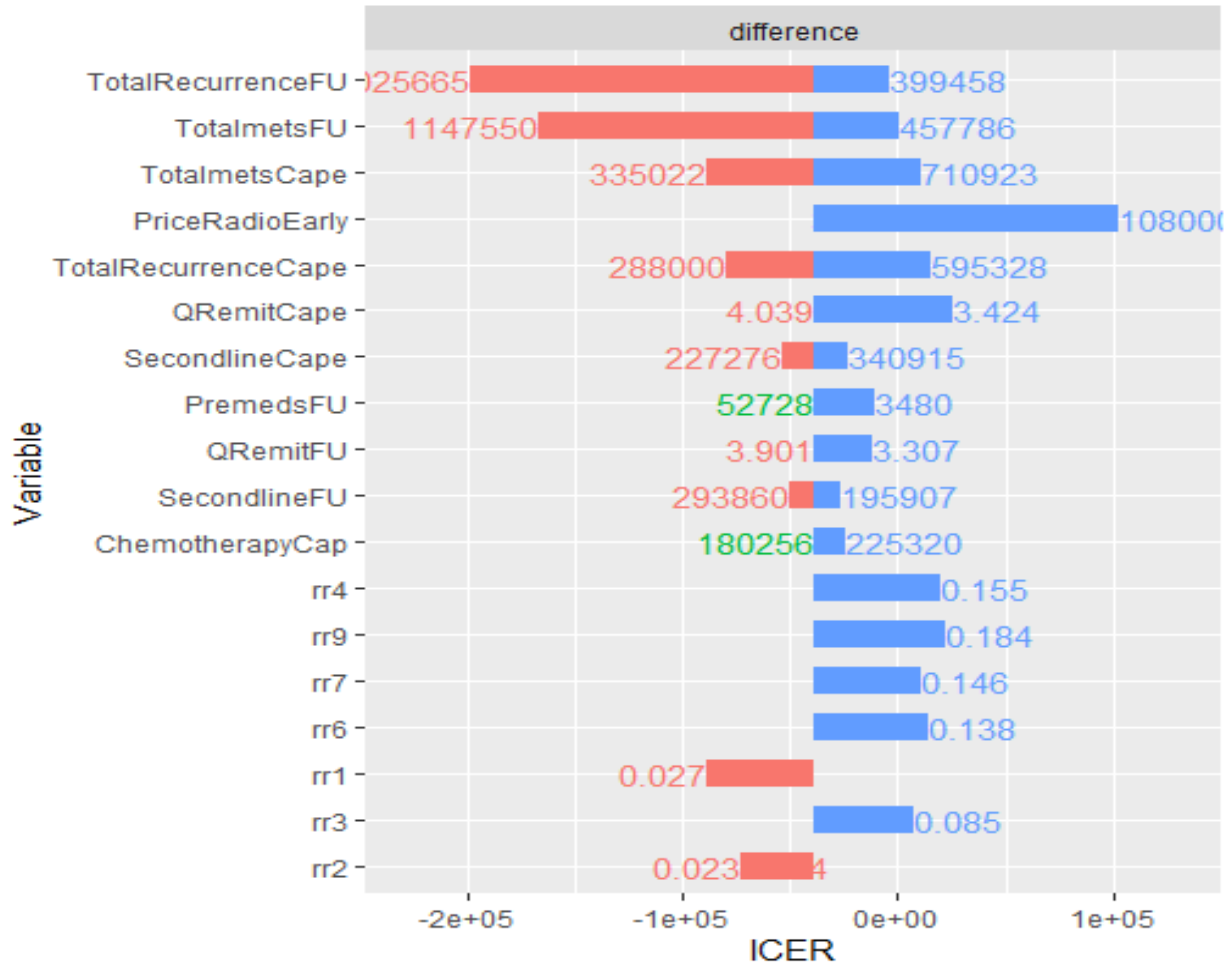
Table 4.18 shows the total costs, QALYs and ICERs for the treatment regimens. FOLFOX was the most expensive regimen. The ICER was Ksh.-38632.74 per QALY gained. The ICER was negative for XELOX due to the lower cost and more QALY gained. FOLFOX was the dominated strategy, as it was more expensive than XELOX from a provider perspective.

*Table 4. 18 Results of the cost utility analysis of FOLFOX versus XELOX*

| | **Five Year Total cost (Million kshs)** | **Total QALYs(5year)** | **Incremental cost** | **Incremental QALY** | **ICER** |
|---|---|---|---|---|---|
| FOLFOX | 439.289 | 20857.69 | | | |
| XELOX | 390.257 | 22126.87 | -49032.05 | 1.269184 | -38632.74 |

## 4.17 One way and probabilistic sensitivity analysis for the incremental cost effectiveness of FOLFOX and XELOX

One way sensitivity analysis was conducted to assess the effects of uncertainties of the variables on the ICER. The results are presented in the tornado diagram in Figure 4.5. The total cost for managing recurrence, metastasis and the cost of radiotherapy had the greatest impact on ICER. Radiotherapy cost and the QALY associated with remission increases ICER.



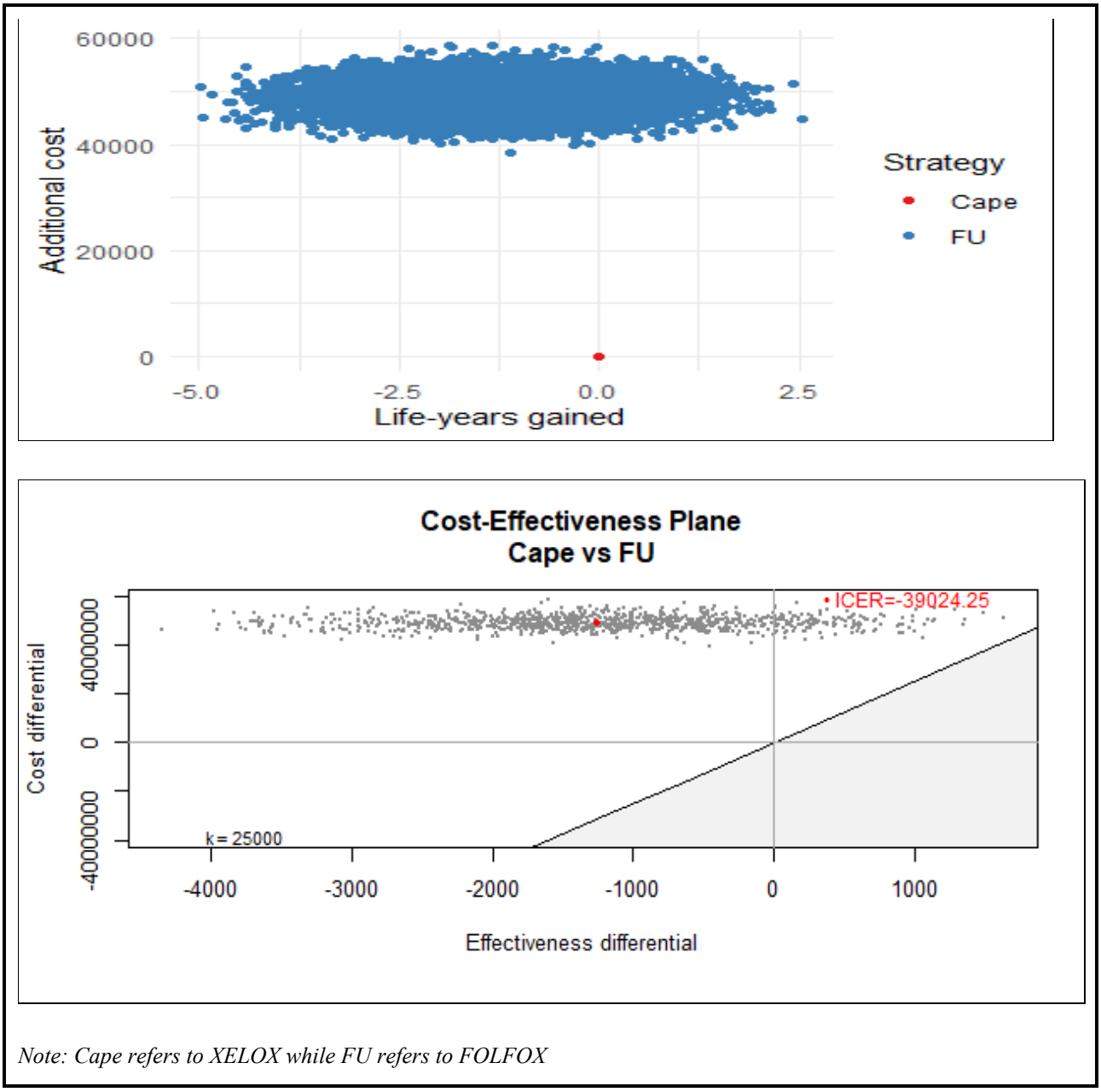

***Note:****TotalRecurrenceFU ,TotalmetsFU , Totalmets Cape, TotalRecurrenceCape= total cost of managing recurrence/metastasis with FU or Capecitabine regimens; PriceRadioEarly= the price of radiotherapy; SecondlineCape or SecondlineFU= Second line treatment with capecitabine or FU regimen; PremedsFU= Cost of premedication with FU treatment; QRemitFU= utility of remission on FU patients; chemotherapyCap=XELOX cost; rr4=odds ratio for transition from recurrence to remission for XELOX; rr6=odds ratio for transition from recurrence to death for XELOX; rr7=odds ratio for transition from metastasis to remission for XELOX; rr9=odds ratio for transition from metastasis to death for XELOX Probability of transition from remission to remission for FU; rr1=Probability of transition from remission to recurrence for FU; rr2=Probability of transition from remission to metastasis for FU;rr3= odds ratio for transition from remission to death for XELOX.*

