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COST ANALYSIS OF COLORECTAL CANCER CHEMOTHERAPY TREATMENT IN PUBLIC AND PRIVATE HEALTHCARE SECTORS IN SOUTH AFRICA

Candice-lee Herbst

A Dissertation submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in fulfilment of the requirements for the degree of Master of Science in Medicine.

Johannesburg, 2017

DECLARATION

I Candice-lee Herbst declare that this Dissertation is my own, unaided work. It is being submitted for the Degree of Master of Science in Medicine at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at any other University.

_____

(Signature of candidate)

_____day of_____20_____in_____

In memory of my grandfather

David John “DJ” Callaghan

1935 - 2015

PUBLICATIONS AND PRESENTATIONS ARISING FROM THIS STUDY

Herbst, C.; Moch, S. and Miot, J. (28th – 29th October 2014). *Cost comparison of chemotherapeutic medicines used in the treatment of breast and colon cancers between public and private health sectors in South Africa.* Poster presentation at University of the Witwatersrand Cross-Faculty Symposium.

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ABSTRACT

Low-middle income countries are experiencing greater increases in cancer incidence due to changes in lifestyle. Colorectal cancer is one cancer that reflects this increase [1, 2]. As cancer incidence increases so do the costs associated with treatment. Although chemotherapy is not the only cost contributor, it increases costs considerably. This problem is not unique to low-middle income countries and requires further research [3]. Therefore this research was conducted to ascertain the cost of colorectal cancer chemotherapy in South Africa for both public and private healthcare sectors and to determine if treatment is equitable between the sectors. Clinical pathways were developed and compared to clinical practice by conducting a retrospective drug utilisation review to determine any variation from the pathways. A costing model was developed to include chemotherapy, supportive medicines, administration fees and administrative fees. The cost was calculated for the developed pathways and the retrospective drug utilisation review allowed for comparison between the sectors and with expected costs. Observations indicate private sector treatments are similar to international standards due to the availability of biological agents however public sector patients have limited access to newer therapies. Comparing the two sectors indicates a higher cost of chemotherapy in the private sector and one such example is the cost difference observed for a commonly prescribed regimen CAPOX for advanced CRC. The observed cost per cycle was R 6 068,28 (public sector) vs. R 9 480,93 (private sector). This is largely due to different access as well as acquisition costs. Nevertheless these patients do have access to newer biological agents. In conclusion, South Africa's two healthcare sectors differ in access to treatment with the public sector per capita cost for therapy being lower.

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NOMENCLATURE

5-FU: 5-Fluorouracil

ACS: American Cancer Society

Admin meds: Administration medicines

ADR: Adverse Drug Reaction

APC/C: Anaphase-promoting complex/cyclosome

ASCO: American Society of Clinical Oncology

ATC classification: Anatomical Therapeutic Chemical Classification

Bev: Bevacizumab

BMI: Body Mass Index

BSA: Body Surface Area

BSC: Best Supportive Care

CDKs: Cyclin dependent kinases

CDL: Chronic Disease List

CEA: Cost-Effectiveness Analysis

Cet: Cetuximab

CINV: Chemotherapy Induced Nausea and Vomiting

CMJAH: Charlotte Maxeke Johannesburg Academic Hospital

CMS: Council for Medical Schemes

CPI: Consumer Price Index

CRC: Colorectal Cancer

CUA: Cost Utility Analysis

CYP: Cytochrome P450

DNA: Deoxyribonucleic Acid

DUR: Drug Utilisation Review

EDP: Essential Drugs Program

EGF: Epidermal Growth Factor

EGFR: Epidermal Growth Factor Receptor

EML: Essential Medicines List

ESMO: European Society for Medical Oncology

FAP: Familial Adenomatous Polyposis

FDA: (U.S.) Food and Drug Administration

G1: Growth phase 1

G2: Growth phase 2

GDP: Gross Domestic Product

HIV: Human Immunodeficiency Virus

HICs: High Income Countries

HNPCC: Hereditary Non-Polyposis Colorectal Cancer

HSRC: Health Sciences Research Council

I.V: Intravenous

IBS: Irritable Bowel Syndrome

ICER: Incremental Cost-Effectiveness Ratio

ICON: Independent Clinical Oncology Network

IgG1: Immunoglobulin G1

LMICs: Low-Middle Income Countries

M: Mitotic phase (Mitosis)

MAPK: MAP kinase

MCC: Medicines Control Council

mBC: metastatic Breast Cancer

mCRC: metastatic Colo-Rectal Cancer

MDG: Millennium Development Goals

Meds: medicines

mnths: months

MoAB: Monoclonal Antibody

MOB: Managed Oncology Benefit

NCCN: National Comprehensive Cancer Network

NCI: National Cancer Institute

NCR: National Cancer Registry

NDP: National Drug Policy

NICE: The National Institute for Health and Care Excellence

NRPL-HS: National Reference Price List for Health Services

OOP: Out-of-pocket

ORR: Overall Reaction/Response Rate

OS: Overall Survival

PFS: Progression Free Survival

PMB: Prescribed Minimum Benefits

PPPM: per patient per month

QALY's: Quality-Adjusted Life-Years

RB: Retinoblastoma

RNA: Ribonucleic acid

RR: Reaction/Response Rate

S phase: Synthesis phase

SAOC: South African Oncology Consortium

SEER: Surveillance, Epidemiology and End Results Programme

SEP: Single Exit Price

STG: Standard Treatment Guideline

T2DM: Type 2 diabetes mellitus

TGF-β: Transformation Growth Factor β

UTG: Uridine 5'-diphospho-glucuronosyltransferase

VEGF: Vascular Endothelial Growth Factor

VEGFR: Vascular Endothelial Growth Factor Receptor

WHO: World Health Organisation

1. CHAPTER ONE – INTRODUCTION

1.1 General Introduction

South Africa's healthcare system is divided into two sectors based on socioeconomic factors, namely the public non-insured (~85% of population) and private insured (~15% of population) healthcare sectors. The healthcare provisions range from basic primary healthcare services to highly specialised healthcare services. While the two sectors may offer similar services there is a notable difference in funding as well as in the population which makes use of the healthcare services. Even though a larger population makes use of the public healthcare sector, the overall expenditures incurred between the two sectors are actually comparable [4].

The comparable expenditures result in an unequal per capital healthcare spending [4]. This means that South African private healthcare sector patients cost more than public healthcare sector patients. Research also shows that this gap between the two healthcare sectors is ever-increasing thus concerns are arising as to whether or not medical schemes and their beneficiaries receive cost effective care whereas public sector patients receive inadequate care. One such area of concern is with the use of chemotherapeutic medicines.

Chemotherapeutic medicines are well known to be of high cost, not only in South Africa but globally. Some of the reasons for these huge costs are due to the fact that these medicines circulate in a non-competitive market and newer agents are not used to replace older ones but rather as add on therapies. In addition many cancers are incurable and patients may be treated with all the available medicines even though there is insufficient evidence to support their usage [3].

Additionally, the financing of the two healthcare sectors differ which ultimately influences the price of medicines within each sector. The private healthcare sector in South Africa is unable to acquire these medicines at lower rates unlike the public sector due to the implementation of a transparent pricing system in 2004 known as single exit pricing [5].The single exit price (SEP) is the price that the manufacturer must sell the medicine to dispensing healthcare professionals regardless of the volume that is ordered. This also applies to the sale of medicines by dispensing healthcare professionals to patients. This transparency ensures that no perverse incentives including rebates or discounts apply thereby ensuring equitable,

availability, affordability and quality of all medicines sold within the country [6]. In addition to the SEP of medicines a dispensing fee may be added by the pharmacist or dispensing doctor based on a scale-base calculation. The high costs of medicines consequently are often carried over to the patients in the form of co-payments as medical schemes are often unwilling to cover all costs. There are also instances where patients cannot afford medical schemes but do not access the public sector in which case they fund their treatment fully out-of-pocket.

On the other hand however, through tender procurement processes and adherence to the Essential Medicines Lists as used in the public sector, patients do not always have access to all the available medicines which circulate within the private healthcare sector. Healthcare financing will be discussed in more detail in section 1.5.7.

Hence given the discrepancies in funding and availability of the medicines in the two sectors, it is important to establish whether or not patients in the private sector are paying more for the same medications available to public sector patients and also to ascertain whether or not access to treatment is at all equitable between the two sectors. Moreover it is unclear as to whether or not patients are treated according to evidence-based clinical pathways as clinical guidelines are lacking in South Africa for a disease such as colorectal cancer.

Therefore the aim of this study was to calculate and compare the costs between the public and private healthcare sectors of South Africa for the treatment of colorectal cancer according to the accepted treatment pathways and formularies such as the standard treatment guidelines and essential medicine lists, which are currently used in practice both in the public and private sectors. Moreover the study will compare the treatment patients receive to the evidence-based clinical pathways available.

1.2 Study Objectives

1. To determine the accepted treatment pathways, based on treatment guidelines, used in the past 12 months in the public and private sectors for systemic treatment of early and late colorectal cancer.
2. To analyse retrospective drug utilisation data of the chemotherapeutic medicines from both sectors based on a sample drawn from a tertiary/quaternary public hospital in

Gauteng (representing the public sector) and a major medical scheme (representing the private sector).

3. To determine the costs included of the chemotherapeutic agents used in the treatment of colorectal cancer per sector and then calculate the total costs, administrative costs (facility fees associated with receiving chemotherapy), administration costs (medicines and costs directly related to the administration of the chemotherapy) and supportive care medicine costs.
4. To compare the costs of chemotherapeutic treatment for the various pathways between the two sectors.

1.3 Study Setting

The public healthcare sector setting is the Charlotte Maxeke Johannesburg Academic Hospital, a tertiary/quaternary hospital in Gauteng, South Africa in which the selected patient cohort represents public healthcare sector patients whereas the private healthcare sector patient cohort is represented by a major medical scheme, Discovery Health, within South Africa.

1.4 Background

Cancer is a broad term used to describe diseases that arise from uncontrolled cellular growth and proliferation that result in abnormal cell morphology. These cancerous cells are able to invade and spread to other tissues and organs if undetected (metastasis). Metastasis is the major contributor to cancer deaths as treatment of advanced cancer can be difficult [7, 8].

Recent cancer data shows that global cancer incidence rates are changing. Namely High Income Countries (HICs) show a decrease in incidence while Low-Middle Income Countries (LMICs) show increases [2]. In 2016, it is still expected that 1,685,210 new cancer cases and 595,690 cancer-related deaths will be recorded in the United States despite the decreases literature cites [9]. This increase, as cited in literature, is due to increasing westernisation which influences an increase in cancers such as colorectal. This adoption of an unhealthy lifestyle, influences factors such as reproduction, diet, metabolism and hormone determinants. These increase the risk of such cancers in LMICs [1, 2]. Assuming constant social and economic development, global cancer incidence is projected to be 22.2 million by 2030 as opposed to the estimated 12.7 million in 2008 [1]. Moreover cancer is one of the leading causes of death worldwide with 8,2 million cancer-related deaths recorded in 2012. Furthermore cancer cases are expected to increase to 22 million over the next two decades, despite the growing HIV/Aids epidemic and cardiovascular disease [10-12].

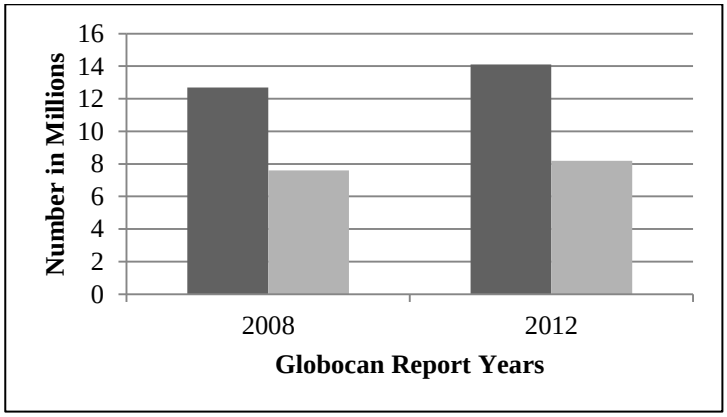


Figure 1.1 New cancer cases and deaths for 2008 and 2012 (excludes non-melanoma skin cancer) [11, 13] – Dark grey (reported new cancer cases) and light grey (reported cancer deaths)

A comparison of GLOBOCAN data taken between 2008 and 2012 displays an increase in new cancer cases as well as cancer deaths (Figure 1.1). According to GLOBOCAN 2012 data,

more than half of the 14,1 million new cases of cancer (excluding non-melanoma skin cancer) occurred in LMICs [11]. This is similar for cancer deaths.

1.4.1 The origins of Cancer

Cancer begins with the deregulation of normal cellular processes. Cells are required to grow and divide in a controlled manner in order to sustain the body in a healthy state. When cells become old or damaged, they die and are replaced [7, 14]. This process is known as the cell cycle. The cell cycle consists of a systematic series of events in which the cells replicate [7]. It is this cellular cycle that allows cells to achieve the task of passing on their genetic material to the next generation of cells. In order to produce two genetically identical daughter cells, the DNA found in the nucleus must replicate fully via a process known as the synthesis phase (S phase) of the cell cycle. The duplicated DNA is then evenly separated into two cells during mitosis (M phase) [7]. A human cell spends 8% of a 24-hr period in mitosis, 29% synthesizing its cellular contents and the remainder of the time in a growth phase [15].

The cell cycle control system is very important in regulating cellular progression via many regulatory proteins and signaling pathways [7]. When this system malfunctions it leads to uncontrolled cell divisions and the development of tumours. These tumours can become cancerous resulting in cancer development. The cell cycle control system ensures that these sequential events occur correctly and at the correct time preventing tumour development. If however the environment becomes unfavourable, such as when there are insufficient growth factors, or when a cell fails to complete an important process, the control system will arrest the cell cycle. This cell cycle arrest is crucial in preventing tumours. The central proteins involved in this control system are cyclin-dependent kinases (CDKs), which are dependent on the cyclins for their activation [7]. The changes in the activities of these various cyclin-CDK complexes are what control the cell cycle phases as well as the mechanism. These changes include phosphorylation, binding of inhibitors such as CDK inhibitor proteins [16], proteolysis of cyclins and changes in the transcription of the genes, which encode these CDK regulatory proteins [7].

1.4.2 APC/C pathway and other ubiquitin ligases

The cell cycle control system is also dependent on APC/C (anaphase-promoting complex/cyclosome) and other ubiquitin ligases. The APC/C is an important regulator in cell cycle progression. The complex allows for the transition from metaphase-to-anaphase during mitosis. These types of enzyme complexes catalyze ubiquitylation and proteolytic destruction of certain regulatory proteins that control the cell cycle phases. The first major target for APC/C is a protein that secures the linkages between sister chromatids in early mitosis. The second target (Figure 1.2) S- and M-cyclins will inactivate most of the CDKs. It is these CDKs, which play a critical role in the control mechanism.

The mitogen stimulation pathway leads to the activation of MYC and E2F [7]. Mitogens stimulate cell division by eliminating intracellular molecular hitches, which would restrain cell progression in the G1 phase. The mechanism by which mitogens do so is via cell-surface receptor activation. The activated mitogen receptor will lead to the activation of a GTPase, RAS. The activation of RAS causes downstream activation of RAF via phosphorylation. This in turn leads to the activation of the MAP kinase pathway (MAPK pathway) and results in an increased expression of the immediate early genes, such as those, which encode the regulatory protein MYC (Figure 1.2). MYC will lead to an increased expression of the delayed response genes including those that lead to an increase in the activity of the G1-Cdk. This allows for phosphorylation of the Retinoblastoma (RB) family of proteins. By phosphorylating RB, it allows for the protein to become inactive and free the E2F gene regulatory protein, which it binds. The activation of E2F leads to the transcription of the G1/S genes as well as the G1/S cyclin and S cyclin genes. Once the S-CDK is activated DNA synthesis can occur as seen in Figure 1.2 below [7].