***Figure 4. 5 Tornado diagram showing the most sensitive variables to the ICER***

Probabilistic sensitivity analysis was performed by Monte Carlo simulation 10,000 times to illustrate the probabilities of cost-effectiveness comparing the two regimens. When the input parameters were jointly altered in PSA, there was no impact on the treatment decision, as XELOX was the favored regimen. The cost-effectiveness plane of FOLFOX versus XELOX in Figure 4.6 and the cost-effectiveness acceptability curve in Figure 4.6 and illustrates that

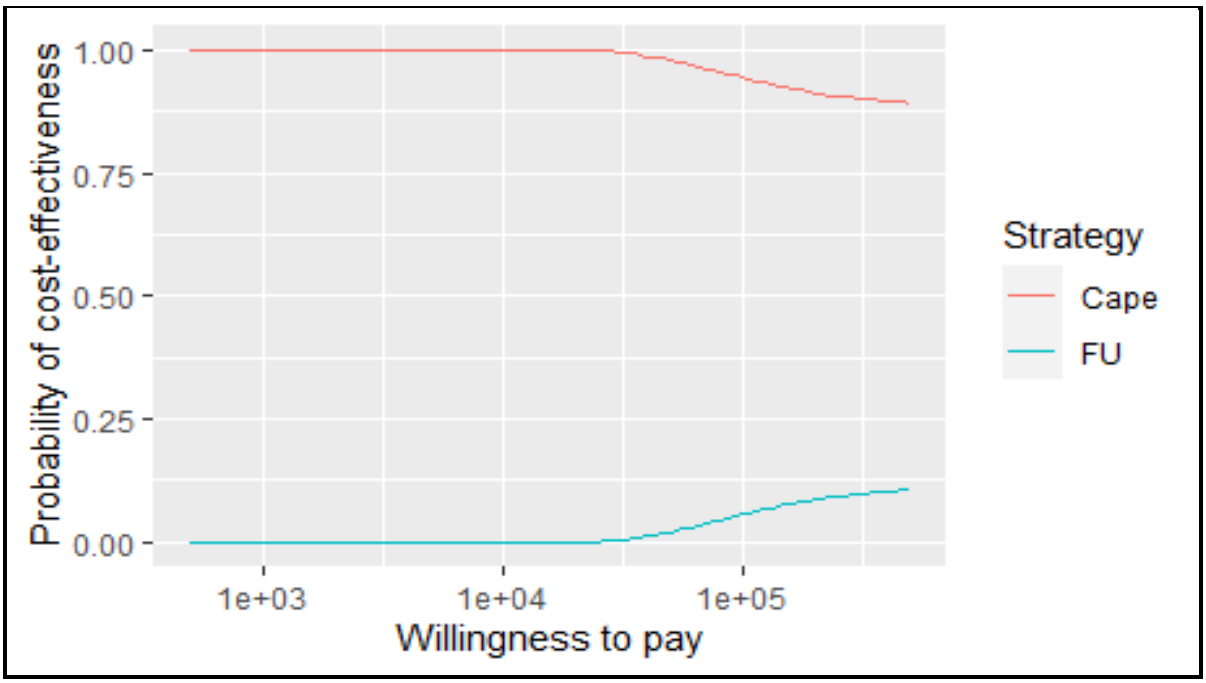
FOLFOX is the dominant regimen in the North west/east quadrant indicating it is more costly in the long run.

From the curve in Figure 4.7, the probability of XELOX being cost effective over FOLFOX was always one when compared to FOLFOX. The willingness to pay threshold was set at Kshs. 150,000.




*Note: Cape refers to XELOX while FU refers to FOLFOX*

***Figure 4. 6 The cost-effectiveness plane of FOLFOX and XELOX***




***Note:*** *Cape refers to XELOX while FU refers to FOLFOX*

***Figure 4. 7 The cost-effectiveness acceptability curve of FOLFOX and XELOX***

### 4.18 Budget impact analysis

The findings from running a five year prediction for the cost of adopting either of the regimens, the cost difference and the budget impact are summarized in Table 4.19. The results show that the use of XELOX for managing colorectal cancer is cost saving each year. The KNH annual budget for the financial year 2019/2020 was 14.5 billion Kenya shillings (Ksh.), with the pharmacy budget being 718.3 million Ksh. and 19.8 million Ksh. of this was allocated for oncology medicines. The impact of adopting XELOX on the KNH annual budget and medicines budget over 5 years ranged between 2.27% to 2.90%. Figure 4.8 shows the cost difference in the use of the two regimens over five years.

***Table 4. 19 Budget impact results for XELOX vs FOLFOX***

| **Variable/ Year** | **2021** | **2022** | **2023** | **2024** | **2025** |
|---|---|---|---|---|---|
| Estimated number of cases year | 4679 | 4974 | 5351 | 5728 | 6105 |

| | | | | | |
|---|---|---|---|---|---|
| FOLFOX cost (Million Kshs.) | 374.464 | 395.902 | 423.299 | 450.695 | 478.092 |
| XELOX cost (Million Kshs.) | 329.924 | 348.794 | 372.908 | 397.023 | 421.138 |
| Cost difference | 44.540 | 47.108 | 50.390 | 53.672 | 56.954 |
| % impact of XELOX on KNH annual budget | 2.27 | 2.40 | 2.56 | 2.73 | 2.90 |

The pharmacy budget in KNH is 3.71% of the annual KNH budget, of which 36.73% of the KNH pharmaceutical budget is allocated for oncology medicines. This implies that 1.36% of the annual KNH budget currently being used for oncology medicines.

According to the 2021 NHIF report, the NHIF oncology utilization package was 1.178 billion Ksh. for radiotherapy and chemotherapy sessions of treatment. This show that from our estimates, approximately 31.8% of this amount would have been spent on FU treatment for CRC treatment, while 28.0% for capecitabine treatment. This implies a very low budgetary allocation and utilization of the oncology package considering the different cancer types in the country.

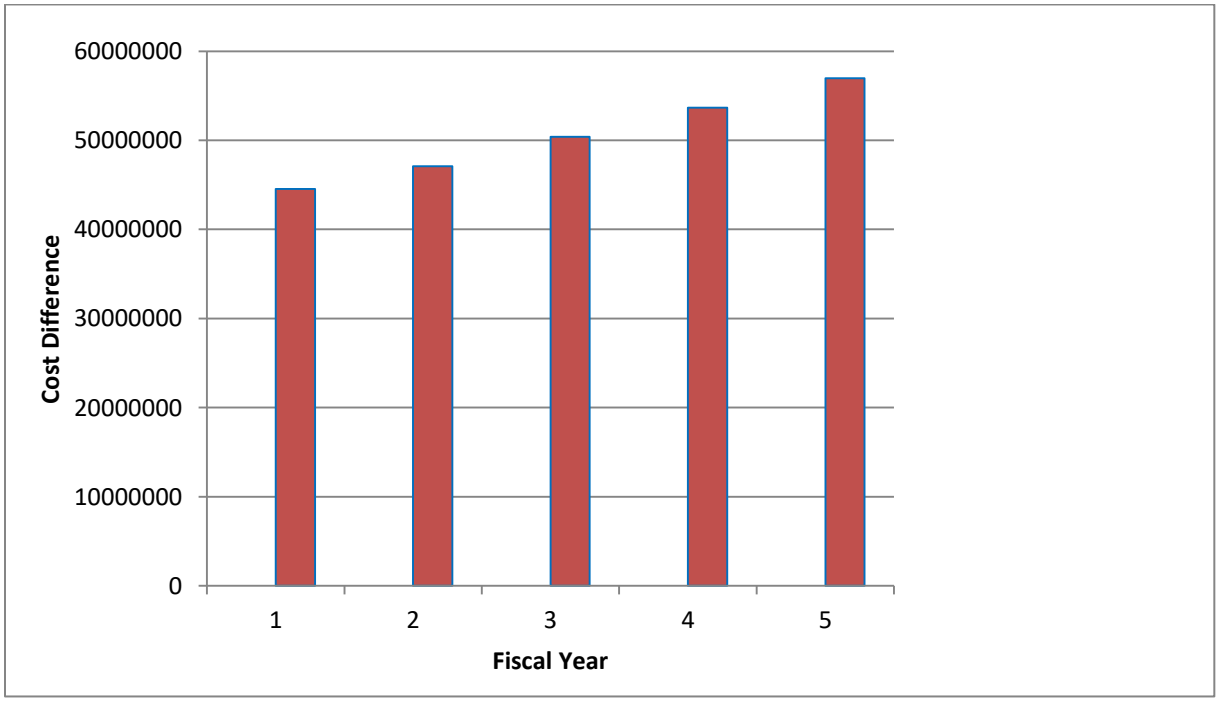


***Figure 4.8 Estimated incremental budget impact with the use of FOLFOX versus XELOX during fiscal years 2021 to 2025***

# CHAPTER FIVE: DISCUSSION, CONCLUSION AND RECOMMENDATIONS

## 5.1 Discussion

The data obtained from the medical records of 332 colorectal cancer patients at KNH was analyzed. Majority of the patients were male and elderly (>55years). This observation is similar to a systematic analysis in Sub-Saharan Africa that indicated a higher incidence of CRC among male patients and peaking at the age above 75 years (Graham et al., 2012). However, it contrasts a study done in Kenya that showed that the age group that was largely affected was between 41-50 years (Saidi et al., 2011). Most patients presented with stage III and IV at diagnosis. Screening for CRC is encouraged for early detection as staging is a determinant of patient prognosis and survival (Kolligs, 2016). The liver was the most common site of metastasis; this is in accordance with data from the American Joint Committee on Cancer (AJCC) (Amin et al., 2017).

Most of the CRC patients were first line therapy (91.0%); with 67.2% being on fluorouracil based regimens. FOLFOX was the mainstay therapy (59.0%). A similar conclusion was made from a study in Kenya that showed patients on capecitabine based regimen were 7.9% (Saidi et al., 2011). Majority of the patients had undergone surgery (62.0%) while 33.1% underwent radiotherapy. This is in accordance with treatment guidelines for management of colorectal cancer (Venook, 2019).

Neutropenia was common among patients on fluorouracil based regimens. The incidence of hand and foot syndrome was common among patients on capecitabine based regimens. This finding is in accordance with data from clinical trials (Schmoll et al., 2014a). Occurrence of anemia and peripheral neuropathy was similar in the two groups. Oxaliplatin has been attributed in contributing to peripheral neuropathy hence occurrence similar since it is found in both XELOX and FOLFOX. The difference in the occurrence of neutropenia, hand and foot syndrome and

diarrhea was statistically significant in the two groups; this is in agreement with data from clinical trials (Guo et al., 2016).

Metastasis was the most common outcome (28.9%). The mortality of CRC patients was at 24.1% while 6.3% of the patients experienced recurrence. A study done in Kenya in 2011 showed that the incidence of mortality and recurrence to be 29.4 % and 37.5% respectively. This indicates a reduction in the incidence of recurrence among CRC patients in Kenya (Saidi et al., 2011), however the big difference in the incidence of recurrence may be attributed to poor recording since most of the records lacked an outcome recording after completion of therapy. The incidence of occurrence of clinical outcomes; remission, recrudesce and death was high among patients fluorouracil based regimen as compared to capecitabine. The difference in the occurrence of the clinical outcomes was statistically significant. Randomized clinical trials conducted showed that capecitabine caused a reduction in the risk of death by 13.0% (Schmoll et al., 2014).

Logistic regression analysis showed that the factors associated with participants who were on capecitabine based regimen were radiotherapy, chemotherapy switch and metastasis. Majority of the patients on capecitabine based regimen were prescribed for capecitabine after being switched from another regimen; mostly fluorouracil based regimen. This resulted in confounding of the clinical outcome in these patients. Patients with advanced disease were less likely to be on capecitabine regimen ($p=0.017$). This is in agreement with data from a study conducted in south Africa that showed that patients on early CRC disease were put on capecitabine based regimens while those with late CRC disease were on 5FU based regimen (Herbst et al., 2020).

A study conducted in Australia to determine the factors impacting treatment choice by patients included distance of the patient from the hospital: the cost of treatment including drugs, hospitalization, transport and caregiver cost. Patients living a distance from the hospital preferred capecitabine to avoid frequent visits. Other factors included; tolerability (adverse reaction), physicians preference, level of education (college degree patients were on capecitabine). In addition, convenience (oral administration motivated patients to choose capecitabine), time from diagnosis to treatment had a positive association with choosing capecitabine (Bloem et al., 2016). The finding on the level of education as a determinant of prescribing capecitabine was in accordance with the results from our study, as capecitabine was more likely to be prescribed to

patients with tertiary level of education. This is because educated patients are able to comprehend the appropriate use and safety measures associated with the use of oral capecitabine.

The difference in overall survival of CRC patients between the 5FU and capecitabine group was statistically significant. This contradicts findings from RCTs that indicated no significant difference in overall survival and the overall response rate (Guo et al., 2016). The finding was limited since the follow up period for these patients was not constant. In addition, it may be attributed to prescribing of capecitabine that was confounded by indication thus given to severely ill patients or patients who had initially been on other chemotherapeutic regimens. From the Kaplan-Meier curve there was no difference in the survival probability of CRC patients on either FU or capecitabine regimens (Log rank=0.473).

From our study, patients with late stage disease and those that had a chemotherapy switched had a high risk of mortality ($p<0.001$ and $p=0.003$ respectively).From the multivariable Cox proportional analysis, surgery was protective and reduces the risk of mortality in CRC patients ($p=0.021$). The factors that did not have a significant effect on the survival of CRC patients included; age at diagnosis, gender, chemo type and education level. This observation is similar to findings from a study carried out in Thailand which concluded that the significant factors affecting the overall survival of CRC patients were; stage at diagnosis, receiving surgery and age group at diagnosis (Kittrongsiri et al., 2020). Another study carried out in Saudi Arabia aimed at identification of survival predictors and the risk of mortality of CRC patients showed that chemotherapy, surgery and radiotherapy lowered the risk of mortality. This finding was however not statistically significant (Azzam et al., 2020).

Remission was found to occur 3.96 times more in early stage disease participants with comorbidities. This contradicts data from literature which showed that a higher Charlson comorbidity score was associated with poorer all-cause survival and disease free survival in stage II and III colorectal cancer (Boakye et al., 2021; Baretti et al., 2018). This finding could be attributed to the confounding effect of the small size of participants with comorbidities in the study. In addition, participants on capecitabine regimen were likely to undergo remission compared to FU participants. The finding was however not statistically significant. Findings from clinical trials demonstrate similarity in the disease free survival (DFS) in the FU and capecitabine regimens (Cheng et al., 2020).

Late stage disease participants who received a chemotherapy switch were more likely to go into recurrence (p=0.031). A study conducted in Iran, had similar findings indicating late stage disease (stage III) to be a risk for recurrence among other risk factors such as old age and rectal cancer (Zare-Bandamiri et al., 2017). The results also indicated a reduction in the risk of recurrence among participants who received radiotherapy (p=0.004). This is in agreement with studies in literature that showed combining chemotherapy with radiotherapy decreased the local recurrence rate. The recurrence risk is important when determining the treatment option to be consider (Osterman et al., 2020; Nakamura et al., 2019).

The reality of increasing costs of cancer treatment provides a good rationale for evaluating the economic effects of oncology regimens in clinical practice. The results indicate that the total treatment cost with FOLFOX is higher compared to XELOX. The cost difference between the two regimens for a six months full course treatment was Ksh.369784. Different costs affect the total cost for the two chemotherapeutic regimens differently; the drug cost, hospitalization, cost of managing neutropenia and personnel cost were the main drivers of the cost difference between the two regimens.

The XELOX regimen comprising capecitabine and oxaliplatin is given as an oral and requires less intravenous administration than FOLFOX, comprising 5-FU, folinic acid and oxaliplatin. Therefore it might be expected that it would cost less overall when costs of hospitalization are taken into account. This study showed that this was indeed the case and that, when the fewer cycles of therapy required with XELOX (8 versus 12) were also taken into account, the savings in other costs outweighed the higher purchase price of the XELOX regimen.

Based on the results, XELOX was cost effective as compared with FOLFOX in the management of stage II and III colorectal cancer since the ICER (Khs.-38,632.74 per QALY gained) was less than the WTP threshold of Khs.196,605 per QALY gained as recommended by WHO (Bertram et al., 2016). The ICER was negative implying that XELOX was less costly and more effective as compared to FOLFOX from the provider perspective. Deterministic sensitivity analysis showed that the ICER was most sensitive to the cost of managing recurrence and metastasis; considering FOLFIRI and XELIRI as the second line therapy for metastasis in the FU and capecitabine regimen. Radiotherapy cost increased the ICER significantly.

Our study results were not in accordance with a study conducted in Thailand that showed that both FOLFOX and XELOX were not cost effective in management of Stage III colorectal cancer, however this was from the societal perspective (Lerdkiattikorn et al., 2015). In the UK, China and Poland, XELOX was found to be the cost effective regimen while in the USA FOLFOX was cost effective (Toumazis et al., 2017; Płaczek et al., 2017; Wen et al., 2014; Shiroiwa et al., 2009).

The budget impact of adoption of XELOX in management of colorectal cancer in KNH showed that it was cost saving, with an impact of about 2.5% to 2.9% on the hospital budget over the next five years. This is in accordance with a study conducted in Italy that concluded that XELOX leads to a positive impact on the national drug budget in terms of costs savings in patients with colorectal cancer (Nuijten et al., 2008). The NHIF oncology package utilization was low (1.178 billion Ksh.) from the 2021 report, implying very low budgetary allocation for oncology treatment in Kenya ("NHIF_Universal_Health_Coverage_14.06.2021.pdf," n.d.). This leads to increased out of pocket payments by the patients' hence catastrophic expenditure. The oncology package needs to be reviewed as a journey to universal health coverage vision 2030.

### 5.2 Implications for policy

This study can be used to inform policy makers in evaluating factors involved in resource allocation and reviewing budgetary allocation of oncology medicines and cancer care. In addition, in has implication for the clinical team and hospital staff in making decisions regarding the best treatment options for individual patients.