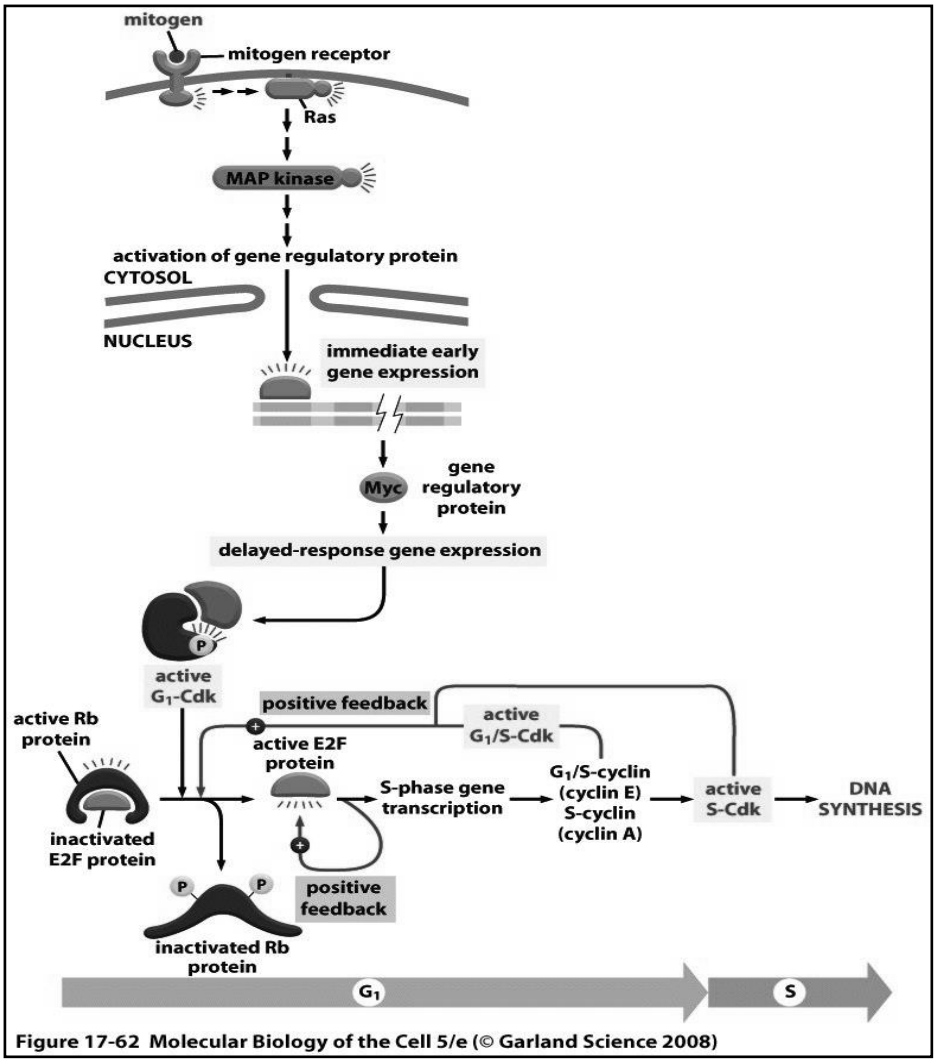


Figure 1.2 Control of the cell cycle [7] – DNA synthesis is activated via the activation of the MAPK pathway. The MAPK pathway activates the gene expression of *MYC* leading to the expression of the MYC protein. MYC causes a delayed response of G1-Cdk expression allowing for inactive E2F to be activated. S phase gene transcription is subsequently activated allowing for DNA synthesis.

1.4.3 Abnormal proliferation signals

If abnormal proliferation signaling occurs, cell-cycle arrest or apoptosis is induced, however, this is not the case in all cells. Cancer cells are an example where apoptotic signals are absent. This is as a result of gene mutation These cancer-promoting genes are referred to as oncogenes. This response by normal cells is one way to prevent the survival and proliferation of cells containing oncogenes [7].

An example of these mutations is seen in a single amino acid mutation encoding the RAS protein (KRAS and NRAS). This causes the protein to become overactive leading to a constant stimulation of the RAS pathway. This occurs even when there is an absence of mitogenic stimulation. Mutations have also been seen in *MYC*, where the corresponding protein becomes overexpressed stimulating unwarranted cellular growth and proliferation and in so doing promoting tumour development [7]. Other unwarranted mitogenic stimulation also leads to the overproduction of a cell-cycle inhibitor protein, ARF. This inhibitor protein binds to MDM2 and inhibits it, which leads to the inhibition of P53 degradation. The increased levels of P53 increases the level of cell-cycle arrest or apoptosis, which is evident in normal cells [7].

Apoptosis is a process whereby cells undergo "suicide" in response to cellular signals. Apoptosis involves a morphological change by the cell including cytoskeleton collapse and nuclear envelope disassembly together with chromatin condensation and fragmentation. Cells undergoing apoptosis form apoptotic bodies, which are engulfed by macrophages so as to eliminate them quickly without any inflammation. Necrosis is another method in which cells can undergo cell death however, unlike apoptosis these cells die in response to trauma or lack of blood supply. The necrotic cells will swell and burst, spilling all their cellular contents into the neighbouring area. This results in an inflammatory response [17].

1.4.4 Types of Cancer

There are over 100 different types of cancer, which can be grouped into categories (

Table 1.1) based on the origin of the cancer cells [14, 18].

Table 1.1 Classification of the different types of Cancer [14, 18].

Category	Description
Carcinoma	Cancer cells arising in the skin or tissues that line or cover the internal organs.
Sarcoma	Cancer cells arising in the bone, cartilage, fat, muscle, blood vessels or any other connective/supportive tissue.
Leukemia	Cancer cells arising in blood-forming tissue such as the bone marrow.
Lymphoma and myeloma	Cancer cells arising in the cells of the immune system.
Central nervous system cancers	Cancer cells arising in the tissues of the brain and spinal cord.

Carcinomas are the most common types of cancer, which cause most of the cancer deaths each year, including lung, prostrate, cervix, stomach, liver, colorectal and breast cancer [11, 12].

1.4.5 Incidence of cancer based on geographical region

The incidence of a cancer type also appears to vary based on the geographical region. Recent cancer mortality data (mortality is influenced by incidence [19] shows that different geographical regions have increased mortality of certain cancers as opposed to other regions. While cancer mortality is decreasing globally, liver cancer mortality is still on the rise and lung cancer mortality in females is also on the increase. A recent analysis of 60 countries from 6 continents showed stomach cancer mortality is greatest for regions such as the former Soviet Union, Japan and Korea whereas colorectal cancer mortality is the greatest in the Oceania region (tropical Pacific Ocean Islands) [20].

The only African country included in the analysis was South Africa and in comparison to other regions, cancer mortality is second lowest however, stomach, lung and uterine cancer are among the highest cancer mortalities. Africa was however grouped with Asia and therefore it can't be directly translated as South Africa's mortality statistics [20].

Research such as this does indicate that geographical region is important as to the cancer type a population may well be at risk of developing as the disparities between the regions are based on the populations characteristics, risk factor prevalence within the population, screening and treatment access [20].

1.4.7 Colorectal Cancer

Colorectal cancer (CRC) is cancer that originates in the large intestine (colon) or the rectum (end of the colon) (Figure 1.3). CRC is most commonly found as carcinomas however rare cases do include lymphomas, carcinoid tumors, melanomas or sarcomas [21].

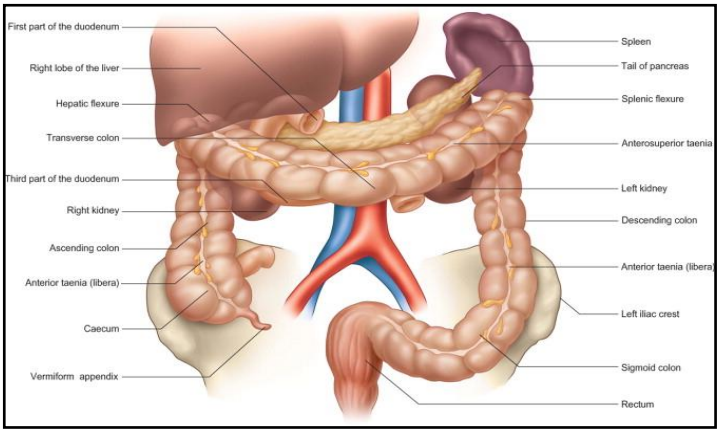


Figure 1.3 Anatomy of the lower gastrointestinal tract [22]

1.4.7.1 Stages of Colorectal Cancer

CRC is staged according to the American Joint Committee on Cancer (AJCC). Stage 1 to 3 cancer (early CRC) is localised where stage 4 cancer (advanced CRC) has spread to other parts of the body (Figure 1.4) [23].

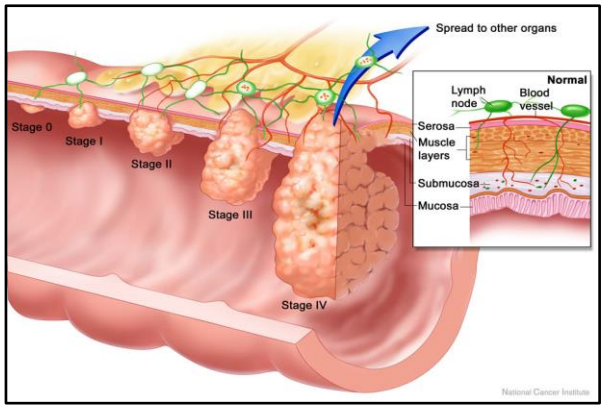


Figure 1.4 AJCC staging of cancer [23] – Stage 1 to 3 is localised where stage 4 has spread to other parts of the body.

1.4.7.2 Causes of Colorectal Cancer

There is no single cause related to CRC however, it is a highly treatable and often curable disease when localised to the bowel area [24, 25]. Most CRCs begin with benign polyps or tumors. These polyps can become cancerous if undetected or ignored. The major problem is that CRC progresses slowly from these benign polyps. This means that symptoms may not be present for many years until the cancer is progressively further along which reduces the survival rate [21, 26]. As the cancer is progressively further along, it will grow into the inner cell layer of the colon or rectum, allowing it to grow into nearby blood or lymph vessels. The

cancer is then able to move to more distant parts of the body, such as the liver, through metastasis [21, 26]. It is the metastasis of CRC that makes it difficult to treat and therefore not surprising to see the survival rate drop. From the latest published data survival rates decrease as the CRC progresses further but there has also been greater increases in survival rates compared to previously published data by SEER (Surveillance, Epidemiology and End Results Programme) [27].

1.4.7.3 Risk factors, symptoms and incidence of Colorectal Cancer

A risk factor is anything that can affect a person's chance of getting a disease such as cancer. It has to be noted that different cancers have different risk factors however, one factor can be a risk for more than one type of cancer, such as smoking [24]. Also if a person has a risk factor, it does not mean that they will develop the disease nor does it mean if a person has no risk factors that will not develop the disease [26]. There are known to be several risk factors associated with developing CRC. These can be grouped into lifestyle related risk factors and risk factors that a person cannot change such as genetics.

1.4.7.4 Lifestyle related risk factors

1.4.7.4.1 Diet

A diet high in red meat such as beef, lamb or pork as well as processed meat (luncheon meats) can increase the risk. Cooking meats at very high temperatures which includes frying, boiling and grilling can result in the formation of carcinogens. Research has also shown that a diet high in fruits, vegetables and whole grains can decrease a person's risk of developing CRC [24, 26].

1.4.7.4.2 Physical inactivity and obesity

Persons who are physically inactive have an increased risk of developing CRC likewise does obesity. The risk of developing CRC does seem to be greater in men than women [26].

1.4.7.4.3 Smoking and heavy alcohol consumption

Smoking has been well documented as a cause of lung cancer however, it has also been linked to other cancers such as CRC. Long-term smokers have a higher risk than non-smokers. The development of CRC has also been linked to heavy alcohol consumption. This is possibly due to lower levels of folic acid in the body of a person who consumes large amounts of alcohol regularly [26].

1.4.7.5 Non-modifiable risj factors

1.4.7.5.1 Age

CRC affects both young and old however, elderly people, particularly from the age of 60, are at an increased risk of developing the disease [24]. It has been reported by the American Cancer Society that 9 out of 10 people diagnosed with CRC are over the age of 50 [26].

1.4.7.5.2 Inflammatory bowel disease

When the colon is inflamed for a long period of time, such as with ulcerative colitis or Crohn's disease (but not irritable bowel syndrome (IBS)); the likelihood of developing dysplasia increases. Dysplasia is when the cells lining the colon or rectum have an abnormal appearance, but are not cancerous however they can result in neoplastic development [26, 28]. The development of dysplasia is thought to contribute to a patient's risk of developing CRC at some stage [21].

1.4.7.5.3 Type 2 diabetes mellitus (T2DM)

Both CRC and T2DM have common risk factors such as excessive weight therefore people who have T2DM are at a risk for developing CRC. These patients, once diagnosed, have a worse prognosis than patients without diabetes. There is also growing evidence to support a strong association between metabolic syndrome and an increased risk of developing CRC [26, 29].

1.4.7.5.4 Personal history of polyps or colorectal cancer

Patients with a history of polyps have an increased risk of developing CRC and more so if the polyps are abundant and large in size. A previous incidence of CRC poses a risk, even if the cancer was successfully removed via surgery. The risk is furthermore increased if the first incidence cancer was at a young age [21, 26].

1.4.7.5.5 Family history

CRC can occur in people who do not have a family history of the disease however, if a person has a family history their risk is increased. This increased risk is even greater if the relatives are first-degree relatives and if the relative was diagnosed at an early age. These cancers, which are said to "run in a family", are due to inherited genes, shared environmental factors or the combination of each [24, 26]. Certain racial and ethnic groups also have a predisposition to CRC such as African Americans and Ashkenazi Jews. Not all the reasons for this is understood, however, it is most likely due to inherited genetic mutations [25, 26].

1.4.7.5.6 Inherited syndromes

Inherited gene mutations can often result in the development of disease and about 5-10% of people diagnosed with CRC have inherited gene mutations. These defects often lead to people developing CRC at an earlier age than statistics show. Two such inherited syndromes include familial adenomatous polyposis (FAP) and hereditary non-polyposis colorectal cancer (HNPCRC). FAP is caused by mutations in the *APC* gene (tumour suppressor gene) (5q22.2) however, only 1% of all CRCs are due to FAP. FAP patients tend to develop many polyps in the colon and rectum at an early age and the cancer develops from one or more of these polyps by the time these people are in their early twenties [21, 26].

HNPCC, also known as Lynch syndrome, is caused by inherited mutations in many DNA repair genes HNPCC is the most common hereditary form of CRC but contributes 2-4% of all diagnosed cases. People who have this syndrome have a lifetime risk of 80% and patients generally develop CRC at a much younger age than non-hereditary cases however, these patients are not as young as the patients with FAP [21, 25, 26].

1.4.7.5.7 Acquired gene mutations

Inherited genetic mutations only account for a small percentage of all CRC cases thus due to the genetic nature of cancer most cases are due to acquired gene mutations. It is not known what causes these acquired mutations but the above mentioned risk factors may play a role [26]. Most CRC cases are adenocarcinomas and as such many somatic mutations have been found. These mutations are more recently used as predictive markers to ensure patient responses to certain therapies as well as targets for drug development. These acquired mutations occur in genes such as *RAS* family (*KRAS, NRAS) and BRAF* [30]. The RAS/RAF pathway (Figure 1.5) is essential for eukaryotic cell survival. This pathway ensures that cells grow, proliferate and undergo programmed cell death (apoptosis) [7] as discussed under sections 1.4.2 and 1.4.3. These genetic mutations affect the cellular pathways seen in Figure 1.5.

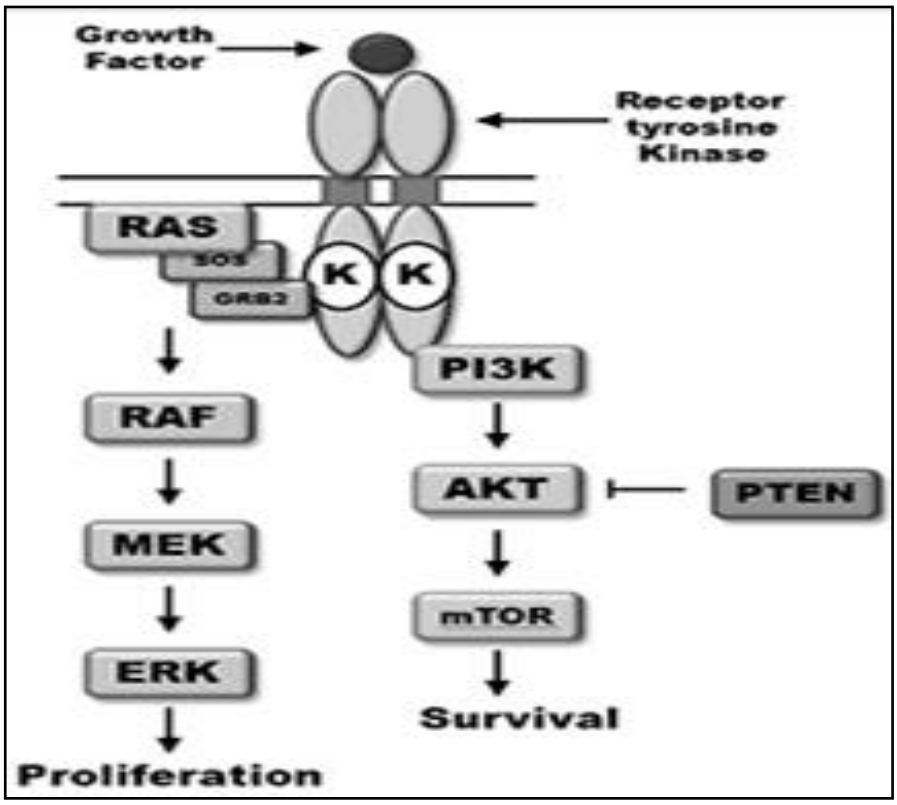


Figure 1.5 Schematic of the MAPK and PI3K pathways – Following activation, the cell will proliferate but genetic mutations occur these pathways result in uncontrolled cell proliferation [31].

1.4.7.6 Symptoms of colorectal cancer

Although most CRCs remain undetected for some time as no symptoms are present in the patient, there can be an onset of symptoms such as abdominal pain. The symptoms that occur

are linked to the primary site of the tumor. As the tumor grows, the symptoms become more apparent. The abdominal pain and tenderness some patients experience can be due to an invasive tumor, which penetrates the muscularis propria and invades the adjacent tissue. However, an acute abdominal pain may actually result from perforation of the colon [21, 24, 26].

Any obstruction of the colonic lumen can result in abdominal distension, pain, nausea and vomiting. Diarrhea and constipation are associated with the development and spread of CRC due to the change in bowel movements. Some patients are reported to have bloody stools. The reason for this is possibly linked to trauma experienced by the fecal stream, this can lead to iron deficiency anemia. Weight loss without reason may also be experienced by patients [21, 26].

1.4.7.7 Incidence of colorectal cancer

CRC is the third most commonly diagnosed cancer in men globally with 746 000 cases reported in the GLOBOCAN 2012 statistics while in women 614 000 cases were reported in the same year however is the second most common cancer in women [11]. In the 2008 GLOBOCAN statistics 60% of all cases reported occurred in LMICs however, a decline to 55% was seen in 2012. This indicates that lifestyle risks are associated with developing CRC moreover it shows that as the LMICs become more developed, diseases such as CRC increase (Figure 1.6) [11, 13]. GLOBOCAN statistics for mortality show more CRC patients have died as a result of the disease in the most recent statistics as opposed to 2008. This includes the HICs however, LMICs display a much larger increase in their mortality statistics than the HICs (Figure 1.7).

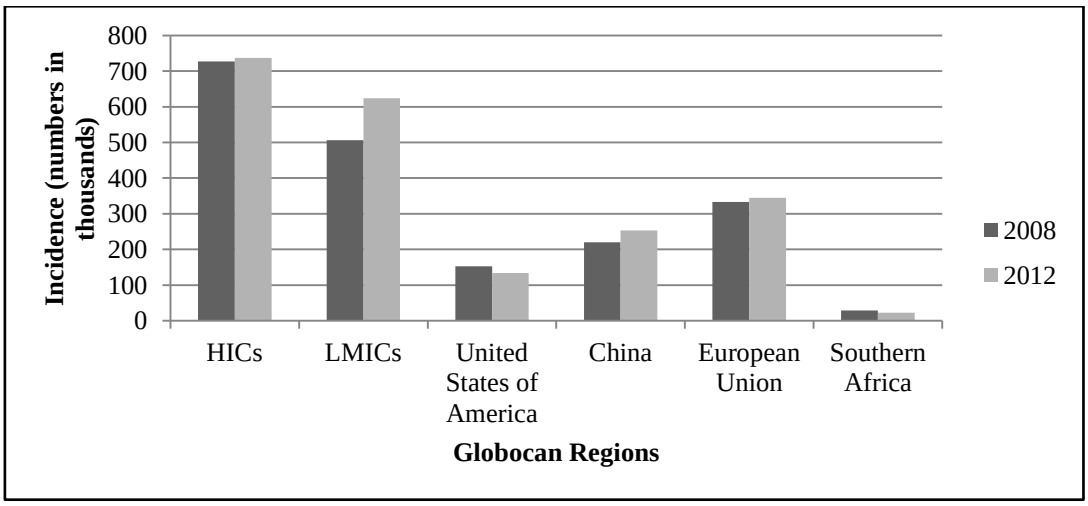


Figure 1.6 Comparative graph of the incidence of colorectal cancer cases for certain GLOBOCAN regions for 2008 and 2012 [11, 13] – dark grey (2008) and light grey (2012)

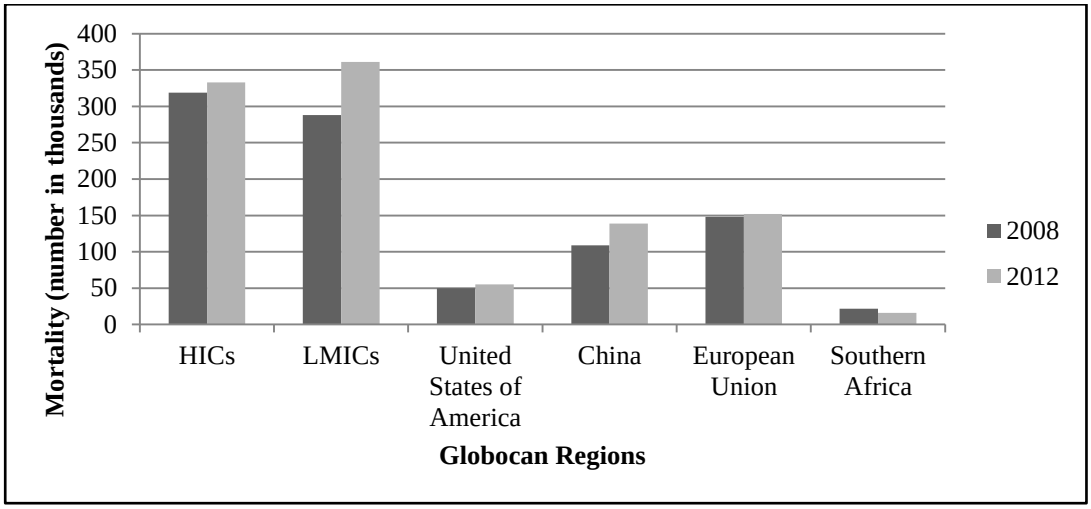


Figure 1.7 Comparative graph for GLOBOCAN colorectal cancer mortality statistics for certain regions for 2008 and 2012 [11, 13] - dark grey (2008) and light grey (2012)

The latest GLOBOCAN statistics indicate that Africa has one of the lowest incidence and mortality rates for CRC however, research shows that Southern Africa, particularly South Africa, has a high incidence rate (Table 1.2) [11, 13]. Although the data indicates a high incidence, the GLOBOCAN data is extrapolated from another population and the transferability could be questioned for the South African population [13]. Notwithstanding this, colorectal cancer has moved into the top three cancers for both sexes in the country. This change is largely due to a decrease in the incidence and mortality rates of esophageal cancer. Mortality rates have also shown a decrease from 2008 to 2012 for the South African population.

The most recent cancer statistics published in South Africa (NCR statistics) for 2012 report the number of confirmed colorectal cancer cases as 3396 and when compared to GLOBOCAN for the same time, a great difference is seen (Table 1.2) [32]. This could be that the South African NCR published data only reports cancer cases which are diagnosed by biopsy and tissue examination and does not account for alternative clinical diagnostic methods in accordance with the NCR regulations [13, 33, 34]. The limitation of the regulations is that the onus for reporting is placed on the pathologists as opposed to the oncologists. In addition to this, private diagnostic laboratories were not required to report confirmed cancer cases until 2011.

Table 1.2 Differences between GLOBOCAN and NCR statistics for South Africa for 2008 and 2011/2 [11, 13, 32, 33, 35].

Data source	Incidence of colorectal cancer cases
GLOBOCAN 2008	5050
NCR 2008	2297
NCR 2011	2913
GLOBOCAN 2012	4697
NCR 2012	3396

Taking into consideration that the Sub-Saharan region consists of 48 countries and 24 711 cases were recorded, the significance of the high incident rate in South Africa is noted even more [13]. It means that over 20% of all cases for Sub-Saharan Africa are diagnosed in South Africa. When comparing South Africa to the USA, the USA still has a higher incidence of 10,7%, regardless of their population size, compared to 6,8% for South Africa [13].

1.4.8 Conventional treatment of Colorectal Cancer

Treatment depends on a number of factors such as the stage of the cancer as well as the preference by both the attending physician and the patient. The age of the patient however should not play a role in the choice of treatment [36, 37]. Although evidence suggests the benefit of chemotherapy for geriatric patients, these patients are found to be undertreated which contributes to the poor outcome geriatric patient's experience [38, 39]. Although literature states that age shouldn't influence the choice of treatment, the likelihood for older patients to receive the same chemotherapeutic regimens is lower and is often due to the patient choosing quality of life over possible adverse events [38].

Apart from patient preference, research conducted in 2010 revealed that oncologists are less likely to prescribe intensive chemotherapy regimens despite the benefits for older patients [40]. Older patients are often not prescribed chemotherapy due to factors such as performance status or ECOG status and not due to a lack of efficacy or safety [41]. Ideally a Comprehensive Geriatric Assessment should take place in order to assess the best treatment plan for the older patient. Additionally studies have shown that even with an increase in age, the survival benefit of adjuvant chemotherapy such as fluorouracil does not decrease [36]. In another study conducted, it was found that elderly patients are able to tolerate adjuvant and palliative chemotherapy similarly to younger patients suggesting that age shouldn't be a factor when considering treatment options [37]. Clinical trial data is few for this group of patients but a pooled analysis of fluorouracil versus observation did show a similar benefit for older and younger patients with similar rates of grade 3 and 4 toxicities [42, 43].

There are three common conventional treatment regimens available to patients diagnosed namely surgery, radiation therapy and chemotherapy which includes biological therapies [21, 26].

1.4.8.1 Surgery

Surgery is used for early stages of cancer however later stages of CRC can be treated with surgery by removing not only cancerous cells but the part of the colon which is cancerous [21, 24, 26]. The type of surgical procedure undertaken will depend on the location of the cancer in the colon or rectum, the size of the cancerous tumor and whether or not metastasis has occurred.

A local resection will be done to remove early stage tumors but also to send the samples obtained to pathology in order to establish the stage of the cancer. With any surgical procedure, nearby healthy tissue will also be removed in order to ensure that no cancerous cells remain behind. If the cancer is not entirely removed, it is likely to continue growing and possibly undergo metastasis [21].

*1.4.8.2 R*adiation

Radiation therapy involves using high-energy x-rays or other radiation in order to kill the cancer cells or to prevent their growth by damaging the cell's DNA. There are two different types of radiation therapy used depending on the various factors such as stage and type of cancer (Table 1.3) [24, 44].

Table 1.3 Factors that influence the type of radiation therapy cancer patients receive [44]

1.	The type of cancer.
2.	The size of the cancer.
3.	The location of the cancer in the body.
4.	The vicinity to normal tissues that is sensitive to radiation.
5.	The distance the radiation has to travel within the body.
6.	The general health and medical history of the cancer patient.
7.	Whether the patient will receive other types of cancer treatment.
8.	Additional factors, such age and comorbidities.

Radiation will either be via external beam or internally via radioactive materials being placed inside the body near the cancer cells (brachytherapy). Alternatively systemic radiation could be used whereby patients either ingest or receive the radioactive material intravenously, radioactive iodine or a monoclonal antibody with a bound radioactive substance [44]. CRC particularly doesn't require radiation however once the cancer spreads to the liver, radiation will be used or if the patient experience severe pain [24].

1.4.8.3 Chemotherapy

Chemotherapy involves the administration of medication to target and destroy cancerous cells. Chemotherapy works to stop or slow down the growth rate of the cancer cells, which are rapidly dividing cells however the treatment also affects healthy cells negatively. The damage incurred by healthy cells determines the side effects of the treatment. Depending on the stage of the CRC, chemotherapy will be administered to cure, prolong life, control or ease the symptoms of the cancer. Adjuvant chemotherapy will be administered to reduce the likelihood of the cancer returning but if the cancer is not cured by the chemotherapy, it will either be slowed down preventing metastasis or administered to shrink the tumors to alleviate any pain or pressure caused by them. The latter is commonly referred to as palliative chemotherapy [21].

Chemotherapy is also used in conjunction with radiation or biological therapy in order to improve the prognosis of the cancer [24]. Combinational chemotherapy is often more effective [24, 26]. Many chemotherapeutic medicines also have a narrow therapeutic index indicating that the therapeutic doses used are very close to toxic levels. This means the side effects of the treatment will be worse and will occur in the majority of patients. Many of the common side effects are as a result of the chemotherapy affecting normal fast dividing cell groups such as those found in the blood, hair, mouth, skin and nails [26, 45].

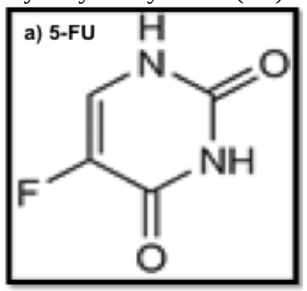
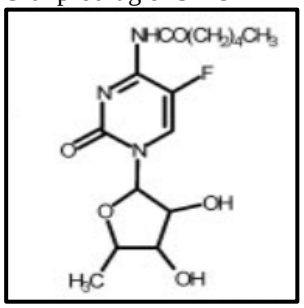
1.4.8.3.1 Adverse drug reactions of Chemotherapy

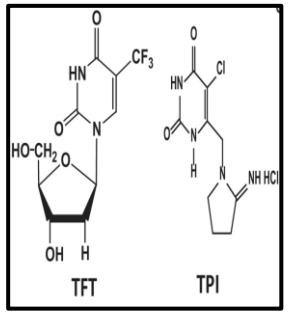
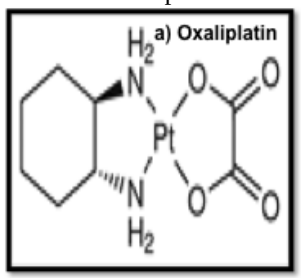
Chemotherapy decreases the level of the blood components namely erythrocytes, leukocytes and thrombocytes resulting in less oxygen been carried from the lungs to the rest of the body resulting in patients feeling tired and short of breath. Hair loss is common for patients due to the cells of the hair follicles, which are responsible for growth and maintenance, being affected by the treatment. The hair loss can also affect the scalp, face and any other parts of the body containing hair. A sore throat and mouth are also likely due to the cells lining the inside of the mouth and throat dividing rapidly and thus are susceptible to harm by the chemotherapy. Diarrhea, constipation, nausea and vomiting are common adverse drug reactions but are easily treated. Allergic reactions or hypersensitivity reactions can also occur in which case patients will need to undergo prophylactic treatment before receiving any further chemotherapy if severe. There are also adverse drug reactions specific to certain of the chemotherapeutic medicines. These include hand-foot-skin (HFS) syndrome with 5-fluorouracil or capecitabine, neuropathy with oxaliplatin treatment and irinotecan can cause severe diarrhoea [26, 45, 46].

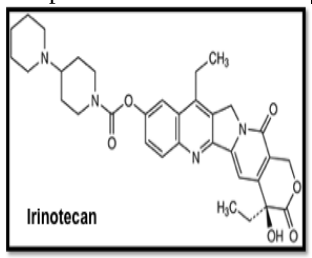
1.4.8.3.2 Conventional Chemotherapy for CRC

Conventional CRC chemotherapy is summarised in Table 1.4 below.

Table 1.4 Summary of conventional CRC chemotherapy medicines

Medicine	Indications	Chemical Structure	Pharmacological Mechanism of Action	Properties of the medicine	Clinical Trial Data
5-Fluorouracil (5-FU)	Early and Advanced CRC	Pyrimidine antagonist of thymidylate synthase (TS).  **Figure 1.8 Chemical Structure of 5-Fluorouracil [47]**	• multiple enzymatic reactions allow for activation • metabolite, *5'fluoro-2'-deoxyuridine-5'-monophosphate (5FdUMP)* will covalently bond to an enzyme thymidylate synthetase. • incorporation of the active form of 5-FU, cell death occurs due to both DNA and RNA processes being inhibited [46]	• immunosuppressant [45] • used in combination with **folinic acid** - formyl derivative of tetrahydrofolic acid, the active metabolite of folic acid and is prescribed to aid augmentation of the neoplastic effects when prescribed with 5-FU [45]. • multiple dosing regimens: **de Gramont regimen (5FULV2)**, **MAYO** regimen [48]. • combination with **oxaliplatin** and **irinotecan**→ demonstrated an improvement in survival [49, 50].	• **GERCOR** (2004) →the sequence of **FOLFIRI** followed **FOLFOX** or the reverse has similar overall survival (OS) rates, progression free survival (PFS) and reaction rates (RR). • the two regimens differ only in the dosing of the **irinotecan** and **oxaliplatin** [51].
Capecitabine (XELODA®; Hoffmann-La Roche, Inc., Basel, Switzerland)	Early and Advanced CRC	Oral prodrug of 5-FU  **Figure 1.9 Chemical Structure of Capecitabine [52]**	• undergoes enzymatic activation by thymidylate phosphatase to form 5-FU	• can be used in place of 5-FU • adverse events: hand-foot syndrome (Figure 1.10), diarrhea, neutropenia [53]. • with **irinotecan** → seems to be more adverse effects [54, 55].  **Figure 1.10 Capecitabine induced hand-foot-skin syndrome (http://jamanetwork.com/data/Journals/DERM/22502/dob110011f1.png)**	• studies have revealed the compatibility of capecitabine with **irinotecan** and **oxaliplatin** [54, 55]. • non-inferior to 5FU plus folinic acid

Trifluridine/ Tipiracil [TAS-102] (LONSURF®; Taiho Pharmaceuticals, Tokyo, Japan & Servier Laboratories, Paris, France)	Refractory Advanced CRC	TAS-102 is made up of trifluridine (thymidine-based nucleic acid analogue) and tipiracil hydrochloride (thymidine phosphorylase inhibitor) [56].  **Figure 1.11 Chemical Structure of TAS-102 [57]**	• trifluridine is the cytotoxic component, tipiracil prevents the degradation of trifluridine by thymidine phosphorylase thus ensuring more active drug is present in the blood stream [56].	• neutropenia and leukopenia are common adverse drug events [56].	• **RECOURSE** (2015) → TAS-102 compared to placebo had a significant improval in overall survival (OS) [56].
Oxaliplatin	Early and Advanced CRC – until disease progression	3rd generation platinum co-ordination compound.  **Figure 1.12 Chemical Structure of Oxaliplatin [47]**	• bind specifically to the guanine and cytosine residues of the DNA, resulting in cross-linkage of the DNA. • thus inhibit the DNA synthesis and function by inducing apoptosis. • also binds to cytoplasmic and nuclear proteins which will also form cross-links [45].	• synergistic with 5-FU → suppresses TS. • dose-limiting factor is peripheral neuropathy [26, 46, 58].	• **MOSAIC** (2004) and **NASBP-C06** (2011) trials → adding oxaliplatin to **5-FU**, significantly increases the 3-year cancer free survival rate of early-staged colon cancer patients [16, 59].