### 5.3 Study Limitations

The study was done retrospectively to obtain pre-recorded information from patient files. Hence incomplete and missing information from the patient files was a major study limitation. Staging of colorectal cancer for patient at diagnosis was not done or clearly stated. There was loss of follow up of most patients hence determining the outcome of these patients was a challenge.

The use of staff time sheets to determine the personnel costs would have provided more accurate personnel time commitment; this should be considered in future research. The costs used for sensitivity analysis were estimated and may not be accurate. The utility score (health related quality of life) used the study was obtained from literature of patients followed up in other countries thus maybe different from the utility score in the Kenyan context given the difference in culture and the healthcare infrastructure. The survival data was also obtained from literature since the data obtained from the study was affected by confounding factors. The Markov model was simulated for five years' time horizon, a consideration of a lifetime time horizon should have been put into account in the study. The study focused on the cost effectiveness of fluorouracil and capecitabine regimen since they are the main stay chemotherapy in our country as targeted chemotherapy for colorectal cancer are too expensive for majority of the patients to access.

The study was conducted for a healthcare perspective, hence the findings were limited as some cost aspects would have been affected if conducted from other perspective such as societal perspective.

Nevertheless, the strength of modeling is that sensitivity analysis can show where the areas of greatest uncertainty lie and can identify areas that warrant future research.

## 5.4 Conclusion

FOLFOX is the mainstay therapy for management of colorectal cancer in Kenya. Based on the survival probability, the clinical effectiveness does not vary across the two regimens (FOLFOX and XELOX). The cost of CRC treatment with FOLFOX is high compared to XELOX, with the main cost drivers being the hospitalization cost, drug cost, cost of managing neutropenia and the personnel cost. XELOX is the most cost effective regimen as compared to FOLFOX from the provider perspective and should be considered as a drug of choice in the management of colorectal cancer in Kenya. However, the uncertainties due to the small difference in the effect between the regimens should be assessed further by conducting the study from the societal perspective.

## 5.5 Recommendations

This study recommends the use of XELOX as the adjuvant chemotherapy of choice in the management of stage II and III colorectal cancer. Screening of high risk patients for colorectal cancer need to be adopted to ensure early diagnosis and treatment of the disease as this leads to good clinical outcomes. Correct staging of colorectal cancer patients and appropriate record keeping of diagnosis and clinical outcomes at the end a treatment course should be advocated for in KNH. The NHIF and other private insurers to review the oncology package upwards. Further studies are needed to obtain the utility score of cancer patients in our local setup, to improve the internal validity of economic evaluation studies. Further research studies to be conducted to investigate the cost effectiveness of new targeted chemotherapy in our local setup.

# REFERENCES


Amin, M.B., American Joint Committee on Cancer, American Cancer Society (Eds.), 2017a. AJCC cancer staging manual, Eight edition / editor-in-chief, Mahul B. Amin, MD, FCAP ; editors, Stephen B. Edge, MD, FACS [and 16 others] ; Donna M. Gress, RHIT, CTR-Technical editor ; Laura R. Meyer, CAPM-Managing editor. ed. American Joint Committee on Cancer, Springer, Chicago IL.

Ananda, S., Kosmider, S., Tran, B., Field, K., Jones, I., Skinner, I., Guerrieri, M., Chapman, M., Gibbs, P., 2016. The rapidly escalating cost of treating colorectal cancer in Australia: Rising cost of colorectal cancer. Asia Pac. J. Clin. Oncol. 12, 33–40. https://doi.org/10.1111/ajco.12350

André, T., de Gramont, Armand, Vernerey, D., Chibaudel, B., Bonnetain, F., Tijeras-Raballand, A., Scriva, A., Hickish, T., Tabernero, J., Van Laethem, J.L., Banzi, M., Maartense, E., Shmueli, E., Carlsson, G.U., Scheithauer, W., Papamichael, D., Möehler, M., Landolfi, S., Demetter, P., Colote, S., Tournigand, C., Louvet, C., Duval, A., Fléjou, J.-F., de Gramont, Aimery, 2015. Adjuvant Fluorouracil, Leucovorin, and Oxaliplatin in Stage II to III Colon Cancer: Updated 10-Year Survival and Outcomes According to *BRAF* Mutation and Mismatch Repair Status of the MOSAIC Study. J. Clin. Oncol. 33, 4176–4187. https://doi.org/10.1200/JCO.2015.63.4238

Arnold, M., Sierra, M.S., Laversanne, M., Soerjomataram, I., Jemal, A., Bray, F., 2017. Global patterns and trends in colorectal cancer incidence and mortality. Gut 66, 683–691. https://doi.org/10.1136/gutjnl-2015-310912

Omondi, A.M., Opanga, S., Martin, A., Kurdi, A., Godman, B., 2018. Pilot study assessing the direct medical cost of treating patients with cancer in Kenya; findings and implications for the future. J. Med. Econ. 21, 878–887. https://doi.org/10.1080/13696998.2018.1484372

Ayvaci, M.U.S., Shi, J., Alagoz, O., Lubner, S.J., 2013. Cost-Effectiveness of Adjuvant FOLFOX and 5FU/LV Chemotherapy for Patients with Stage II Colon Cancer. Med. Decis. Making 33, 521–532. https://doi.org/10.1177/0272989X12470755

Azzam, N., AlRuthia, Y., Alharbi, O., Aljebreen, A., Almadi, M., Alarfaj, M., Alsaleh, K., Almasoud, A., Alsharidah, M., Alseneidi, S., Alali, F., Alalwan, M., 2020. Predictors of Survival Among Colorectal Cancer Patients in a Low Incidence Area. Cancer Manag. Res. Volume 12, 451–459. https://doi.org/10.2147/CMAR.S233215

Baretti, M., Rimassa, L., Personeni, N., Giordano, L., Tronconi, M.C., Pressiani, T., Bozzarelli, S., Santoro, A., 2018. Effect of Comorbidities in Stage II/III Colorectal Cancer Patients Treated With Surgery and Neoadjuvant/Adjuvant Chemotherapy: A Single-Center, Observational Study. Clin. Colorectal Cancer 17, e489–e498. https://doi.org/10.1016/j.clcc.2018.03.010

Bertram, M.Y., Lauer, J.A., De Joncheere, K., Edejer, T., Hutubessy, R., Kieny, M.-P., Hill, S.R., 2016. Cost–effectiveness thresholds: pros and cons. Bull. World Health Organ. 94, 925–930. https://doi.org/10.2471/BLT.15.164418

Bloem, L.T., De Abreu Lourenço, R., Chin, M., Ly, B., Haas, M., 2016. Factors Impacting Treatment Choice in the First-Line Treatment of Colorectal Cancer. Oncol. Ther. 4, 103–116. https://doi.org/10.1007/s40487-016-0020-4

Boakye, D., Nagrini, R., Ahrens, W., Haug, U., Günther, K., 2021. The association of comorbidities with administration of adjuvant chemotherapy in stage III colon cancer patients: a systematic review and meta-analysis. Ther. Adv. Med. Oncol. 13, 175883592098652. https://doi.org/10.1177/1758835920986520

Böckelman, C., Engelmann, B.E., Kaprio, T., Hansen, T.F., Glimelius, B., 2015a. Risk of recurrence in patients with colon cancer stage II and III: A systematic review and meta-analysis of recent literature. Acta Oncol. 54, 5–16. https://doi.org/10.3109/0284186X.2014.975839

Bray, F., Ferlay, J., Soerjomataram, I., Siegel, R.L., Torre, L.A., Jemal, A., 2018. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA. Cancer J. Clin. 68, 394–424. https://doi.org/10.3322/caac.21492

Briggs, A., Sculpher, M., 1998. An Introduction to Markov Modelling for Economic Evaluation: PharmacoEconomics 13, 397–409. https://doi.org/10.2165/00019053-199813040-00003

Cassidy, J., Clarke, S., Díaz-Rubio, E., Scheithauer, W., Figer, A., Wong, R., Koski, S., Lichinitser, M., Yang, T.-S., Rivera, F., Couture, F., Sirzén, F., Saltz, L., 2008. Randomized Phase III Study of Capecitabine Plus Oxaliplatin Compared With Fluorouracil/Folinic Acid Plus Oxaliplatin As First-Line Therapy for Metastatic Colorectal Cancer. J. Clin. Oncol. 26, 2006–2012. https://doi.org/10.1200/JCO.2007.14.9898

Cassidy, J., Clarke, S., Díaz-Rubio, E., Scheithauer, W., Figer, A., Wong, R., Koski, S., Rittweger, K., Gilberg, F., Saltz, L., 2011. XELOX vs FOLFOX-4 as first-line therapy for metastatic colorectal cancer: NO16966 updated results. Br. J. Cancer 105, 58–64. https://doi.org/10.1038/bjc.2011.201

Charan, J., Biswas, T., 2013. How to calculate sample size for different study designs in medical research? Indian J. Psychol. Med. 35, 121. https://doi.org/10.4103/0253-7176.116232

Cheng, J., Shuai, X., Gao, J., Wang, G., Tao, K., Cai, K., 2020. Comparative efficacy and tolerability of adjuvant systemic treatments against resectable colon cancer: a network meta-analysis. Ther. Adv. Med. Oncol. 12, 175883592097419. https://doi.org/10.1177/1758835920974195

Chitai, A.M., n.d. An assessment of the patients' perception of colorectal Cancer management cancer at Kenyatta National Hospital 2018.