Irinotecan	Advanced CRC – upfront, reoccurrence or disease progression but has no benefit in early CRC.	3rd generation derivative of camptothecin  **Figure 1.13 Chemical structure of Irinotecan [47]**	• inhibits the topoisomerase 1 enzyme → prevents the re-ligation of the DNA strands, resulting in double DNA strand breakages and cell death. • S-phase specific [46].	• a prodrug that undergoes conversion in the liver to a more potent metabolite, SN-38 [46]. • limiting factor for the metabolite's action → inefficient enzyme conversion by human liver carboxylesterase [60]. • Adverse drug reactions: severe diarrhea →prescribe loperamide as soon as this starts so as to avoid dehydration; cholinergic syndrome → treated with atropine [45, 46, 58].	• **CALGB 89803** and **PETACC3** trials → adding irinotecan to **5-FU**, has no significant benefit to patients [61, 62].

1.4.8.3.3 Biological therapies

Biological therapies involve the use of monoclonal antibodies or other agents in cancer treatment. These agents can be used alone or in combination with chemotherapeutic agents such as those mentioned above. The development of these newer agents has brought about new methods to the management of advanced CRC colorectal cancer. Combining these agents with the conventional chemotherapeutic agents and resection where possible has been found to increase the overall survival of patients from a few months to as much as 30 months [63]. There are a number of both FDA and MCC (Medicines Control Council) approved agents and which target specific cellular receptors or growth factors. These are thought to increase the capacity for metastasis [64].

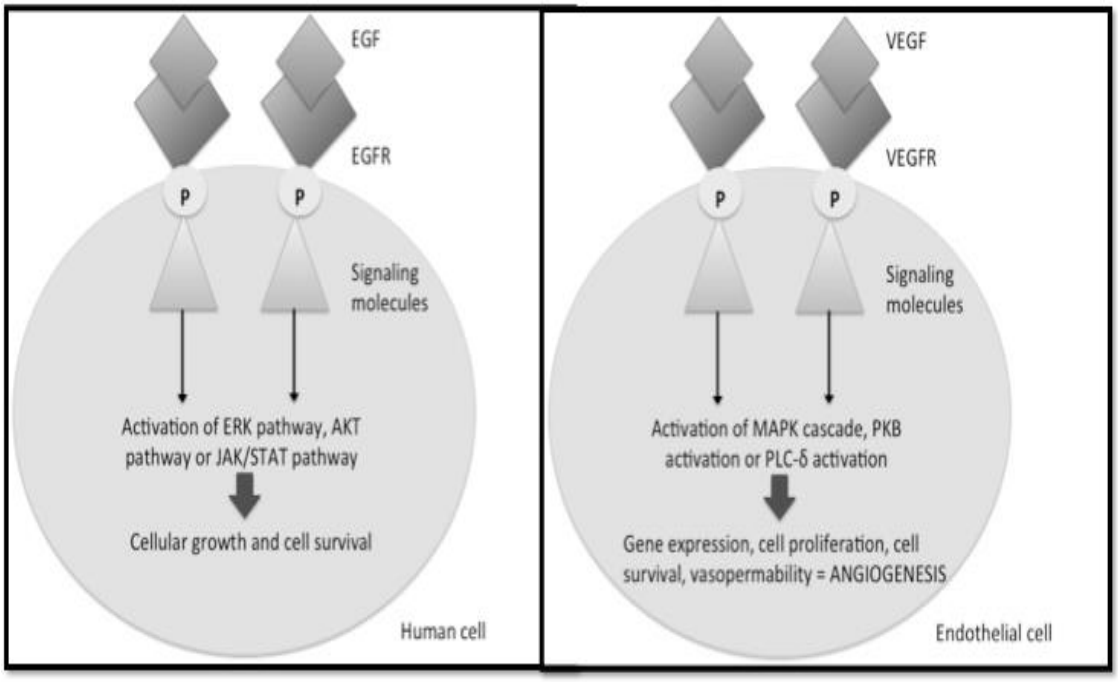


Figure 1.14 The EGF and VEGF pathways – Both the EGF and VEGF pathways are activated by the growth factor binding to its receptor initiating a signal transduction pathway. EGF leads to the activation of the RAS/RAF/MEK/ERK, PI3K/AKT/mTOR or JAK/STAT pathways resulting in tumour cellular growth and cell survival. VEGF results in the MAPK cascade activation and then the PKB/PLC-δ pathways in endothelial cells, which leads to angiogenesis [65].

Figure 1.14 shows the respective pathways that are activated by either the EGF or VEGF growth moreover it can be seen that if either one is over-expressed, the cells will experience a remarkable increase in proliferation, growth and survival thus increasing the risk of tumor formation and spread. Approximately 70% of colorectal cancers have an increased expression

of EGFR contributing to advanced disease stage along with poor prognosis. Due to increased angiogenesis and vascular permeability as a result of increased VEGF expression, there is a greater ability for metastasis to occur. [64]. Table 1.5 summarises all the approved biological therapies for CRC.

Table 1.5 Summary of the biological agents available for CRC

Medicine	Indications	Chemical Structure	Pharmacological Mechanism of Action	Properties of the medicine	Clinical Trial Data
***Bevacizumab** (Avastin ®; Hoffmann-La Roche, Inc., Basel, Switzerland and Genentech, South San Francisco, CA)	Advanced CRC	Humanised Recombinant Monoclonal Antibody (MoAB)	• VEGF inhibitor → block endothelial cell proliferation (Figure 1.14) • results in decreased angiogenesis [65]. • Binds circulating VEGF in the blood, reducing the ability of VEGF to bind to its endothelial receptor (VEGFR) [64, 66].	• Used in combination with chemotherapy → leads to the induction of apoptosis. • combination will stabilise the tumor vasculature increasing the delivery of the chemotherapeutic agent to the tumor thus it is standard practice to administer bevacizumab in combination with a **chemotherapeutic agent** [64, 66].	• Hurwitz *et al.* (2004) [67] → clinically meaningful and statistically significant result for OS, PFS and duration of response • Saltz *et al.* (2008) [68] → only PFS was statistically significant • Giantonio *et al.* (2007) [69] → clinically meaningful and statistically significant result for OS, PFS and duration of response • **AVEX (elderly patients)** [70] → only PFS was statistically significant
Aflibercept (ZALTRAP®; Sanofi, Paris, France and Regeneron Pharmaceuticals, Tarrytown, NY)	Relapsed Advanced CRC	Recombinant fusion protein made up of the VEGFR-1 and -2 with human IgG1	• Binds to VEGF-1, VEGF-2 and Placental Growth Factor [71]. • free aflibercept had to be in excess of bound aflibercept in order for pharmacological action to be optimal [72].		• Early phase clinical trials → aflibercept as a single agent and combinational treatments • a phase 2 trial established a suitable dose in combination with **FOLFIRI** which allowed for disease control [72]. • **VELOUR** (2012) study was able to prove an improved benefit when aflibercept is used in combination with **FOLFIRI** in patients failing **FOLFOX.** • Furthermore all efficacy endpoints for the study were in favour of aflibercept when compared to placebo [73].
Ramucirumab (CYRAMZA®; Eli Lilly Indianapolis, IN)	Relapsed Advanced CRC	Fully Human IgG1 Monoclonal Antibody (MoAB)	• Selectively blocks VEGFR-2 • Acts directly on the receptor resulting in a decreased angiogenesis [74].	• found to cause hemorrhages in patients and as such contains a black box warning for this adverse drug reaction [74].	• **RAISE** (2015) → used in combination with **FOLFIRI**, significant median overall survival was increased by 1,6 months [74-76].

***Cetuximab** (ERBITUX®; Merck Serono, Darmstadt, Germany and Eli Lilly, Indianapolis, IN)	Advanced CRC; Irinotecan-Refractory Advanced CRC	Chimeric human/mouse IgG1 EGFR Monoclonal Antibody (MoAB)	• EGFR inhibitor → bind to EGFR extracellularly preventing the ligand from binding and downstream activation [65]. • inhibits tumour cell growth and survival (Figure 1.14)	• *RAS* wildtype tumor (patients where *RAS* is not mutated) are the only patients that gain benefit from EGFR inhibitors [77]. • Anaphylactic reactions are common during infusion particularly with cetuximab [66].  **Figure 1.15 Anti-EGFR therapy induced skin rash (https://3c1703fe8d.site.internapcdn.net/newman/gfx/news/hires/2016/1-prophylactic.jpg)** • Used in combination with **FOLFOX** and **FOLFIRI**.	• The cetuximab combination also proved to be more effective than cetuximab monotherapy for irinotecan-refractory patients moreover, the use or nonuse of oxaliplatin previously had no effect on the efficacy of cetuximab thus patients who have been previously treated with oxaliplatin or FOLFOX can potentially benefit from cetuximab [78]. • **CRYSTAL** (2009)→ advanced CRC is treated initially with **FOLFIRI** and cetuximab as opposed to **FOLFIRI** alone, disease progression decreases and response rate increases [77].
Panitumumab (Vectibix®; Amgen, Thousand Oaks, CA)	Advanced CRC	Fully human IgG2 Monoclonal Antibody (MoAB)		• Apart from the *RAS* benefits as with cetuximab, panitumumab does not mediate antibody-dependent cell-mediated cytotoxicity or complement-mediated cytolysis [79]. • Used in combination with **FOLFOX** and **FOLFIRI**.	• Panitumumab monotherapy is well tolerated and effective → compared to **best supportive care** alone there is no overall survival benefit but is comparable to other studies in response rates, duration of response and progression free survival [80]. • **PRIME** (2013) → compared panitumumab - **FOLFOX4** to FOLFOX4, significant improvement for PFS and ORR [81, 82]. • randomised phase 3 study → combination with **FOLFIRI** increased the median OS and PFS by 2 months as well as reduced the risk of progression or death in patients progressing on FOLFOX [83].

***Regorafenib** (STIVARGA®; Bayer HealthCare Pharmaceuticals Inc., Leverkusen, Germany)	Advanced CRC following chemotherapy and other biological therapy failure	Oral tyrosine kinase inhibitor	• Targets multiple kinase molecules in the angiogenic and tumour growth promoting pathways.	• Undergoes enterohepatic circulation, highly plasma bound and a CYP enzyme inducer. • Interaction with medicines that are UCT substrates such as **irinotecan**. • Possible adverse drug reaction: Hand-foot syndrome [64, 84].	• **CORRECT** (2013) → improvement in overall survival, PFS and disease control rate • Regorafenib stabalises the disease rather than decrease the tumour size [85].

Note: Medicines with a * next to the name are unavailable to South African patients [86]

1.4.8.3.4 Colorectal cancer medicine combinations

Combinations of the medicines mentioned above are often used in an effort to make them more effective. Table 1.6 shows the most common combinations and regimens that are available for the treatment of advanced colorectal treatment. Early CRC chemotherapy treatment consist of capecitabine, 5FU-folinic acid, FOLFOX and CAPOX regimens only. There is no place for irinotecan or biological therapies in adjuvant therapy of CRC **[26]**.

Table 1.6 Chemotherapy combinations prescribed for advanced colorectal cancer treatment according to the American Cancer Society [26] Note: 1. Medicines in **bold** are unavailable to South African patients [86]**;** 2. XELIRI (Capecitabine + irinotecan) is not recommended by the American Cancer Society however is used in practice).

Combination	Medications included
FOLFOX	*FOLFOX:* 5-FU+Folinic acid+oxaliplatin
FOLFIRI	*FOLFIRI:* 5-FU+Folinic acid+irinotecan
CAPOX	*CAPOX:* Capecitabine+oxaliplatin
FOLFOXFIRI	*FOLFOXIRI:* 5-FU+Folinic acid+oxaliplatin+irinotecan
FOLFOX+biological	**Biological therapies include**
FOLFIRI+biological	Bevacizumab or **Aflibercept** or **Ramucirumab** or Cetuximab or Panitumumab
CAPOX+biological	
FOLFOXFIRI+ biological	
5-FU+Folinic acid with/without biological	
Capecitabine with/without biological	
Irinotecan with/without biological	
Cetuximab monotherapy	
Panitumumab monotherapy	
Regorafenib monotherapy	
Trifluridine + tipiracil	

1.4.8.3.4.1 CRC treatment and liver resection

Research has shown that patients treated with oxaliplatin as opposed to irinotecan for liver metastases in the first line, perform better when undergoing liver resection surgery. Although the mechanisms for this remain unclear, it has been found that patients on a FOLFOX regimen can develop sinusoidal dilatation known as a "blue liver". This blue liver can lead to an increased amount of bleeding when liver resection is done. Patients treated with FOLFIRI on the other hand can develop chemotherapy-associated steatohepatitis (CASH) known as a "yellow liver" [87].

Patient selection for liver resection does seem to vary however, patients who have more than 50% or 6 segments which are diseased, any extra-liver disease or who are unfit are unable to undergo any resection and will be deemed unsuitable for conversion therapy [88]. The choice of neoadjuvant chemotherapy does seem to impact the outcome of patients who are eligible for liver resection. Likewise the PRIME study showed that the resection rate was higher with the addition of panitumumab for patients that were able to undergo resection [81, 82].

1.4.8.3.4.2 Acquired mutations and CRC treatment

1.4.8.3.4.2.1 RAS mutations

Cetuximab and panitumumab (EGFR inhibitors) have led to the discovery that the RAS (KRAS and NRAS) (section 1.4.3) status is important for anti-EGFR treatment to be effective. Initial and updated analysis of both the CRYSTAL and OPUS trials have shown that the KRAS mutation status can be used as a predictive marker for a clinical outcome with anti-EGFR monoclonal antibodies [89, 90]. Karapetis and colleagues (2008) [91] showed that KRAS mutation status is associated with overall survival for advanced CRC colorectal cancer patients who are treated with cetuximab. Wild-type KRAS tumours had nearly double the median OS and PFS when compared to the best supportive care group. There was also no significant survival benefit for patients with mutated KRAS [91]. The CRYSTAL trial showed that KRAS mutational status is important for patient's response to cetuximab [77]. Likewise the PRIME study showed that a wild-type KRAS is important for clinical benefit as the final analysis shows a significant improvement for PFS and ORR. When panitumumab was compared to cetuximab, patients treated with panitumumab had worse outcomes [81, 82, 92]. Another study compared the addition of panitumumab to chemotherapy and bevacizumab. The addition of panitumumab decreased patients PFS and increased the number of toxicities. This indicates that adding multiple biological therapies is not always in the best interest of the patient [93].

1.4.8.3.4.2.2 BRAF mutations

Unlike RAS mutations which are predictive for patient's response to treatment, BRAF tumour mutations are prognostic [89, 90]. BRAF mutations have been found to play no role in a patient's response to anti-EGFR therapy (cetuximab or panitumumab). Thus doesn't appear to

have a predictive role in treatment [94, 95]. The prognostic role has however been well studied whereby patients with BRAF mutations have a poorer prognosis. This was clearly illustrated in a study whereby BRAF mutations had a significant effect on the patient's overall survival [96].

1.4.8.3.4.3 Left-sided vs Right-sided CRC and treatment

New analysis of the FIRE-3 and CALGB/SWOG 80405 trials have found that RAS wildtype patients response to treatment may be based on whether the CRC is of left-sided or right-sided origin [97, 98]. Initially the data from the CALGB/SWOG 80405 trial indicated no difference in either PFS or OS between the two treatment arms. However, recent preliminary analysis shows that patients with left-sided CRC have longer survival and better outcomes, regardless of which treatment arm they were randomised to. Patients with left-sided CRC that received cetuximab in their treatment regimen had a greater median overall survival (36 mnths vs. 16.7 mnths) and those that received bevacizumab also displayed a greater median overall survival (31.4 mnths vs. 24.2 mnths) when compared to right-sided CRC [97].

The authors also found that patients with right-sided CRC do not benefit from cetuximab (or other EGFR-inhibitors) but rather benefit from bevacizumab. Post-hoc analysis of the FIRE-3 trial has shown that the side of origin is prognostic for OS or PFS and that right-sided CRC has worse outcomes. This new data does suggest that RAS wildtype CRC patients treatment should be stratified based on the side of origin of the colorectal region [98].