Comella, P., Massidda, B., Filippelli, G., Farris, A., Natale, D., Barberis, G., Maiorino, L., Palmeri, S., Cannone, M., Condemi, G., on behalf of the Southern Italy Cooperative Oncology Group, 2009. Randomised trial comparing biweekly oxaliplatin plus oral capecitabine versus oxaliplatin plus i.v. bolus fluorouracil/leucovorin in metastatic colorectal cancer patients: results of the Southern Italy Cooperative Oncology study 0401. J. Cancer Res. Clin. Oncol. 135, 217–226. https://doi.org/10.1007/s00432-008-0454-7

Compton, C.C., Greene, F.L., 2004. The Staging of Colorectal Cancer: 2004 and Beyond. CA. Cancer J. Clin. 54, 295–308. https://doi.org/10.3322/canjclin.54.6.295

Dent, J., Manner, C.K., Milner, D., Mutebi, M., Ng'ang'a, A., Olopade, O.I., Rebbeck, R., Stefan, D.C., 2017. Africa's Emerging Cancer Crisis: A Call to Action 8.

Derissen, E.J.B., Jacobs, B.A.W., Huitema, A.D.R., Rosing, H., Schellens, J.H.M., Beijnen, J.H., 2016a. Exploring the intracellular pharmacokinetics of the 5-fluorouracil nucleotides during capecitabine treatment: Intracellular pharmacokinetics of the 5-FU nucleotides. Br. J. Clin. Pharmacol. 81, 949–957. https://doi.org/10.1111/bcp.12877

Díaz-Rubio, E., Tabernero, J., Gómez-España, A., Massutí, B., Sastre, J., Chaves, M., Abad, A., Carrato, A., Queralt, B., Reina, J.J., Maurel, J., González-Flores, E., Aparicio, J., Rivera, F., Losa, F., Aranda, E., 2007. Phase III Study of Capecitabine Plus Oxaliplatin Compared With Continuous-Infusion Fluorouracil Plus Oxaliplatin As First-Line Therapy in Metastatic Colorectal Cancer: Final Report of the Spanish Cooperative Group for the Treatment of Digestive Tumors Trial. J. Clin. Oncol. 25, 4224–4230. https://doi.org/10.1200/JCO.2006.09.8467

Drummond, M., Weatherly, H., Ferguson, B., 2008. Economic evaluation of health interventions. BMJ 337, a1204. https://doi.org/10.1136/bmj.a1204

Ducreux, M., Bennouna, J., Hebbar, M., Ychou, M., Lledo, G., Conroy, T., Adenis, A., Faroux, R., Rebischung, C., Bergougnoux, L., Kockler, L., Douillard, J.-Y., 2011a. Capecitabine plus oxaliplatin (XELOX) versus 5-fluorouracil/leucovorin plus oxaliplatin (FOLFOX-6) as first-line treatment for metastatic colorectal cancer. Int. J. Cancer 128, 682–690. https://doi.org/10.1002/ijc.25369

Gao, Y.N., Mamo, A., Palumbo, M.O., Batist, G., Chaudhury, P., Melnychuk, D., Metrakos, P., Panasci, L., Kavan, P., 2013. Are XELOX and FOLFOX equivalent in colorectal cancer? Dose intensity, toxicity, and treatment duration in clinical practice. J. Clin. Oncol. 31, e14556–e14556. https://doi.org/10.1200/jco.2013.31.15_suppl.e14556

Geng, F., Wang, Z., Yin, H., Yu, J., Cao, B., 2017. Molecular Targeted Drugs and Treatment of Colorectal Cancer: Recent Progress and Future Perspectives. Cancer Biother. Radiopharm. 32, 149–160. https://doi.org/10.1089/cbr.2017.2210

Graham, A., Adeloye, D., Grant, L., Theodoratou, E., Campbell, H., 2012a. Estimating the incidence of colorectal cancer in Sub–Saharan Africa: A systematic analysis. J. Glob. Health 2. https://doi.org/10.7189/jogh.02.020404

Granados-Romero, J.J., Valderrama-Treviño, A.I., Contreras-Flores, E.H., Barrera-Mera, B., Herrera Enríquez, M., Uriarte-Ruíz, K., Ceballos-Villalba, J.C., Estrada-Mata, A.G., Alvarado Rodríguez, C., Arauz-Peña, G., 2017. Colorectal cancer: a review. Int. J. Res. Med. Sci. 5, 4667. https://doi.org/10.18203/2320-6012.ijrms20174914

Gress, D.M., Edge, S.B., Greene, F.L., Washington, M.K., Asare, E.A., Brierley, J.D., Byrd, D.R., Compton, C.C., Jessup, J.M., Winchester, D.P., 2017. Principles of cancer staging. AJCC Cancer Staging Man. 8th Ed N. Y. NY Springer.

Guo, Y., Xiong, B.-H., Zhang, T., Cheng, Y., Ma, L., 2016a. XELOX vs. FOLFOX in metastatic colorectal cancer: An updated meta-analysis. Cancer Invest. 34, 94–104. https://doi.org/10.3109/07357907.2015.1104689

Hammond, W.A., Swaika, A., Mody, K., 2016. Pharmacologic resistance in colorectal cancer: a review. Ther. Adv. Med. Oncol. 8, 57–84. https://doi.org/10.1177/1758834015614530

Hanly, P., Céilleachair, A.Ó., Skally, M., O'Leary, E., Staines, A., Kapur, K., Fitzpatrick, P., Sharp, L., 2013a. Time Costs Associated with Informal Care for Colorectal Cancer: An Investigation of the Impact of Alternative Valuation Methods. Appl. Health Econ. Health Policy. 11, 193–203. https://doi.org/10.1007/s40258-013-0013-5

Hanly, P., Céilleachair, A.Ó., Skally, M., O'Neill, C., Sharp, L., 2015. Direct costs of radiotherapy for rectal cancer: a microcosting study. BMC Health Serv. Res. 15. https://doi.org/10.1186/s12913-015-0845-9

Hanly, P., Walsh, P.M., Ó Céilleachair, A., Skally, M., Staines, A., Kapur, K., Fitzpatrick, P., Sharp, L., 2013b. Work-Related Productivity Losses in an Era of Ageing Populations: The Case of Colorectal Cancer. J. Occup. Environ. Med. 55, 128–134. https://doi.org/10.1097/JOM.0b013e3182820553

Herbst, C., Miot, J.K., Moch, S.L., Ruff, P., 2020. Colorectal Cancer (CRC) treatment and associated costs in the public sector compared to the private sector in Johannesburg, South Africa. BMC Health Serv. Res. 20, 290. https://doi.org/10.1186/s12913-020-05112-w

Hillner, B.E., Schrag, D., Sargent, D.J., Fuchs, C.S., Goldberg, R.M., 2005. Cost-effectiveness projections of oxaliplatin and infusional fluorouracil versus irinotecan and bolus fluorouracil in first-line therapy for metastatic colorectal carcinoma. Cancer 104, 1871–1884. https://doi.org/10.1002/cncr.21411

Iacovelli, R., Pietrantonio, F., Palazzo, A., Maggi, C., Ricchini, F., Braud, F. de, Bartolomeo, M.D., 2014. Incidence and relative risk of grade 3 and 4 diarrhoea in patients treated with capecitabine or 5-fluorouracil: a meta-analysis of published trials. Br. J. Clin. Pharmacol. 78, 1228–1237. https://doi.org/10.1111/bcp.12449

Ilinca, S., Di Giorgio, L., Salari, P., Chuma, J., 2019. Socio-economic inequality and inequity in use of health care services in Kenya: evidence from the fourth Kenya household health expenditure and utilization survey. Int. J. Equity Health 18, 196. https://doi.org/10.1186/s12939-019-1106-z

Inoue, Y., Kusunoki, M., 2014. Advances and directions in chemotherapy using implantable port systems for colorectal cancer: a historical review. Surg. Today 44, 1406–1414. https://doi.org/10.1007/s00595-013-0672-8

Jeong, K., Cairns, J., 2016. Systematic review of health state utility values for economic evaluation of colorectal cancer. Health Econ. Rev. 6, 36. https://doi.org/10.1186/s13561-016-0115-5

Kamal, K.M., Covvey, J.R., Dashputre, A., Ghosh, S., Shah, S., Bhosle, M., Zacker, C., 2017. A Systematic Review of the Effect of Cancer Treatment on Work Productivity of Patients and Caregivers. J. Manag. Care Spec. Pharm. 23, 136–162. https://doi.org/10.18553/jmcp.2017.23.2.136

Katanyoo, K., Chitapanarux, I., Tungkasamit, T., Chakrabandhu, S., Chongthanakorn, M., Jiratrachu, R., Kridakara, A., Townamchai, K., Muangwong, P., Tovanabutra, C., Chomprasert, K., 2018. Cost-utility analysis of 5-fluorouracil and capecitabine for adjuvant treatment in locally advanced rectal cancer. J. Gastrointest. Oncol. 9, 425–434. https://doi.org/10.21037/jgo.2018.01.11

Katsidzira, L., Gangaidzo, I., Thomson, S., Rusakaniko, S., Matenga, J., Ramesar, R., 2017. The shifting epidemiology of colorectal cancer in sub-Saharan Africa. Lancet Gastroenterol. Hepatol. 2, 377–383. https://doi.org/10.1016/S2468-1253(16)30183-2