1.4.9 Drug Utilisation Review as a means to determine the resource utilisation in theory and clinical practice

Drug utilisation research is "the marketing, distribution, prescription, and use of medicines in society, with special emphasis on the resulting medical, social and economic consequences." [99] Drug utilisation reviews (DURs) are structured in order to review the prescribing of the practitioner, the dispensing by the pharmacist and the use of the medicines by the patients [100]. DURs are therefore used to assess if the prescribed medicine therapies are rational in the real-world setting. These reviews can be prospective (before the patient receives the medicines), concurrent (while the patient is being treated and taking the medicines) or retrospective (after the patient has received the medicines) [100]. Data sources for DURs

include but are not limited to drug regulation agency data, distribution (supplier) data, practice or community setting data. All these data sources will be reviewed and will illustrate different facets of drug utilisation. Subsequent to this economic analysis can take place and economic outcomes analysis, i.e. cost-effectiveness or cost-benefit amongst others, can be performed [99].

1.5 Literature Review

The literature review covers topics including a brief introduction pertaining to medical costs and cancer, healthcare expenditure as a proportion of GDP, the incidence and expenditure of cancer, secondary costs associated with cancer, assessing the value of these treatments and how costs can be controlled. The literature review will then cover colorectal cancer costs in particular in relation to the concept of clinical pathways and the current treatments available. Finally the literature review will cover the South African healthcare system in more depth in terms of the financing and expenditure.

The literature search strategy involved searching for published research using databases such as PubMed and Google Scholar using key words such as colorectal cancer, cancer incidence, chemotherapy, cancer treatment, treatment/clinical/care pathways, healthcare expenditure, resource utilisation, costs, secondary costs, public healthcare and private healthcare.

1.5.1 Introduction

Medical costs worldwide have been increasing for a number of years in developed countries, largely due to an aging population but also due to the technological advances within medicine. The problem posed by such a situation is the burden placed on the healthcare system. This in turn can have dire economic impacts such as the recession experienced by Japan and the impact this had on their social health insurance system [101]. Cancer, due to its high incidence imposes substantial financial burdens on both the patient and society. This is largely due to the prevention and management of the disease [102].

However, LMICs seem to have weaker healthcare systems that lack adequate infrastructure in order to deal with diseases such as cancer [103]. Much research has been done around the issue of health inequalities which has shown that it is often related to the economic system and therefore health outcomes are impacted [104].

According to the WHO technical report (No. 804) more than 50% of cancer patients live in these low-middle income countries. These patients account for less than 10% of all cancer control and care expense. Thus it is no surprise that only 5% of cytotoxic medicines are consumed by LMICs [105]. Igene (2008) also noted that developing countries have larger corruption issues and although the budgets assign finances to programs, it is not always spent

on these programs or where it is spent it yields substandard results due to mismanagement. The result is a lack of resources. This could present as unavailable treatment or unaffordable treatment to the majority of patients but also the use of outdated technology [104].

1.5.2 Healthcare expenditure as a proportion of the Gross Domestic Product

Levels of national income – which is measured by the gross domestic product or GDP – can be the same among many countries however health expenditure is not the same. The United States in comparison to the EU and other countries spends approximately 16% GDP on healthcare. The EU and other countries have much lower expenditure i.e. <12% but this doesn't mean that the US has better health outcomes for patients. Thus GDP isn't a good indicator that more spend has a better outcome. Also Luengo-Fernandez and colleagues (2013) [102] found that although some countries within the EU have the same levels of national income, which is not unusual, health expenditure and in particular cancer expenditure can vary. Therefore expenditure is expected to vary thoughout developed and developing countries and therefore is difficult to compare. [102, 106].

1.5.3 The incidence of cancer and implications for expenditure on treatment

Cancer data shows that global incidence patterns for cancer are changing. While most developed countries such as the United States show cancer incidence rates decreasing, developing countries show increases [2]. This change in incidence has been attributed to increasing westernisation of such countries as cancers such as breast or colon are ever increasing. The adoption of unhealthy lifestyles, which influence factors such as reproductive, dietary, metabolic and hormonal determinants increase the risk of such cancers in these less developed countries [1, 2]. Assuming constant social and economic development, global cancer incidence is projected to be 22.2 million by 2030 as opposed to the estimated 12.7 million in 2008 [1]. As cancer incidence rates increase so too do the costs of cancer treatment. The costs involved in such treatment include chemotherapy medicines, supportive care medicines and the administration of these but to name a few.

1.5.4 The cost of chemotherapy

The high cost of chemotherapy also appears to be a global issue however, less-developed countries with lower-median incomes show that the costs largely fall on the patient [3]. In addition to this, there are also differences within the access and provision to services and treatment within countries. One such country is South Africa. About 15% of South Africa's population belong to private voluntary medical insurance which allows a greater access to better healthcare [107].

These increasing problems with oncology costs are attributed to chemotherapeutic medicines circulating in a non-competitive market. In other words, the introduction of newer chemotherapeutic medication does not result in lower-costs for older medicines, as most cancer patients will be treated with all the available medicines at some point. This is largely due to the limited efficacy of these medicines together with the fact that newer version medications are add-on's to older versions and do not provide alternative treatment. This therefore sustains the current non-competitive pricing [3].

The costs associated with having such a disease have been assessed in many developed countries across Europe and the Americas [102, 108]. In the United States, it has been estimated that cancer care spending exceeds $125 billion annually and is projected to further increase in the near future according to a projection study published by Mariotto and colleagues [109] in 2011. A recent population-based cost analysis study looked at the economic burden of cancer across the European Union (EU) and found that the total cost was more than €126 billion in 2009. Interestingly the countries with the highest populations - Germany, France, Italy and the United Kingdom – accounted for majority of these costs. When comparing the contributing factors to cancer care costs, the medicine expenditure for 2009 was in excess of €13,5 billion. This is 27% of the total costs incurred for the disease [102]. Importantly, this analysis only included chemotherapeutics and hormone therapies, immunosuppressants, antiemetics and opioids were excluded, thus the total medicine expenditure should in fact be much greater as these additional medications are dispensed however could not be included due to insufficient information. These differences are attributed to medicine acquisition costs, medicine consumption and the differences in the type of medicines been consumed [102].

Other factors that influence the cost could be the price setting, reimbursement mechanisms as well as clinical practice variation [102]. Hassett and Elkin [106] describe reasons as to why there are increases in the per-unit medicine costs as indicated in Table 1.7. These together with the increasing costs of existing medication and increased use of chemotherapeutics all contribute to the increased spending for the treatment of cancer [106].

Table 1.7 Reasons for increasing per-unit medicine costs [106]

Increase in per-unit medicine costs are a result of:
1. Increased drug development costs
2. Newer agents are more targeted and are not suitable for all patients
3. Regulatory approval is not based on cost effectiveness or affordability
4. Laws and policies in certain countries limit the negotiation of lower medicine costs
5. Willingness to pay for the newer therapies by private and public funders

1.5.4.1 Secondary costs associated with chemotherapy

Importantly the costs associated with such a disease are not only restricted to the chemotherapy but patients also experience substantial costs due to supportive care medicines and adverse drug reactions. Montero and colleagues (2012) [110] found that in the chemotherapeutic subgroup of patients with advanced breast cancer, the highest pharmacy costs were incurred. These costs included antiemetic's, analgesics as well as anticoagulants and antidepressants among others. The cost amounted to $725 per patient per month (PPPM) [110]. Out-of-pocket costs are also likely to be incurred by cancer patients however these have rarely been studied in the literature.

1.5.4.2 Assessing the value of treatments and controlling cancer costs

Assessing the value of medical treatments is important as some treatments may not be worth the financial implications such as the use of ixabepilone in combination with capecitabine for taxane- and anthracycline- resistant advanced CRC breast cancer. The addition of ixabepilone costs an additional $4000 per cycle of chemotherapy while providing just over 1 month progression-free survival (PFS). The incremental cost-effectiveness ratio (ICER) is the preferred method for assessing such treatments. The cost utility analysis (CUA) is measured in quality-adjusted life-years or QALYs which allows for comparisons between treatments within disease areas. The cost-effectiveness threshold or gold standard for QALYs in the USA ranges from $50 000-$100 000 and is estimated to be equivalent to the cost/QALY renal

dialysis for end-stage renal disease patients [106]. The cost differences include medicine acquisition costs as well as administrative costs, costs related to monitoring the effect and treating of the adverse drug related costs [111]. However, CEAs do not give information as to how much is too much to spend on healthcare treatments (i.e. affordability) or what patients would be willing to pay for a medical intervention [106].

Therefore in order to control expenditure, a number of strategies can be employed such as restricting specific treatment coverage to formularies determined by principles of cost, efficacy and cost-effectiveness as well as limiting access to certain plan types within the medical scheme (i.e. only high-income plans or plan with differing financial limits on expenditure). This also limits the overuse of certain high cost medications, especially where cost-effectiveness is uncertain or not proven. Other ways include reducing the reimbursement rates for specific medications or introduction of capitated agreements with service providers. [106].

1.5.5 Colorectal cancer costs

Resource utilisation studies for colorectal cancer are far fewer than cancers such as breast. It could possibly be attributed to a lower incidence rate for colorectal cancer. Costs associated with colorectal cancer are substantial particularly when newer medicines and biologicals are included in the treatment regimens as seen in literature.

Adjuvant chemotherapy with FOLFOX was found to cost € 3 743 per cycle as opposed to € 6 085 per cycle when bevacizumab is added to FOLFOX for advanced CRC [112]. Other research has calculated per patient costs to average $97 400 for CRC treatment. These costs include chemotherapy and biological in addition to other medicines that may be required as well as the outpatient and inpatient costs [113]. Costs in South Africa may be very different depending on a number of factors. However, it is noted that bevacizumab substantially increases the total cost which is also seen in South Africa. What is similar between the two studies is that as disease progression occurs and patients advance from 1st line therapy onwards costs increased considerably. Recent publications studying the clinical outcomes of patients with advanced CRC colorectal cancer show that both first-line treatment regimens of FOLFOX and FOLFIRI - these two regimens are similar in response rate, progression-free survival and time to progression as well as overall survival but do have different toxicity profiles - are compatible with Bevacizumab [114, 115].

However, Bevacizumab is an antiangiogenic monoclonal antibody and once included in the treatment plan increases the costs substantially. Randomised trials have also shown that in the absence of a biologic agent, such as Bevacizumab, the 1st line treatment regimens appear to be non-inferior and the sequence of the first line agent exposure is less important than receiving all three agents, namely oxaliplatin, 5-FU and irinotecan [114]. Despite this, the availability of these biological agents seems to place pressure on both clinicians and patients to use biologics regardless of the cost implications or benefit patients may receive. A biologic such as bevacizumab has been publically funded in Ontario, Canada since 2008 however recently was one of 21 cancer medicines cut from the reformed UK cancer drug fund at the end of 2015. In addition to bevacizumab for colorectal cancer, anti-EGFR monoclonal antibodies, cetuximab and panitumumab were also removed during the new reformation of the UK's cancer drug fund [115-117]. These biologics however have never been made available to public sector patients in South Africa.

1.5.5.1 Cost-effectiveness of biological treatment

A study done by Ewara and colleagues (2014) [115] looked at the cost-effectiveness of bevacizumab plus FOLFIRI as opposed to cetuximab or panitumumab plus FOLFIRI. The bevacizumab treatment arm dominated despite the other two biologics having showed improved patient outcomes compared to patients using FOLFIRI or FOLFOX alone, however when compared to the current practice (FOLFIRI + bevacizumab) these other biologics may not be cost-effective options in Ontario. Comparing FOLFIRI+bevacizumab to FOLFIRI+cetuximab resulted in an incremental loss of 0.008 QALYS per person at an incremental cost of $3 159 whereby FOLFIRI+panitumumab resulted in an incremental loss of 0.033 QALYS per person at an incremental cost of $23 359 thus FOLFIRI+bevacizumab was favoured.

In addition, both 1st line treatment regimens (FOLFIRI and FOLFOX) are compatible with bevacizumab with respect to effectiveness and treatment patterns however, the use of the FOLFOX regimen with bevacizumab is more costly due to the cost of oxaliplatin in comparison to FOLFIRI+bevacizumab. This could be the reason for the approval of FOLFIRI plus Bevacizumab in the public sector in Ontario [114, 115].

Studies such as these have led to the development of "clinical pathways" which are used in order to reduce the rising costs of treatment.

1.5.6 Clinical/care pathways

A clinical or care pathway was first defined in 2007, by Vanhaecht and colleagues (2007) [118] as: "A care pathway is a complex intervention for the mutual decision-making and organisation of care processes for a well-defined group of patients during a well-defined period." [118]. The aim of the pathway is not only to improve patient outcomes but also to enhance the use of the available resources [111]. Oncology, particularly in the United States, have made use of pathways as they are multi-disciplinary and have been found to reduce costs and improve care. Moreover, companies and health plans in the US have been involved with the development and implementation of clinical pathways for a while now however, some view this as counterproductive to the age of personalised medicine [119, 120]. While others believe that it has and will continue to ensure that beneficial medicines based on the correct pathway will be prescribed to patients thus reducing resource wastage while improving patient outcomes [121].

In order for the clinical pathways to benefit patients, many health schemes and companies have had to employ reimbursement schemes for oncologists to use the pathways but nonetheless research has shown the benefit [119, 122]. Pathway programs such as those reported by Feinberg and colleagues (2013) [123] showed that more than $ 8 million of savings were acquired from the Cardinal Health program. Savings were obtained from medicine and non-medicine expenses [123]. Other studies looking at colorectal cancer and non-small cell lung cancer have shown that when pathway programs are compared to patients who are not on treatment pathways, the costs are lower while survival rates are similar [124, 125].

Based on the definition of a clinical pathway, South Africa does not have well-defined pathways for oncology however looking at both sectors there are guidelines (Standard Treatment Guidelines - STGs, Independent Clinical Oncology Netwotk - ICON and South African Oncology Consortium - SAOC protocols) and formularies (Essential Medicine Lists - EMLs and private medical insurance formularies) which do allow oncologists and other medical professionals to make clinical decisions based on what is available [126-129]. Although these resources are evidence-based as stated by the relevant bodies, the healthcare

professionals may select any medicine or regimen that is listed. This can result in wastage of resources and increase the costs of treatment which the patient will need to cover should their medical insurance funds run short. In the public sector it means that the cost to state is higher when patients receive unnecessary treatments but moreover resource utilisation becomes an issue. The PMBs and STGs are, in effect, clinical pathways.

1.5.7 The South African healthcare system

At present, South Africa's healthcare system is divided into two sectors. Each sector, namely public and private, has a range of healthcare provisions. These range from basic primary healthcare to highly specialised health services such as oncology treatment. While these two sectors offer similar services and data published has shown similar expenditure, there is a difference in both funding and the population that makes use of these services [4, 130]. The larger proportion of the population (85%) makes use of public healthcare whereby a smaller percentage of the population (15%) subscribe to medical insurance and have access to private healthcare services [4, 131].

1.5.7.1 The public healthcare sector

1.5.7.1.1 Medicine selection in the public healthcare sector

Since 1996, the National Drug Policy (NDP) has aimed to provide equal access to medications for all South Africans by establishing the Essential Drugs Programme (EDP). This EDP is overseen by the National Department of Health and comprises Essential Medicines Lists (EMLs) and Standard Treatment Guidelines (STGs) [132]. The National Essential Medicines List Committee (NEMLC) has four subcommittees, namely primary care, adult, paediatric and tertiary/quaternary EMLCs.

The World Health Organisation [133] [133] has promoted a set of EML guidelines to encourage equal access for all patients to certain medicines on a sustainable basis. This is because healthcare is a basic human right in most constitutions [134]. The WHO also define essential medicines as medicines, which satisfy the healthcare needs of a population, therefore EMLs can differ from one country to the next. The WHO provides a 'model' which allows for the selection of essential medicines in order to improve the health of the relevant population.

The models considers aspects relating to the rational for the medicine use, regulation and quality in addition to the procurement and supply of the necessary medicines [135]. Essential medicines are not only meant to be available in adequate quantities in the healthcare sector but also in the suitable dosage forms and at a price that both individuals and the community can afford. Therefore the medicines are selected based on the efficacy and safety of the medicine, disease prevalence and comparative cost [132]. With regard to comparative cost, the WHO guidelines also state that generic substitution may take place in order to provide affordable medicines to the public thus it is not uncommon to find many low-cost generics on the South African EMLs [134]. The process of EML selection in South Africa is evidence-based and includes pharmacoeconomic considerations (Figure 1.16). There is constant review of the EML be it at primary healthcare, paediatric, adult hospital level or tertiary/quaternary level healthcare. As of February 2014, a total of 1 279 medicines can be found on the EML which covers primary, paediatric, adult hospital level and tertiary/quaternary healthcare [135].