Kittrongsiri, K., Wanitsuwan, W., Prechawittayakul, P., Sangroongruangsri, S., Cairns, J., Chaikledkaew, U., 2020. Survival analysis of colorectal cancer patients in a Thai hospital-based cancer registry. Expert Rev. Gastroenterol. Hepatol. 14, 291–300. https://doi.org/10.1080/17474124.2020.1740087

Kolligs, F.T., 2016a. Diagnostics and Epidemiology of Colorectal Cancer. Visc. Med. 32, 158–164. https://doi.org/10.1159/000446488

Laiyemo, A.O., Brawley, O., Irabor, D., Boutall, A., Ramesar, R.S., Madiba, T.E., 2016. Toward colorectal cancer control in Africa: Letter to the Editor. Int. J. Cancer 138, 1033–1034. https://doi.org/10.1002/ijc.29843

Lee, J.Y., Ock, M., Jo, M.-W., Son, W.-S., Lee, H.-J., Kim, S.-H., Kim, H.J., Lee, J.L., 2017. Estimating utility weights and quality-adjusted life year loss for colorectal cancer-related health states in Korea. Sci. Rep. 7, 5571. https://doi.org/10.1038/s41598-017-06004-6

Lerdkiattikorn, P., Chaikledkaew, U., Lausoontornsiri, W., Chindavijak, S., Khuhaprema, T., Tantai, N., Teerawattananon, Y., 2015. Cost-utility analysis of adjuvant chemotherapy in patients with stage III colon cancer in Thailand. Expert Rev. Pharmacoecon. Outcomes Res. 15, 687–700. https://doi.org/10.1586/14737167.2015.972379

Loree, J.M., Sha, A., Soleimani, M., Kennecke, H.F., Ho, M.Y., Cheung, W.Y., Mulder, K.E., Abadi, S., Spratlin, J.L., Gill, S., 2018a. Survival Impact of CAPOX Versus FOLFOX in the Adjuvant Treatment of Stage III Colon Cancer. Clin. Colorectal Cancer 17, 156–163. https://doi.org/10.1016/j.clcc.2018.01.010

Makau-Barasa, L.K., Greene, S.B., Othieno-Abinya, N.A., Wheeler, S., Skinner, A., Bennett, A.V., 2018. Improving Access to Cancer Testing and Treatment in Kenya. J. Glob. Oncol. 1–8. https://doi.org/10.1200/JGO.2017.010124

Mamo, A., Easaw, J., Ibnshamsah, F., Baig, A., Rho, Y.S., Kavan, T., Batist, G., Kavan, P., 2016. Retrospective analysis of the effect of CAPOX and mFOLFOX6 dose intensity on survival in colorectal patients in the adjuvant setting. Curr. Oncol. 23, 171. https://doi.org/10.3747/co.23.3059

Mar, J., Errasti, J., Soto-Gordoa, M., Mar-Barrutia, G., Martinez-Llorente, J.M., Domínguez, S., García-Albás, J.J., Arrospide, A., 2017. The Cost of Colorectal Cancer According to the TNM Stage. Cir. Esp. Engl. Ed. 95, 89–96. https://doi.org/10.1016/j.cireng.2017.01.001

Mariotto, A.B., Yabroff, K.R., Shao, Y., Feuer, E.J., Brown, M.L., 2011. Projections of the cost of cancer care in the United States: 2010-2020. J. Natl. Cancer Inst. 103, 117–128. https://doi.org/10.1093/jnci/djq495

Martoni, A.A., Pinto, C., Fabio, F.D., Lelli, G., Rojas Llimpe, F.L., Gentile, A.L., Mutri, V., Ballardini, P., Giaquinta, S., Piana, E., 2006. Capecitabine plus oxaliplatin (xelox) versus protracted 5-fluorouracil venous infusion plus oxaliplatin (pvifox) as first-line treatment in advanced colorectal cancer: A GOAM phase II randomised study (FOCA trial). Eur. J. Cancer 42, 3161–3168. https://doi.org/10.1016/j.ejca.2006.08.034

Nakamura, T., Sato, T., Hayakawa, K., Koizumi, W., Kumagai, Y., Watanabe, M., 2019. Strategy to avoid local recurrence in patients with locally advanced rectal cancer. Radiat. Oncol. 14, 53. https://doi.org/10.1186/s13014-019-1253-9

NHIF_Universal_Health_Coverage_14.06.2021.pdf, n.d.

Nuijten, M., Giuliani, G., de Reydetde, V.F., 2008. PCN12 BUDGETARY IMPACT OF XELOX IN COLORECTAL CANCER IN ITALY. Value Health 11, A463. https://doi.org/10.1016/S1098-3015(10)66549-7

Ó Céilleachair, A., Costello, L., Finn, C., Timmons, A., Fitzpatrick, P., Kapur, K., Staines, A., Sharp, L., 2012. Inter-relationships between the economic and emotional consequences of colorectal cancer for patients and their families: a qualitative study. BMC Gastroenterol. 12. https://doi.org/10.1186/1471-230X-12-62

Olaleye, O., Ekrikpo, U., 2017. Epidemiology of Cancers in Sub-Saharan Africa, in: Adedeji, O.A. (Ed.), Cancer in Sub-Saharan Africa. Springer International Publishing, Cham, pp. 3–19. https://doi.org/10.1007/978-3-319-52554-9_1

Osterman, E., Hammarström, K., Imam, I., Osterlund, E., Sjöblom, T., Glimelius, B., 2020. Recurrence Risk after Radical Colorectal Cancer Surgery—Less Than before, But How High Is It? Cancers 12, 3308. https://doi.org/10.3390/cancers12113308

Pandor, A., Eggington, S., Paisley, S., Tappenden, P., Sutcliffe, P., 2006. The clinical and cost-effectiveness of oxaliplatin and capecitabine for the adjuvant treatment of colon cancer: Systematic review and economic evaluation. Health Technol. Assess. 10, iii–89.

Parker, R.K., Ranketi, S.S., McNelly, C., Ongondi, M., Topazian, H.M., Dawsey, S.M., Murphy, G.A., White, R.E., Mwachiro, M., 2019. Colorectal cancer is increasing in rural Kenya:

challenges and perspectives. Gastrointest. Endosc. 89, 1234–1237. https://doi.org/10.1016/j.gie.2018.12.003

Paulden, M., 2020. Calculating and Interpreting ICERs and Net Benefit. PharmacoEconomics 38, 785–807. https://doi.org/10.1007/s40273-020-00914-6

Płaczek, J., Feldheim, M., Żurawski, B., Krysiński, J., 2017. Cost-effectiveness analysis of treatment of patients with colorectal cancer with FOLFOX4 and XELOX regimens. Nowotw. J. Oncol. 66, 470–476. https://doi.org/10.5603/NJO.2016.0084

Porschen, R., Arkenau, H.-T., Kubicka, S., Greil, R., Seufferlein, T., Freier, W., Kretzschmar, A., Graeven, U., Grothey, A., Hinke, A., Schmiegel, W., Schmoll, H.-J., 2007. Phase III Study of Capecitabine Plus Oxaliplatin Compared With Fluorouracil and Leucovorin Plus Oxaliplatin in Metastatic Colorectal Cancer: A Final Report of the AIO Colorectal Study Group. J. Clin. Oncol. 25, 4217–4223. https://doi.org/10.1200/JCO.2006.09.2684

Ralaidovy, A.H., Gopalappa, C., Ilbawi, A., Pretorius, C., Lauer, J.A., 2018. Cost-effective interventions for breast cancer, cervical cancer, and colorectal cancer: new results from WHO-CHOICE. Cost Eff. Resour. Alloc. 16. https://doi.org/10.1186/s12962-018-0157-0

Rothenberg, M.L., Cox, J.V., Butts, C., Navarro, M., Bang, Y.-J., Goel, R., Gollins, S., Siu, L.L., Laguerre, S., Cunningham, D., 2008. Capecitabine plus oxaliplatin (XELOX) versus 5-fluorouracil/folinic acid plus oxaliplatin (FOLFOX-4) as second-line therapy in metastatic colorectal cancer: a randomized phase III noninferiority study. Ann. Oncol. 19, 1720–1726. https://doi.org/10.1093/annonc/mdn370

Saidi, H., Abdihakin, M., Njihia, B., Jumba, G., Kiarie, G., Githaiga, J., Abinya, N., 2011a. Clinical Outcomes of Colorectal Cancer in Kenya. Ann. Afr. Surg. 7. https://doi.org/10.4314/aas.v7i1.67029

Schaeybroeck, S.V., n.d. 77 - Colorectal Cancer 72.

Schmoll, H.-J., Tabernero, J., Maroun, J., de Braud, F., Price, T., Van Cutsem, E., Hill, M., Hoersch, S., Rittweger, K., Haller, D.G., 2015. Capecitabine Plus Oxaliplatin Compared With Fluorouracil/Folinic Acid As Adjuvant Therapy for Stage III Colon Cancer: Final Results of the NO16968 Randomized Controlled Phase III Trial. J. Clin. Oncol. 33, 3733–3740. https://doi.org/10.1200/JCO.2015.60.9107

Schmoll, H.-J., Twelves, C., Sun, W., O'Connell, M.J., Cartwright, T., McKenna, E., Saif, M., Lee, S., Yothers, G., Haller, D., 2014a. Effect of adjuvant capecitabine or fluorouracil, with or without oxaliplatin, on survival outcomes in stage III colon cancer and the effect of oxaliplatin on post-relapse survival: a pooled analysis of individual patient data from four randomised controlled trials. Lancet Oncol. 15, 1481–1492. https://doi.org/10.1016/S1470-2045(14)70486-3

Shankaran, V., 2015. Cost Considerations in the Evaluation and Treatment of Colorectal Cancer. Curr. Treat. Options Oncol. 16. https://doi.org/10.1007/s11864-015-0354-4

Shiroiwa, T., Fukuda, T., Tsutani, K., 2009. Cost-effectiveness analysis of XELOX for metastatic colorectal cancer based on the NO16966 and NO16967 trials. Br. J. Cancer 101, 12–18. https://doi.org/10.1038/sj.bjc.6605114

Soni, A., Chu, E., 2015. Cost-Effectiveness of Adjuvant Chemotherapy in the Treatment of Early-Stage Colon Cancer. Clin. Colorectal Cancer 14, 219–226. https://doi.org/10.1016/j.clcc.2015.05.002

Stefan, D.C., 2015. Cancer Care in Africa: An Overview of Resources. J. Glob. Oncol. 1, 30–36. https://doi.org/10.1200/JGO.2015.000406

Stintzing, S., 2014. Management of colorectal cancer. F1000Prime Rep. 6. https://doi.org/10.12703/P6-108

Tilson, L., Sharp, L., Usher, C., Walsh, C., S, W., O'Ceilleachair, A., Stuart, C., Mehigan, B., John Kennedy, M., Tappenden, P., Chilcott, J., Staines, A., Comber, H., Barry, M., 2012. Cost of care for colorectal cancer in Ireland: a health care payer perspective. Eur. J. Health Econ. 13, 511–524. https://doi.org/10.1007/s10198-011-0325-z

Toumazis, I., Kurt, M., Toumazi, A., Karacosta, L.G., Kwon, C., 2017. Comparative Effectiveness of Up To Three Lines of Chemotherapy Treatment Plans for Metastatic Colorectal Cancer. MDM Policy Pract. 2, 238146831772965. https://doi.org/10.1177/2381468317729650

Vanderpuye, V.D., 2014. Cost Effectiveness of Cancer Therapies in Africa. J. Med. Diagn. Methods 03. https://doi.org/10.4172/2168-9784.1000e108

Vasileiou, K., Barnett, J., Thorpe, S., Young, T., 2018. Characterising and justifying sample size sufficiency in interview-based studies: systematic analysis of qualitative health research over a 15-year period. BMC Med. Res. Methodol. 18, 148. https://doi.org/10.1186/s12874-018-0594-7

Venook, A.P., 2019. NCCN Guidelines Index Table of Contents Discussion 181.

Wen, F., Yao, K., Du, Z.-D., He, X.-F., Zhang, P.-F., Tang, R.-L., Li, Q., 2014. Cost-effectiveness analysis of colon cancer treatments from MOSIAC and No. 16968 trials. World J. Gastroenterol. 20, 17976–17984. https://doi.org/10.3748/wjg.v20.i47.17976

Xu, R., Wang, Feng, Wang, Feng-hua, Bai, L., 2014. Role of capecitabine in treating metastatic colorectal cancer in Chinese patients. OncoTargets Ther. 501. https://doi.org/10.2147/OTT.S38843

Y Peterson, C., 2015. Risk Factors for Colorectal Cancer. MOJ Surg. 2. https://doi.org/10.15406/mojs.2015.02.00015

Zare-Bandamiri, M., Fararouei, M., Zohourinia, S., Daneshi, N., Dianatinasab, M., 2017. Risk Factors Predicting Colorectal Cancer Recurrence Following Initial Treatment: A 5-Year Cohort Study. Asian Pac. J. Cancer Prev. 18. https://doi.org/10.22034/APJCP.2017.18.9.2465

# APPENDICES

## APPENDIX 1: ELIGIBILITY CHECKLIST

### Eligibility checklist

Participant file number…….....

1. Date of first appointment

☐ Before 2013

☐ Between Jan 2013- Dec 2019

☐ After 2019

2. Age

☐ <18 years

☐ ≥18 years

3. Primary site of the tumor:

☐ Colon

☐ Rectum

☐ Colon and rectum

☐ Other

4. The stage of CRC

☐ Stage I

☐ Stage II

☐ Stage III

☐ Stage IV

5. Treatment records available

☐ Yes

☐ No

6. Eligibility

☐ Yes

☐ No

**APPENDIX 2: DATA COLLECTION TOOL**

Study No: …….  Date filled: ……

1. **BIO DATA AT DIAGNOSIS**

Date of first appointment…….

Sex: ☐Female ☐Male

Weight……. Height…… BMI…….

Age at diagnosis (years)……

Highest level of education attained

☐No formal schooling ☐ Primary ☐ Secondary ☐ Tertiary

Eligibility ☐ Yes ☐ No

2. **Disease and diagnostic information**

Stage of disease at diagnosis: ☐ Stage 1 ☐ Stage II ☐ Stage III ☐ Stage IV

Primary site of the tumor: ☐ Colon ☐ Rectum ☐ Colon and rectum ☐ Other

Site of metastatic disease: ☐ Liver ☐ Lung ☐ Other

Other chronic diseases: ☐ Diabetes ☐ Hypertension ☐ Asthma ☐ None

☐ Other(specify)…….

**Routine laboratory and radiological tests and costs**

| **Test** | **Cost/test** | **No. of tests done** | **Total cost** |
|---|---|---|---|
| **Lab test** | | | |
| Full blood count | | | |
| Serum creatinine | | | |
| Enzymes SGOT | | | |
| Others | | | |
| **Radiological tests** | | | |
| X ray | | | |
| Ultrasound | | | |
| Ct scans | | | |
| Others | | | |

3. **Treatment information**

☐ **Surgery**

| **Surgical procedure** | **Scheduled sessions** | **Cost per session** | **Total cost** |
|---|---|---|---|
| Partial colectomy | | | |

| | | | |
|---|---|---|---|
| Resection | | | |
| Total colectomy | | | |
| Other | | | |

☐ **Chemotherapy**

| **Drug and regimen** | **Dosage form** | **Strength dose per $m^2$** | **Cost per unit** | **Scheduled sessions** | **Total costs** |
|---|---|---|---|---|---|
| Capecitabine | | | | | |
| Fluorouracil | | | | | |
| Leucovorin | | | | | |
| Oxaliplatin | | | | | |
| Irinotecan | | | | | |
| **Pre-medications** | | | | | |
| Dexamethasone | | | | | |
| Ondansetron | | | | | |
| Palonosetron | | | | | |
| Hyoscine | | | | | |
| Others | | | | | |

☐ **Radiotherapy**

| **Dose selected** | **Scheduled sessions** | **Cost per session** | **Total cost** |
|---|---|---|---|
| 20-40 | | | |
| 40-60 | | | |
| 60-80 | | | |

**Management of side effects of chemotherapy**

| **Side effects** | **Medications used** | **Unit cost** | **Total units used** | **Total cost** |
|---|---|---|---|---|
| Neutropenia | Granulocyte colony stimulating factor (GCSF)<br><br>other | | | |
| Febrile neutropenia | Levofloxacin<br>other | | | |
| Grade 3-4 diarrhea | | | | |
| Hand and foot syndrome | | | | |

**4. Follow up**

Follow up visits

☐Neutropenia ☐ Recrudesce

☐ Alive ☐ Remission

☐ Hand and foot syndrome ☐ Metastasis

Any other complications ...…….

5. **Hospital admission**

| **Ward** | **Duration of admission (days)** | **Bed charges per day** | **Total charges** |
|---|---|---|---|
| Private wards | | | |
| Public wards | | | |
| | | | |

6. Date of last appointment /review …….

7. **Outcome of colorectal cancer treatment at the end of the review period**

☐ Remission
☐ Metastasis
☐ Relapse
☐ Alive
☐ Other(specify)

**APPENDIX 3: INFORMED CONSENT FOR KEY INFORMANT INTERVIEW**

Title of the study

**COST UTILITY AND BUDGET IMPACT ANALYSIS OF 5-FLUOROURACIL AND CAPECITABINE BASED REGIMENS FOR MANAGEMENT OF COLORECTAL CANCER AT KENYATTA NATIONAL HOSPITAL**

**Institution:** Department of Pharmacology and Pharmacognosy, school of pharmacy,

University of Nairobi, P.O BOX 30197-00400, Nairobi.

Investigator: Dr Nancy Jebet Koech, P.O BOX 30197-00400, Nairobi.

Supervisors:

Prof F.A Okalebo

Department of Pharmacology and Pharmacognosy

Dr E. Owiti

School of Economics, UON

Dr. D. Wata

Cancer treatment centre, KNH

Ethical approval

Kenyatta National Hospital/University of Nairobi Ethical and research committee, P.O BOX 20723-00100, Nairobi. Tel 2726300/2716450 Ext 4410

**INTRODUCTION**

This study seeks to evaluate the costs and effectiveness of chemotherapy regimens used in the management of colorectal cancer.

**Purpose of the study**

The purpose of the study is to assess and compare the costs of managing CRC using 5FU and capecitabine based regimens and to model their cost utility and budget impact from the provider perspective.

Permission is requested from you to participate in this study. You should understand that the following general principles apply to all participants in a medical research:

i. Your agreement to participate in this study is voluntary
ii. You may withdraw from the study at any time without necessarily giving a reason for your withdrawal.

iii. After you have read the explanation, please fee free to ask any questions that will enable you understand clearly the nature of the study.