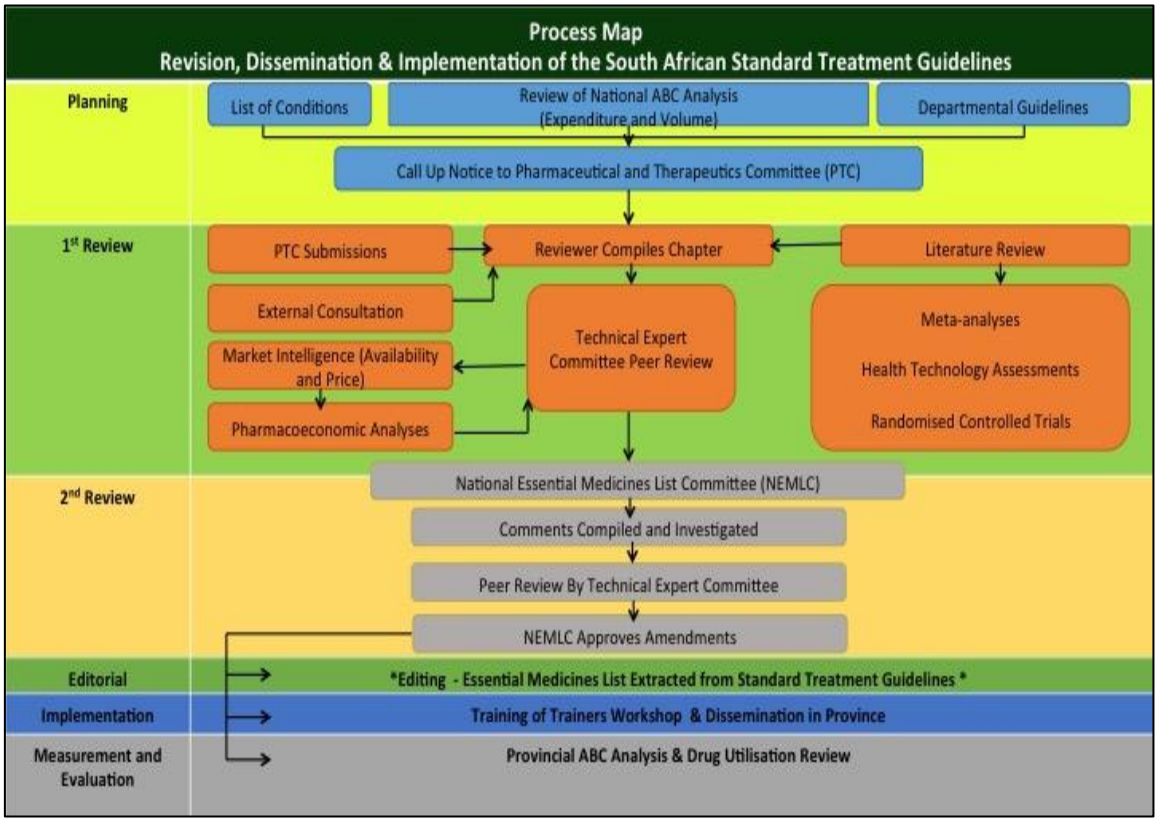


Figure 1.16 The process of selection of the EML and STGs in the South African Public Healthcare Sector [135]

1.5.7.1.2 Availability of the essential medicines

According to the United Nations MDG report (2008), most LMICs have lower medicine availability in the public sector and these regions also appear to have considerable availability differences between the public and private sectors [136]. Poor availability therefore becomes an obstacle to accessing affordable medicines. Access to essential medicines by all citizens is possible in a country such as South Africa however availability of these medicines has, in recent years, become more of a problem. This led the National Department of Health to appoint a task team in 2015 to advise as to why the non-availability of medicines is occurring and what can be done by it. The task team discovered that the supply issues surrounding many of the essential medicines is due to ordering and supply issues between the medicine depots and relevant facilities. Furthermore intercontinental transport system delays, manufacturer difficulties and supply accounts that are in arrears contribute to the lack of availability of the necessary medicines [137].

Most notably it was recognised that the non-availability of essential medicines is a global issue and not unique to South Africa but communications need to be strengthened and directed to include healthcare professionals and patients with regard to how long the shortage is expected, what alternative therapies are available and any additional information that maybe required. Locally it was suggested that monitoring tools should be implemented to keep track of the stock levels at all types of facilities. These include tools such as the mobile stock visibility technology adopted for clinics. In addition to monitoring, a forecasting tool should also be developed to avoid the current erratic ordering and poor quantification [137].

1.5.7.1.3 Medicine procurement in the public sector

Medicine procurement is influenced by the STGs and EMLs and the tender procurement process influences the pricing of the medicine in the public sector. This process is government regulated and in recent years has been taken over by the National Department of Health however is still in line with National Treasury procedures [138]. The aim for medicine procurement, according to the NDP, is to maintain the healthcare system in such a way so that medical supplies are obtained at the best possible price [139]. In order for this procurement process to occur, a competitive bidding process was implemented and has provided the necessary reform in the sector. The process for awarding tenders, as stated in the NDP, is transparent and conducted according to the Tender Board recommendations however,

negotiations with preferred bidders does take place. This ensures that additional savings are also acquired by the Department of Health. Thus the medicine acquired is more cost-effective within the public sector [138, 139].

1.5.7.2 The private healthcare sector

The private medical sector in South Africa is aimed at middle- and higher-income earners who "voluntarily" join medical schemes in order to substitute cover. While the scheme will pay for services and medications, co-payments are frequent and covered by the beneficiaries. All schemes are non-profit organisations while their administrators are profitable [4]. South Africa has around 97-registered medical schemes with approximately 15% of the population covered, however the expenditure is very similar to the public sector [131, 140].

The private healthcare sector also attracts most of the country's healthcare professionals resulting in unequal distribution of resources [141]. A survey conducted by the Human Sciences Research Council (HSRC) in 2005 found that public sector facilities and majority of private facilities have a copy of the National STGs even though it is not officially applicable to this sector [142]. This is understandable as the National Department of Health, has encouraged the private sector to make use of the STGs and EMLs, wherever applicable [132]. What remains unclear is whether or not the training of these professionals or the Department's encouragement influences the use of the STGs and EMLs and if these private sector patients pay more for the same treatment when these guidelines are used.

1.5.7.2.1 Regulation of the private healthcare sector

The Council for Medical Schemes (CMS) is a statutory body established by the Medical Schemes Act (131 of 1998) which regulates medical schemes. It has sought to provide regulatory supervision of the private healthcare financing offered by these schemes [140]. The council regulates the industry in a fair and transparent manner by a number of means (Table 1.8) [143].

Table 1.8 The mission statements of the Council for Medical Schemes [143]

Protecting the public and informing them about their rights, obligations, and other matters in respect of medical schemes.
Ensuring that complaints raised by members of the public are handled appropriately and speedily.
Ensuring that all entities conducting the business of medical schemes, and other regulated entities, comply with the Medical Schemes Act.
Ensuring the improved management and governance of medical schemes.
Advising the Minister of Health of appropriate regulatory and policy interventions that will assist in attaining national health policy objectives.

1.5.7.2.2 Medicine selection in the private sector

Funding for medicine in the private sector is largely based on the medical scheme formularies and medical scheme benefit designs. In 2004 the South African government implemented a single exit price on medicines to ensure transparency in the sector. It is set out to discourage perverse practices such as bonusing and discounting. Practices such as this often led to the use of "high-cost" medicine inappropriately. This law also ensures that only a dispensing fee is added to the SEP and no other additional levies or discounts can be applied [144]. Thus the selection of medicines for medicine formularies is largely based on price and will often include the lowest cost generics. High cost medicines however are evaluated according to their cost-effectiveness together with their clinical efficacy and effectiveness [138]. Prescribed minimum benefits (PMB) ensure that all medical scheme beneficiaries have access to a minimum package of care, which are comparable to public healthcare treatment. According to the Medical Schemes Act (131 of 1998), this coverage includes the diagnosis, medical management and medications listed on the chronic disease list (CDL). Treatment algorithms for each CDL condition have also been set up by the CMS. The PMB formulary allows patients to access medications regardless of the remaining funds on the medical scheme or whether or not a medical savings account exists. The PMB formulary is used in conjunction with the medical scheme formulary as the PMB formulary will most often only specify a class of medicine to be used thereby lacking the specificity of the particular medication to prescribe [138].

Under the PMB, medical schemes can use certain measures (Table 1.9) to help manage their benefits and control their costs but at the same time a PMB level of care must be maintained for all patients [138].

Table 1.9 Measures that enable medical schemes to manage benefits and control costs under PMB [138]

Designating service providers for PMB services.
Employing a formulary and associated management tools such as a pre-authorisation (i.e. patients must fulfill certain requirements as laid down by the medical scheme prior to authorisation for funding being issued) and protocols.
Establishing risk-sharing arrangements with different types of providers.
Contracting with specified hospitals or hospital groups to provide services.

1.5.7.3 Healthcare financing in South Africa

The current healthcare system is financed by the general population and follows a progressive financing mechanism. This means that all South Africans contribute to healthcare financing in some way. The proportion to which different sectors of the population contribute to this system is based on the household income. The norm is that the higher the household income, the greater the contribution made to the healthcare system [145].

Research done in this area has displayed that the richest 20% of the population spend 18% of their resources on healthcare in comparison to the 5% spend by the poorest 20% (Figure 1.17) [4]. The healthcare financing in South Africa is funded through the general taxation revenue, of which around 12% was allocated to healthcare by the South African National Treasury for 2007. Private medical scheme contributions and out-of-pocket (OOP) payments also fund the sector. The OOP payments are however regressive but the overall financing remains progressive. This research also captured medical scheme contributions as the major driver for this progressive financing mechanism (Figure 1.17) [4].

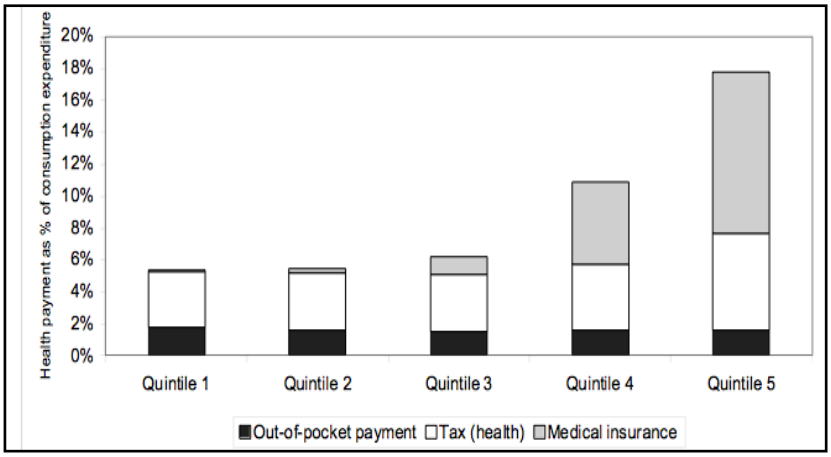


Figure 1.17 The total healthcare financing distribution for South Africa [4] **–** Quintile 1 represents the poorest while quintile 5 represents the richest.

The same research also found that the benefits received from using the healthcare system in South Africa favoured the population that contributed more towards the financing. The poor therefore receive less benefit but require the healthcare benefits the most (Figure 1.18) [4]. The majority of the population (around 55 million people) most likely found in the first two quintiles, depend on the public sector for healthcare. This also places pressure on service delivery and facilities thereby contributing to the lower benefits received (Figure 1.18) [131].

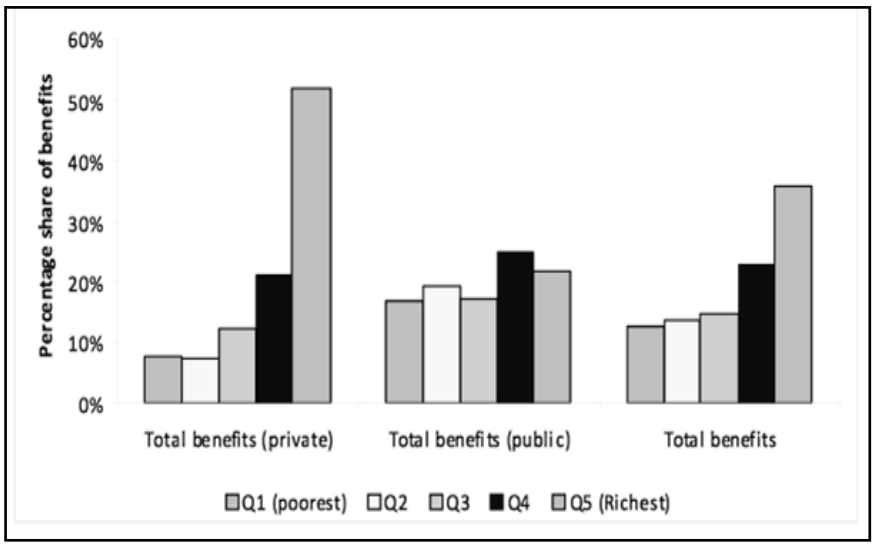


Figure 1.18 The benefit distribution received based on the contributions toward healthcare financing in South Africa [4] – Patients that receive the highest benefits, irrespective of sector, favour those who contribute the most (quintile 5).

1.5.7.4 Healthcare expenditure between the sectors in South Africa

The public healthcare sector utilises approximately 11% of the national budget each year however in research conducted it was found that the healthcare sector of the budget has been declining from 2000/2001 to 2007/2008 and is far below the 15% as set out by the Abuja declaration [145, 146]. These taxation revenue funds are allocated to the 9 provinces but the way in which resources are distributed to the provinces and service delivery carried out by the provinces varies [145].

Total expenditure on healthcare for 2011/2012 was R258.4-billion (8.6% of GDP), but the expenditure is split equally between the National Department of Health and the private sector however; the private sector only services approximately 16% of the population [4, 130]. The percentage of GDP has increased since 2005 whereby it was only 7.7% and had decreased

from a level around 8% in the late 1990s/early 2000s [147]. Therefore government spending is only around 3.5% of GDP and 2007 expenditure figures indicate that approximately 41% of all healthcare expenditure comes from the government. The remaining 59% is consequently private funding [148].

This means that the per capita spending is far greater in the private sector and in fact has remained this way since 1996. The gap per capita spending between the public and private sectors however has increased over the subsequent years. For example the per capita spending in 1996 was triple in the private sector than the public sector and by 2004 that gap had increased to more than seven times [4]. The total healthcare expenditure per capita has once again decreased between 2011 and 2014 from $ 686.94 to $ 570.21 as reported by the World Bank. Interestingly the out-of-pocket expenses have decreased from 7% to 6.5% over the same period. The reason for this appears to be unclear but does relate to an increased expenditure on public healthcare (48% vs. 48.24%) [149-151]. This raises concerns as to whether or not medical schemes and their beneficiaries receive value for money and whether or not these two healthcare sectors provide equitable treatments for the same medical conditions.

From the literature review it can be seen that the colorectal cancer cost evaluation literature for low-middle income countries and in particular South Africa is not comprehensive and many studies available from LMICs are outcome costing studies. This makes it difficult to quantify the actual costs associated with colorectal cancer in LMICs or South Africa. In addition for the outcome analysis and costing models, such as decision analysis, to be used, comprehensive cost evaluation needs to take place [152].

Therefore, this research aims to calculate how much the actual (observed) cost of colorectal cancer is in South Africa, in comparison to reported figures but also to calculate and compare the costs for each healthcare sector in South Africa for colorectal cancer treatment.

2. CHATPTER TWO – METHODOLOGY

2.1 Assumptions

2.1.1 Patient classification for advanced CRC disease

2.1.1.1 Public healthcare sector

Patients were only classified as advanced CRC if they were initially diagnosed with metastasis or the disease progressed to an advanced CRC state at some point as noted in the patient records. If no indication of metastasis occurred, patients were classified as early CRC from the records. These classifications were based on the staging system mentioned in section 1.4.7.1. Certain instances, treatment plans revealed that metastasis might well have occurred however, this can't be confirmed but is noted in the analysis and results.

2.1.1.2 Private healthcare sector

Similarly to the public sector and using the staging system in section 1.4.7.1, advanced CRC disease was noted if patients were initially diagnosed with metastasis or the disease progressed to an advanced CRC state at some point. However, the treatment pathways were used to finalise the advanced CRC status due to the discrepancy between data sets A1 (initial claims data received from the medical scheme) and A3 (demographical data for all memebers included in dataset A1). Based on the treatment pathways patients were reclassified as advanced CRC if biological agent was used in their 1st or 2nd line treatment or more than two lines of therapy followed by a biological agent.

2.1.2 Dosages

Information such as dosages are not recorded in claims data thereby the data for the number of vials or tablets and their strength are used to calculate the final dosages. The claims data for these medicines claimed were assumed to be the dosages prescribed for and used by the patients.

2.1.3 Treatment lines for private sector patient cohort

A change in treatment line was considered to have occurred when a change in treatment occurred between oxaliplatin and irinotecan or if a biological agent was included or changed to another biological agent. Patients were considered to have remained on the same treatment line if an agent was dropped for a certain number of cycles, if 5-FU was changed to capecitabine or vice versa and lastly if an oxaliplatin/irinotecan-containing regimen was changed to 5-FU/capecitabine monotherapy.