**Procedure to be followed**

With your permission, I will engage in a discussion on costs involved in acquisition of chemotherapy drugs and the costs of procedures in the management of CRC. I will audio record and take notes using a pen and a paper. The audio recorded will be transcribed within 24 hours of recording. The information obtained will be handled with confidentiality and used only for the purpose of this study.

**Risks**

No risks will be involved in this study.

**Benefits**

There will be no direct benefits to you but the findings will be used in decision making of the most cost-effective regimen to be used and the informing policy on budgetary allocation for the management of cancers at the Ministry of Health and the NHIF in Kenya.

**Assurance of confidentiality**

All information obtained from you will be kept in confidence. Your name will not be mentioned or used during data handling or in any resulting publications. Codes will be used instead.

**Contacts**

In case you need to contact me, my academic department or the KNH/UON Ethics and Research Committee concerning this study please feel free to use the contacts provided above.

I request you to sign the consent form attached.

**APPENDIX 4: CONSENT FORM**

**COST UTILITY AND BUDGET IMPACT ANALYSIS OF 5-FLUOROURACIL AND CAPECITABINE BASED REGIMENS FOR MANAGEMENT OF COLORECTAL CANCER 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 investigator. I understand that the information gathered will be used for the purposes 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 in the study and the risks and benefits involved.

Investigator …….

Sign ……Date……

## APPENDIX 5: KEY INFORMANT INTERVIEW GUIDE

My name is Nancy Jebet Koech, a pharmacist pursuing a Masters course in Pharmacoepidemiology and Pharmacovigilance at the University of Nairobi.

**Purpose of the interview**

I am carrying out a study on **cost utility and budget impact analysis of 5-fluorouracil and capecitabine based regimens for management of colorectal cancer at Kenyatta National Hospital** and would wish to know the details on the costs of items and the various procedures involved in the management of colorectal cancer.

**General background**

Would you please tell me your position in the organization and how long you have worked at this organization?

**Part A: Respondent's characteristics**

Position …….

Specialty ……

Age…….

Number of years worked in the hospital…….

**Part B: Interview topics**

**Personnel costs**

i. Which personnel are involved in the medical care of CRC patients?

ii. How long on average does the following personnel spent with an inpatient per day?

| Personnel | Time spent (Mins) |
|---|---|

| | |
|---|---|
| Nurse | |
| Oncologist | |
| Medical officer | |
| Pharmacist | |

iii. How long on average does the following personnel spent with an outpatient per day?

| Personnel | Time spent (Mins) |
|---|---|
| Nurse | |
| Oncologist | |
| Medical officer | |
| Pharmacist | |

iv. What is the average monthly salary for these personnel?

| Personnel | Monthly wage (Ksh) |
|---|---|
| Nurse | |
| Oncologist | |
| Medical officer | |
| Pharmacist | |

**Drug costs**

i. Which treatment guidelines are being used in the management of colorectal cancer in KNH?

ii. Are all the drugs listed in the guideline readily available in the hospital?

iii. What is the unit price of each of the following chemotherapeutic agents?

| **Drug** | **Unit** | **Unit Cost (Ksh)** | **Quarterly consumption** |
|---|---|---|---|
| Capecitabine | | | |
| Fluorouracil | | | |
| Oxaliplatin | | | |
| Irinotecan | | | |
| Leucovorin | | | |

iv. What was the quarterly consumption of these agents in the last financial year?

**Cost of laboratory tests**

i. What laboratory tests are performed before each cycle of chemotherapy for the patients receiving the following regimens?

ii. How often are these tests conducted?

iii. What is the unit cost of these tests?

| Drug | Test name | Frequency | Unit cost (Ksh) | Total cost (Ksh) |
|---|---|---|---|---|
| Capecitabine | | | | |
| XELOX | | | | |
| FOLFOX | | | | |
| FOLFIRI | | | | |
| XELIRI | | | | |

**Costs of managing health states**

**a) Neutropenia**

i. How often do you get patients presenting with neutropenia?

ii. Does neutropenia results in hospitalization?

iii. What laboratory tests are performed for these patients?

iv. How often are these tests performed?

v. What is the average payment of a nurse caring for this patient over this period?

vi. Does the patient have to be seen by a specialist?

vii. How often does the patient have to be followed up by the specialist?

viii. What is the ideal approach for managing neutropenia in this facility?

ix. What is the cost of Granulocyte stimulating factor (GSF)?

**b) Hand and foot syndrome**

i. Have you come across a case of hand and foot syndrome?

ii. How often do you come across these cases?

iii. How did you manage the case?

iv. What are the common analgesics used to manage the condition?

v. For how long are they prescribed?

vi. What is the cost of these analgesics?

**c) Grade 3 diarrhea**

i. Have you had cases of grade 3 diarrhea for CRC patients on 5FU or capecitabine based regimens?

ii. How often do you experience these cases?

iii. Does grade 3 diarrhea lead to admission?

iv. If so, what are the average admission days?

v. How do you manage this condition?

vi. What is the cost of these agents used to manage grade 3 diarrhea?

vii. Are there any other additional agents used to manage this condition?

**d) Remission**

i. How often do you get patients with stage III CRC going on remission?

ii. Are there any drugs the patient uses during remission?

iii. What lab tests are performed during remission?

iv. How often are these tests conducted?

**e) Recurrence**

i. Do you have patients going on recurrence?

ii. If so, how often does this occur?

iii. Is the management of recurrence different from the use of first line therapy?

iv. What do you use to manage recurrence?

v. What are the costs of these agents used in recurrence?

vi. What routine tests are done during recurrence?

vii. What is the unit cost of these tests?

**f) Metastases**

i. How often do you have patients on adjuvant chemotherapy going into metastases?

ii. How do you manage metastases?

iii. What tests are done in case of metastasis?

iv. What are the costs of these tests?

**NHIF**

i. How many cycles of the following chemotherapy covered by NHIF?

ii. Are all inpatient charges covered by NHIF?

iii. Are all outpatient charges covered by NHIF?

iv. Are the costs of managing the side effects covered by NHIF?

v. Are all laboratory tests covered by NHIF?

vi. Does NHIF covers costs of treatment in case of recurrence or metastasis?

vii. Are the laboratory tests in case of remission covered?

viii. Does NHIF cover the costs of drugs used during remission?

**Any recommendations /additional comments…….**

## APPENDIX 6: ETHICAL APPROVAL LETTER

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

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

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

Ref. No.KNH/ERC/R/143

27th July, 2021

Nancy Jebet Koech
Reg. No.U51/12212/ 2018
Dept.of Pharmacology and Pharmacognosy
School of Pharmacy
College of Health Sciences
University of Nairobi

Dear Nancy

**Re: Approval of Annual renewal and Study timelines – Cost utility and budget impact analysis of 5-Fluorouracil and Capecitabine based regimens for management of colorectal cancer at Kenyatta National Hospital (P924/11/20219)**

Refer to your communication dated 7th July 2021.

This is to acknowledge receipt of the study progress report and hereby grant annual extension of approval for ethical research protocol P924/11/2019.

The approval dates are 6th February 2021 – 5th February 2022.

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 severe adverse events (SAEs) or unexpected adverse events whether related or unrelated to the study must be reported to the KNH- UoN ERC within 72 hours of notification.
d) Any changes, anticipated or otherwise that may increase the risks or affect safety or welfare of study participants and others or affect the integrity of the research must be reported to KNH- UoN ERC within 72 hours.
e) Submission of a request for renewal of approval at least 60 days prior to expiry of the approval period. (*Attach a comprehensive progress report to support the renewal*).
f) Clearance for export of biological specimens must be obtained from KNH- UoN-Ethics & Research Committee for each batch of shipment.
g) Submission of an *executive summary* report within 90 days upon completion of the study.

This information will form part of the data base that will be consulted in future when processing related research studies so as to minimize chances of study duplication and/or plagiarism.

The changes made to the study timelines are also approved.

Yours sincerely,

**PROF. M.L. CHINDIA**
**SECRETARY, KNH-UON ERC**

c.c. The Principal, College of Health Sciences, UoN
The Senior Director CS, KNH
The Chairperson, KNH-UoN ERC
The Dean, School of Pharmacy, UoN
The Chair, Dept.of Pharmacology and Pharmacognosy, UoN

**APPENDIX 7: PLAGIARISM REPORT**

Thesis - COST UTILITY AND BUDGET IMPACT ANALYSIS OF 5-FLUOROURACIL AND CAPECITABINE BASED REGIMENS FOR MANAGEMENT OF COLORECTAL CANCER AT KENYATTA NATIONAL HOSPITAL

ORIGINALITY REPORT

| 14% | 11% | 11% | 2% |
|---|---|---|---|
| SIMILARITY INDEX | INTERNET SOURCES | PUBLICATIONS | STUDENT PAPERS |

PRIMARY SOURCES

| | | |
|---|---|---|
| 1 | erepository.uonbi.ac.ke:8080<br>Internet Source | 2% |
| 2 | erepository.uonbi.ac.ke<br>Internet Source | 1% |
| 3 | onlinelibrary.wiley.com<br>Internet Source | 1% |
| 4 | www.wjgnet.com<br>Internet Source | 1% |
| 5 | docplayer.net<br>Internet Source | <1% |
| 6 | www.ncbi.nlm.nih.gov<br>Internet Source | <1% |
| 7 | "Encyclopedia of Cancer", Springer Science and Business Media LLC, 2017<br>Publication | <1% |