2.2 Overview of Methodology

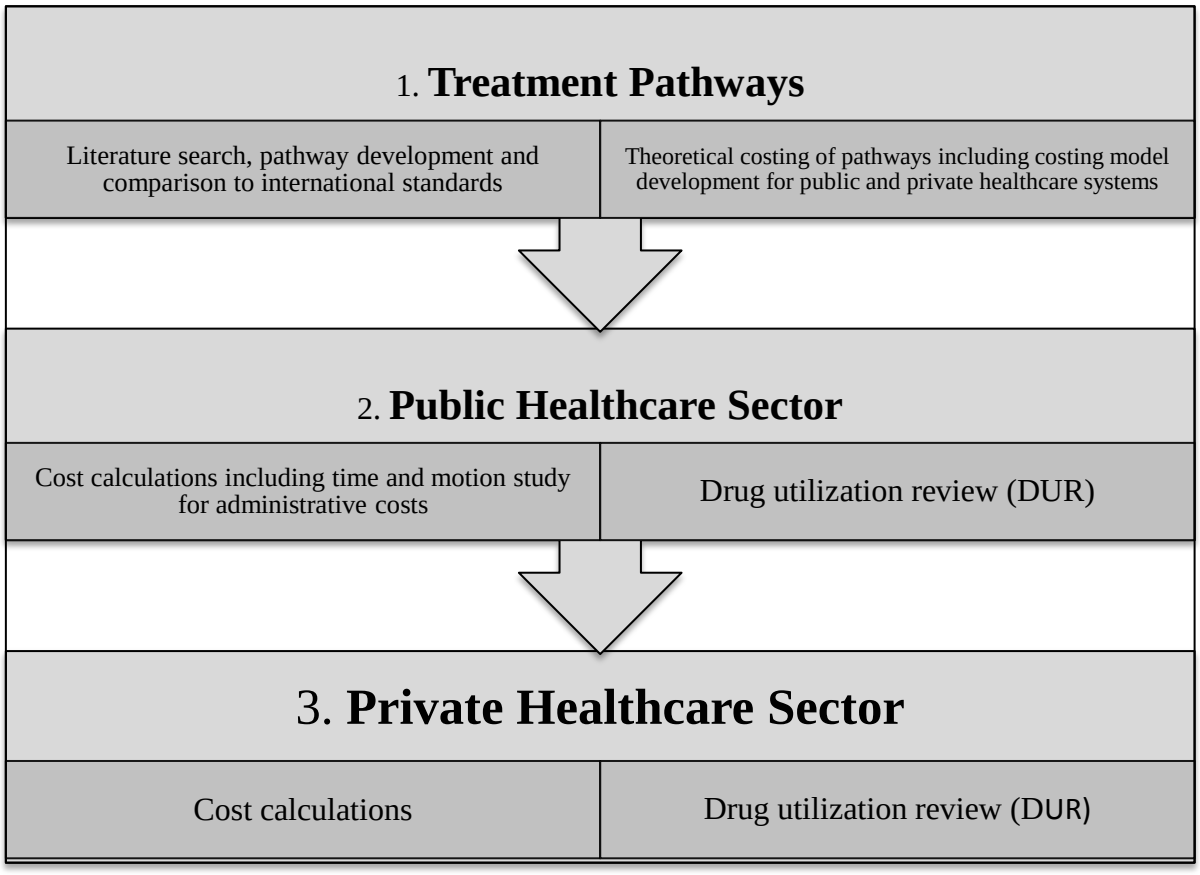


Figure 2.1 Overview of the methodology used in the study including all the constituents of each section

2.3 Treatment pathways

2.3.1 Literature search

2.3.1.1 Treatment reviews and clinical trial identification

In order to construct the clinical pathways that encompassed all current available medicines globally, a literature search for treatment reviews was conducted on PubMed (http://www.ncbi.nlm.nih.gov/pubmed) and SCOPUS (http://0-www.scopus.com.innopac.wits.ac.za). The search terms were broad search terms and included what is known as personalised medicine. Personalised medicine referred to all the newer biological treatments available to patients globally. The search terms included "colorectal cancer", "treatment review", "personalised treatment". Not only did these articles gave a basis of which medicines where currently available but also at what stage of treatment they should be used for i.e. early or late.

Articles with titles containing the search terms were selected and the exclusion criteria was applied. Articles were included if all approved colorectal cancer chemotherapry treatment was discussed. Articles were excluded if specific treatments were considered or subsequent analysis of specific regimens were conducted. Articles that were also excluded were those that considered cost analysis and model development (as the developed pathways were to reflect the flow of treatment and were not based on cost or cost outcomes analysis), genetics, monotherapy/specific regimen reviews, clinical effectiveness/efficacy (clinical trials were used subsequent to identifying the medicines), diagnostic factors/predictor. In addition to this any articles that included interventions other than chemotherapy or studied only various routes of administration, or were published before the year 2000 were excluded.

From the CRC chemotherapy identified in the included papers (based on selection criteria discussed above), the relevant clinical trials and references were identified. Clinical trials were excluded if they were exclusively done in only one population and not globally, published before 2000, for the treatment of liver resection, observational studies, pooled analysis or meta-analysis conducted prior to 2000, published guidelines or recommendations (these were used in the comparisons), alternate formulations of the same chemotherapy medicines were compared or if it was simply a review of chemotherapy treatment. Clinical trials based on treatment targeted specifically to the patient's BRAF status were also

excluded, as current treatment is not available based on this unlike the RAS status. Clinical trials that discussed treatment other than chemotherapy (radiation or surgery) were excluded as this study looked at chemotherapy.

The published clinical trials were included if the studies were Phase 3 randomised controlled trials, included only one monoclonal antibody or similar targeted therapy as treatment, only included chemotherapy (monotherapy or a regimen) and was a completed published article.

These results of this published literature, was verified using UpToDate® (http://0-www.uptodate.com.innopac.wits.ac.za/contents/search). If the relevant literature was included in UpToDate® and cited in literature, the results were used to guide the development of the treatment pathways.

2.3.1.2 Clinical trials that were identified

The relevant published clinical trials were retrieved, using the exact publication title as cited in the reviews, through PubMed (http://www.ncbi.nlm.nih.gov/pubmed) or SCOPUS (http://0-www.scopus.com.innopac.wits.ac.za). The results of these clinical trials were then used to construct the pathways, as these are the evidence-base (i.e. published clinical outcomes) which has contributed to the use of these medicines in clinical practice.

2.3.2 Treatment pathway development

The clinical treatment pathways were then developed, with the help of a medical oncologist, based on clinical trial data. The medicines included in the treatment pathways for colorectal cancer were compared to the available medicines in both healthcare sectors of South Africa, so as to ensure the pathways would be relevant to the South African setting. Medicines for the public healthcare sector were found in the standard treatment guidelines (STG) and essential medicines lists (EML) where the private healthcare sector uses the South African Medicine Price Registry (2014) and South African Oncology Consortium (SAOC) and Independent Clinical Oncology Network (ICON) guidelines [127, 153-155]. Medicines approved on Section 21 of Act 101 of 1965 were also included (Figure 2.2).

The pathways were validated against the key clinical trial data for the relevant treatment regimens. The pathways were also compared against international guidelines such as American Cancer Society (ACS – United States of America), National Comprehensive Cancer Network (NCCN – United States of America) and National Cancer Institute (NCI – United States of America) as well as National Institute for Health and Care Excellence (NICE – United Kingdom) and European Society for Medical Oncology (ESMO – Switzerland based for Europe) [25, 26, 156-162].

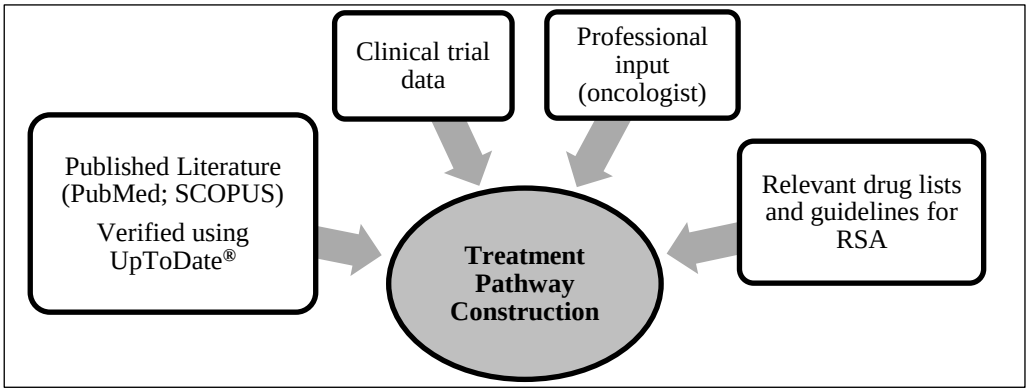


Figure 2.2 The sources consulted and used in the construction of the treatment pathways for South Africa

2.3.3 Cost analysis of the treatment pathways

The study was conducted between 2014 and 2016 in order to calculate the costs based on the developed treatment pathways for both the public and private healthcare sectors for 2014. The dataset for the costs obtained were for the year 2014.

2.3.3.1 Cost data source

2.3.3.1.1 Public Healthcare sector

All medicine costs, including chemotherapy and supportive care, for the public healthcare sector were obtained from the essential medicines list tariff document for February 2014 [154]. Administrative costs were obtained via a time and motion study performed at the oncology unit of CMJAH – unit 495 (section 2.3.4.4.1).

2.3.3.1.2 Private healthcare sector

In the private sector, all medicine costs were obtained from the single exit price (SEP) tariff document for August 2014. It was found on the South African Medicine Price (SEP) Registry website [153]. Administrative costs for this sector were based on the 2015 National Reference Price List for Health Services (NRPL-HS) tariff guidelines for medical schemes. The NRPL-HS is published by the Council for Medical Schemes in order to reimburse service providers [163]. There were two sets of codes depending on whether or not facilities are accredited or not. Non-accredited costs were excluded in this study so as to try and simplify the already complex costs that will be charged by approved service providers. The non-accredited costs pertain to service providers who are not approved i.e. private.

2.3.4 Costing model development

The costing model for both healthcare sectors was developed in Microsoft Excel for Mac 2011 and was based on the treatment pathways that were developed. Each pathway comprised 6 spreadsheets. The spreadsheets reflected different components required to calculate the total costs involved in chemotherapy treatment. Figure 2.3 shows an example of the various components required by the model. The number of columns will however, vary depending on how many origins/stages are included as well as the regimens used in treatment of each.

Total Costs					
	Stage and/or origin				
	Regimen 1	Regimen 2	Regimen 3	...	Regimen x
Chemotherapy costs					
Administration costs					
Supportive care medicine costs					
Administrative costs					
Total treatment costs per cycle	(Chemotherapy + Administration + Supportive medicine + Admisnitrative)				
Number of cycles					
Treatment costs per X cycles	(Total treatment costs per cycle x Number of cycles)				
Total costs for pathway	(Sum of Treatment costs per X cycles for each regimen)				

Figure 2.3 Total costs included for each regimen in order for the total costs of each pathway to be calculated

Colour coding in the first column is the same for the corresponding cost spreadsheet. From Figure 2.3 it can be seen that the treatment costs per cycle is calculated first in order to calculate the total treatment cost for the selected number of cycles. The total cost for the treatment pathway is a summation of the individual treatment regimens, this is however, more relevant for advanced CRC as seen in the results.

2.3.4.1 Chemotherapy medicine costs

The total chemotherapy medicine costs were calculated based on the number of cycles, the number of administrations per cycle (as a few oral medicines require multiple dosing), as well as the dose per administration (Figure 2.4). The dose per administration was calculated based on doses used in literature and prescribed by the relevant manufacturers (Table 2.1). The average human body surface area of 1,73 m^2 and ideal body weight of 70kg was used to calculated the total dosages [164-166]. A retrospective drug utilisation review was conducted (section 2.4) in order to determine how many vials/ tablets are actually prescribed in clinical practice in order to make dispensing and administration easier. This was incorporated into the costing model to more accurately reflect current clinical practice.

Chemotherapy costs						
Medicine cost per cycle is based on cost per vial (tabs), not on cost per mg.						
	Medicine 1	Medicine 2	Medicine3	...	Medicine x	Rationale / Reference
No. of cycles						Databases or guidelines used
No. of administration per cycle						
Average BSA (m2) or BW (kg)	1,73 or 80	1,73 or 80	1,73 or 80	1,73 or 80	1,73 or 80	
Dose (mg)						
Dose per administration (mg)	(Dose x Average BSA or BW)					
Dose per cycle (mg)	(Dose per admin x No. of admin per cycle)					
No. of vials (tabs) per cycle						
Medicine price / vial (tabs)						
(drug 1, drug 2 ect)						
Medicine costs per cycle	(No. of vials (tabs) per cycle x Drug costs per cycle)					
Total medicine costs (X cycles)	(Total drug costs x No. of cycles)					

Figure 2.4 Chemotherapy medicine cost spreadsheet for the costing model

Table 2.1 Prescribed treatment regimen# doses

5-FU/LV (LV5FU2) every 2 weeks	○ LV *400mg/m^2 over 2hrs ○ 5-FU bolus 400mg/m^2 + IV 2400mg/m^2 over 48hrs (D1 & 2)
FOLFIRI [51] every 2 weeks	○ LV *400mg/m^2 over 2hrs ○ Irinotecan 180mg/m^2 over 2hrs ○ 5-FU bolus 400mg/m^2 + IV 2400mg/m^2 over 48hrs (D1 & 2)
FOLFOX-6 [51] every 2 weeks	○ LV *400mg/m^2 over 2hrs ○ Oxaliplatin 85mg/m^2 over 2hrs ○ 5-FU bolus 400mg/m^2 + IV 2400mg/m^2 over 48hrs (D1 & 2)
Capecitabine every 3 weeks	○ Capecitabine 650-1250mg/m^2 twice daily (D1 – 14) ○ Rest one week
CAPOX every 3 weeks	○ Oxaliplatin 130mg/m^2 over 2hrs ○ Capecitabine 650-1250mg/m^2 twice daily (D1 – 14) ○ Rest one week
PANITUMUMAB [80-83, 167] every 2 weeks	○ 6mg/kg over 60 – 90min
CETUXIMAB [77, 78, 91]	○ 400mg/m^2 over 2hrs (loading dose) ○ 250mg/m^2 over 1hr weekly or 500mg/m^2 over 1 hour every 2 weeks
BEVACIZUMAB [67, 68, 70]	○ **1st line**: 5mg/kg over 90/60/30min (2 weeks) OR 7,5mg/kg (3 weeks) ○ **2nd line**: 10mg/kg over 90/60/30min (2 weeks) OR 15mg/kg (3 weeks)
RAMUCIRUMAB [76] every 2 weeks	○ 8mg/kg over 60-90 minutes
AFLIBERCEPT [73] every 2 weeks	○ 4mg/kg over 1hr
REGORAFENIB [85] Every 4 weeks	○ 160mg once daily for 3 weeks (flat dose) ○ Rest 1 week
Trifluridine/tipiracil [56] Every 4 weeks	○ 35mg/m^2 for 5 days, 2 days rest (total 10 days) i.e.. days 1-5 and 8-12 ○ Rest 14 days
BSC in combination with **'the provision of the necessary services for those living with or affected by cancer to meet their informational, emotional, spiritual, social, or physical needs during their diagnostic, treatment, or follow-up phases encompassing issues of health promotion and prevention, survivorship, palliation, and bereavement.' [168]**	○ **CHEMO**: including Dexamethasone 16 – 20mg + 5HT3 receptor blocker antiemetic + atropine ½ amp (irinotecan only) ○ **CETUXIMAB/PANITUMUMAB**: including Cyclizine 12.5mg iv and Doxycycline/Minocycline 100mg/day ○ **BEVACIZUMAB including cyclizine 12.5mg iv** *** Not only symptomatic relief**

#Doses for patients without renal/hepatic impairments or sub-populations (elderly); * LV is a racemic mixture

2.3.4.2 Administration costs

The administration costs for the public sector were based on baseline costs from [169] and CMJAH special dispensary book for 2015. All costs were adjusted for CPI to reflect 2014 costs (http://www.inflation.eu/inflation-rates/south-africa/historic-inflation/cpi-inflation-south-africa.aspx). The administration costs and admixture costs were calculated according to Figure 2.5.

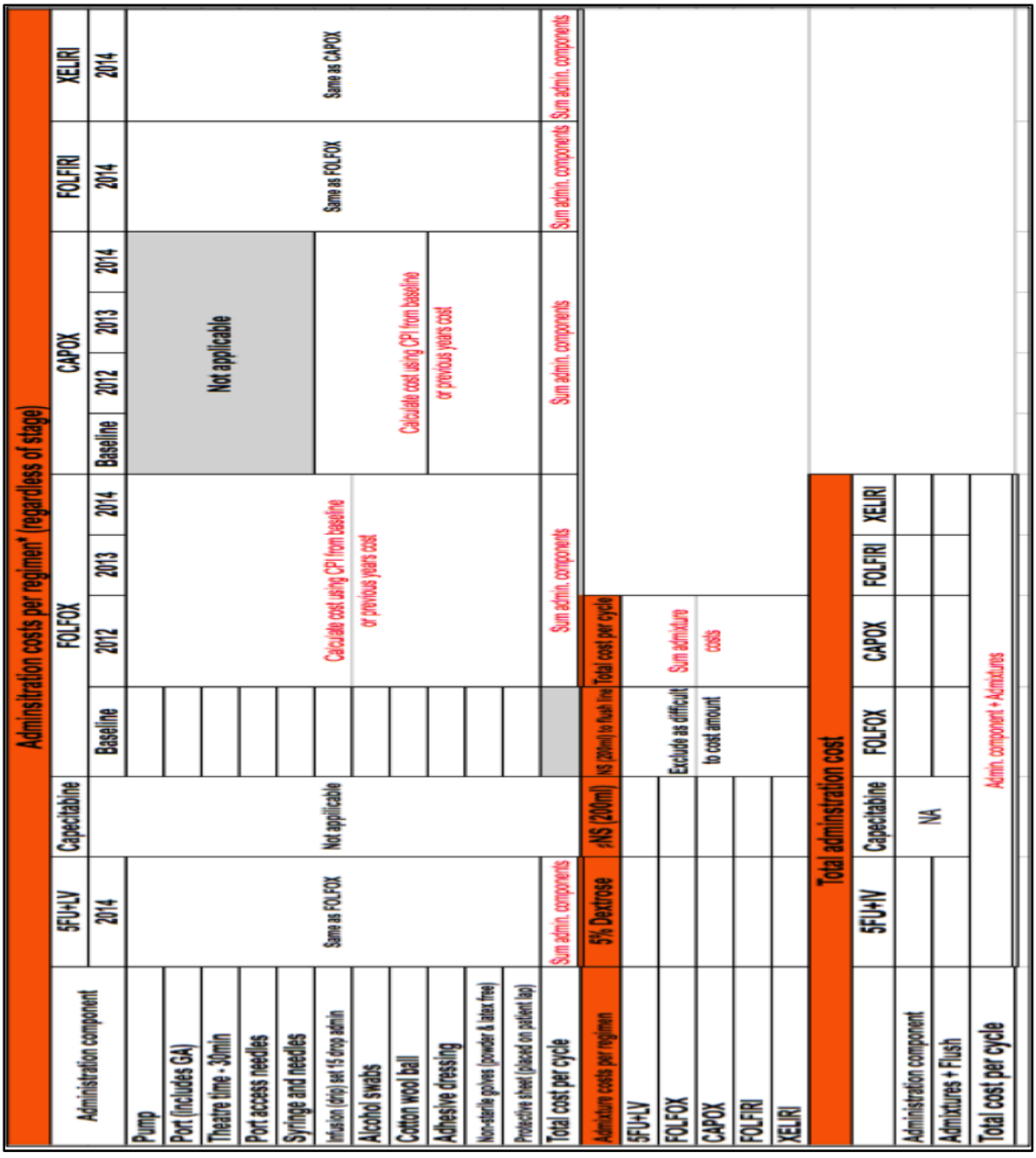


Figure 2.5 Administration cost spreadsheet for the costing model

The administration costs for the public sector only comprised of the admixtures such as 5% dextrose and normal saline as well as ports, pumps, syringes, swabs etc.

2.3.4.3 Supportive care medicines costs

Supportive care medicines were based on relevant evidence found on UpToDate® (http://0-www.uptodate.com.innopac.wits.ac.za/contents/search) for use in cancer chemotherapy. For the public sector however, the information found on UpToDate® was then refined to reflect what is available on the EML. The supportive care medicines corresponded to the emetogenic potential of the regimen as this would influence prescriptions. The model included all the medicines that could be prescribed even for low emetogenic regimens (Figure 2.6).

Furthermore the retrospective drug utilisation review conducted helped to improve the model so as to better reflect medicines that were actually used in clinical practice. Figure 2.6 indicates that the model was developed to include a range of supportive care medicine costs as doses of particular medicines vary, the number of medicines within a class vary as well as the use of a mixture of generic and originators. This variation not only applies to the private sector but does play a role in public healthcare. This therefore influenced the notion of the "basket" approach for supportive care medicines. The "basket" approach allows classes of medicines to be grouped together regardless of the number of medicines within the class and then assigned to each regimen. This means that for every regimen there is a "basket" and the costs range from lowest to highest for that basket. The ranges of costs per basket were due to the number of possibilities of medicine combinations possible. This "basket" approach was however, much more simplified for the public sector as in some instances there is only one medicine available, usually a generic, in the class of medicines but there is a range of doses prescribed. The average "basket" cost for the supportive care medicines was used in order to calculate the final costs for each regimen. For the private sector however, it was the average of the lowest cost SEP "basket", as this is more comparable to the public sector.

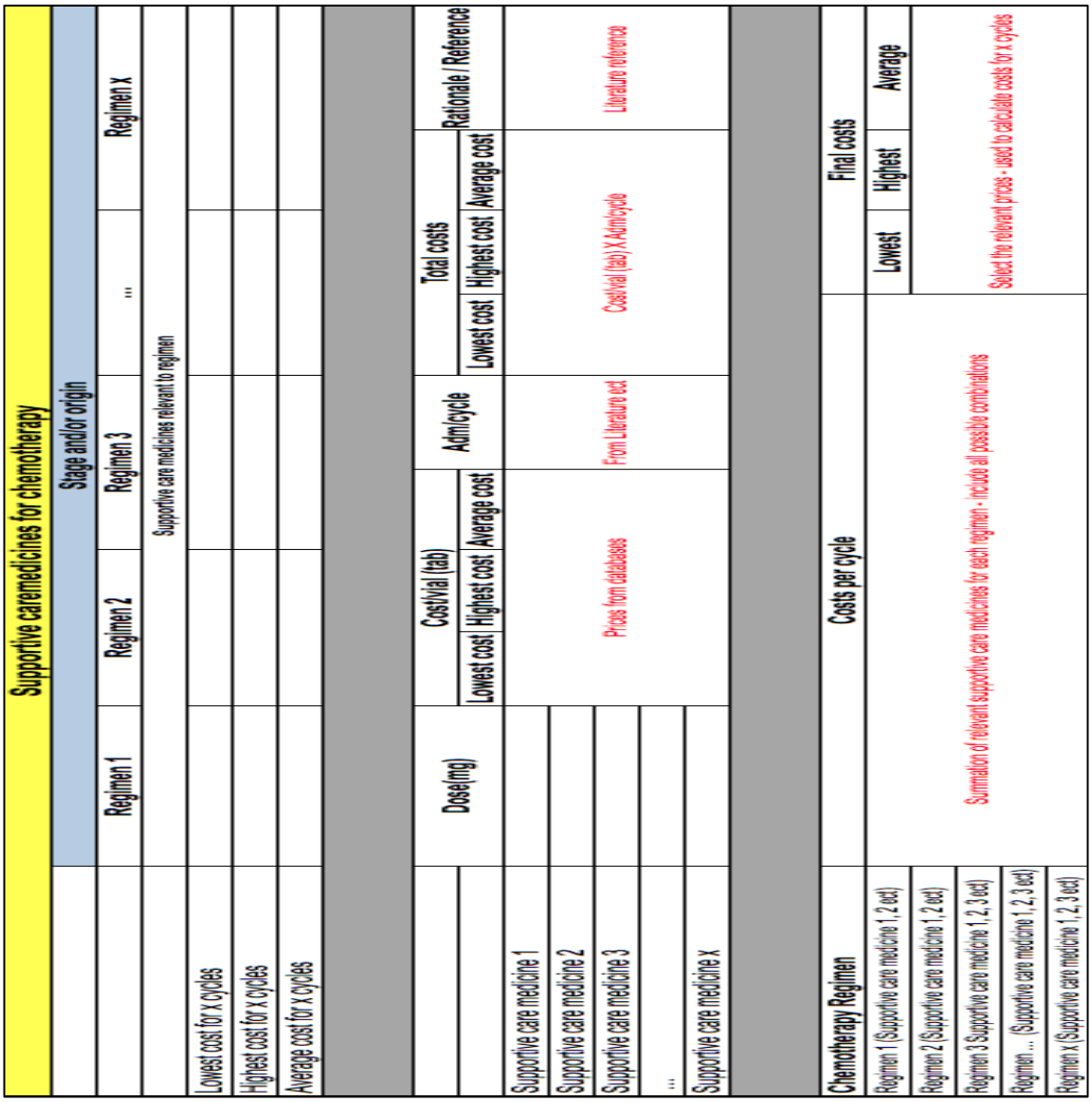


Figure 2.6 Supportive care medicine costs spreadsheet for the costing model

2.3.4.4 Administrative costs

The administrative costs included all the costs associated with patients receiving chemotherapy. For the public sector this cost is unknown and therefore a Time and Motion study was performed and included all the tasks associated with the administrative component to a patient receiving chemotherapy. These included tasks performed by the administrative clerks, nurses, pharmacists and physicians (section 2.3.4.4.1). The costs obtained from the Time and Motion study were compared to the NRPL-HS costs used in the private sector.

Administrative resources and utilisation are consistent within a sector no matter which chemotherapy medicines are prescribed or how much of the chemotherapy medicine is

prescribed. The only difference within a sector is whether or not the regimen consists only of oral medication or intravenous medication. For oral regimens, the administrative costs are fewer as the patient does not have to wait in the facility/clinic in order for an intravenous script to be prepared and dispensed nor wait for a drip to be administered.

2.3.4.4.1 Time and Motion Study

A Time and Motion (T&M) study was conducted in the Adult Medical Oncology Unit (Unit 495) at the CMJAH for the process of patients receiving chemotherapy. The workflow diagram was constructed based on similar studies [170, 171]. Each step in the workflow diagram was a step that needed to be timed in the study using the relevant data collection sheet (Appendix A). The workflow diagram was updated following observations and timing in the outpatient clinic. The study was done in triplicate (i.e. on 3 separate days) and each step consisted of 9 readings per round/day. This resulted in a total of 27 readings per step. Figure 2.7 shows the methodology employed in order to obtain the final time per step and associated cost.

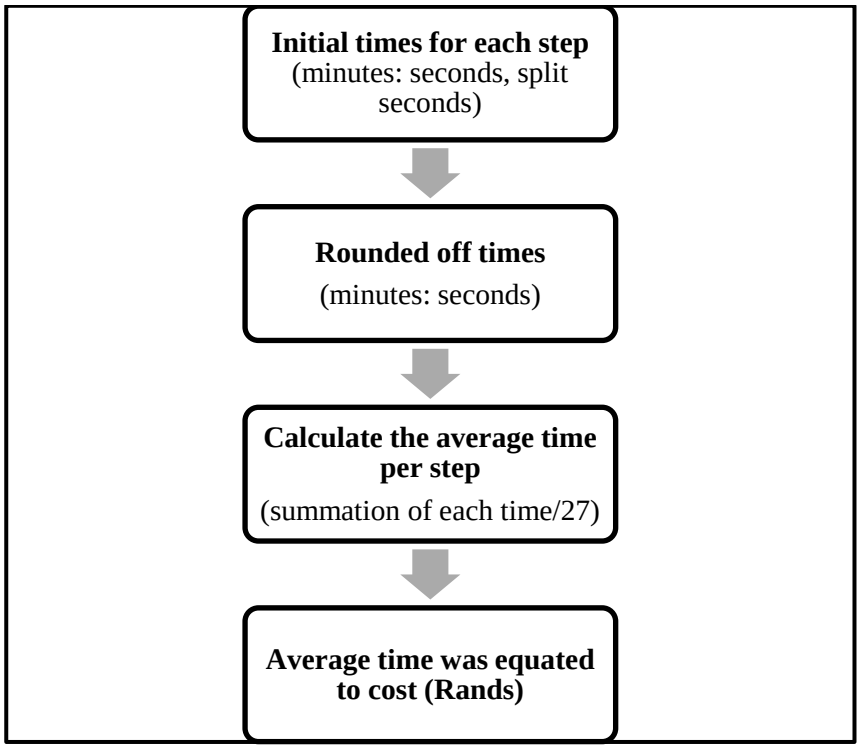


Figure 2.7 Methodology used in order to obtain final times (minutes: seconds), which were equated, to cost (Rands)

The administrative cost (Rands) was calculated using the administrative clerk, nursing pharmacy, and physician salaries per annum for the respective Gauteng Department of Health employee based on the vacancy website (https://www.govpage.co.za/gauteng-health-vacancies.html) [172]. Due to the number of tiers employed by the Government for the respective positions, an average salary per annum was calculated. The reason for this is that any one of the employees, regardless of the tier they are on, can interact with a patient. Following similar costing studies performed elsewhere, an average 2080 hours per annum was used in order to calculate the costs (https://www.opm.gov/policy-data-oversight/pay-leave/pay-administration/fact-sheets/computing-hourly-rates-of-pay-using-the-2087-hour-divisor/). This allowed the average cost per hour to be obtained and the average cost per minute. The average times could then be equated to an average cost (standard deviation). If a final time was less than 30 seconds, it was rounded down to that minute reading and if greater than 30 seconds, rounded up to the next minute reading. All calculations were performed using Microsoft Excel for Mac 2011.

2.3.4.4.2 NRPL-HS

The private sector administrative costs were based on the NRPL-HS prices for 2015, as 2014 costs were unattainable. The administrative costs comprised of a global fee and a facility fee. The global fee pertained to the method of administration of the chemotherapy (oral or I.V) and the facility fee was based on the type of facility whereby patients receive their treatment (Table 2.2).

Table 2.2 NRPL-HS tariffs for the selected medical scheme for 2015

NRPL Code	Description	Medical Scheme Rate
5790	Non Infusional Chemotherapy: Global Fee for the management of and for related services delivered in the treatment of cancer with oral chemotherapy (per cycle), intramuscular, subcutaneous, intrathecal or bolus chemotherapy or oncology specific drug administration per treatment day - for exclusive use by doctors with appropriate oncology training (consultations to be charged separately)	R473.00
5791	Non Infusional Chemotherapy Facility Fee: A facility where oncology medicines are procured or scripted for oral chemotherapy, intramuscular, subcutaneous, intrathecal or bolus chemotherapy or oncology specific drug administration per treatment day. This fee is chargeable by doctors with appropriate oncology training who owns or rents the facility, and by others e.g. hospitals or clinics that provide the services as per the appropriate billing structure	R269.70
5792	Non Infusional Chemotherapy Facility Fee: A facility where oncology medicines are purchased, stored and dispensed during oral chemotherapy (per cycle), intramuscular, subcutaneous, intrathecal or bolus chemotherapy or oncology specific drug administration per treatment day. This fee is chargeable by doctors with appropriate oncology training who owns or rents the facility, and by others e.g. hospitals or clinics that provide the services as per the appropriate billing structure	R337.10
5793	Infusional Chemotherapy: Global fee for the management of and for services delivered during infusional chemotherapy per treatment day - for exclusive use by doctors with appropriate oncology training using recognised chemotherapy facilities(consultations to be charged separately)	R1404.90
5794	Infusional Chemotherapy Facility Fee: A facility where oncology medicines are procured, stored, admixed and administered, and in which appropriately-trained medical, nursing and support staff are in attendance. This fee is chargeable by doctors with appropriate oncology training who owns or rents the facility, and by others e.g. hospitals or clinics that provide the services as per the appropriate billing structure	R991.40
5795	Infusional Chemotherapy Facility Fee: A facility where oncology medicines are purchased, stored, dispensed, admixed and administered and in which appropriately-trained medical, nursing and support staff are in attendance. This fee is chargeable by doctors with appropriate oncology training who owns or rents the facility, and by others e.g. hospitals or clinics that provide the services as per the appropriate billing structure	R1239.30

The administrative costs were then calculated according to the model in Figure 2.8.

Administrative costs						
	Medicine 1	Rationale / Reference	Medicine 2	Rationale / Reference	Medicine 3	Rationale / Reference
Global fee						
Facility fee						
Total cost per visit	(Global fee + Facility fee)					
Number of visits per cycle						
Total administration cost per cycle	(Total cost per vist x Number of visits per cycle)					
Number of cycles per treatment						
Total administration cost	(Total admisnitration cost per cycle x Number of cycles)					

Figure 2.8 Administrative cost spreadsheet for the costing model

2.3.5 Cost comparisons

The theoretical chemotherapy and supportive care medicine costs were calculated using the relevant medicine lists and databases described in section 2.3.3.1.1 and section 2.3.3.1.2 respectively. Administrative fees for the public sector were calculated from the Time and Motion study (section 2.3.4.4.1) and the private sector fees came from the NRPL-HS (section 2.3.4.4.2).

In addition the theoretical number of cycles for each regimen was found in literature and treatment guidelines such as the NCCN. Theoretical dosages were calculated based on the BSA (m^2) or BM (kg) of the average cancer patient [165, 166]. The observed costs however, were calculated based on the data collection from the DUR for both sectors (2.4).

The costing model was then applied in order to calculate the theoretical (based on literature) and observed (based on the retrospective DURs) costs for the treatment of CRC. For each stage of CRC, the theoretical and observed costs for each sector was compared and furthermore the two healthcare sectors were compared to each other, where appropriate.

Similarities and differences were recorded and reasons as why these occurred were formulated.

2.4 Retrospective Drug Utilisation Review (DUR)

2.4.1 Public healthcare sector

2.4.1.1 Patient identification from "new case" books

The "new case" books from the CMJAH adult oncology clinic – unit 495 for the period 2012 – 2014 were used to identify patients who were newly diagnosed with colorectal cancer. Patient information was obtained, which could then be used to extract the relevant patient files from the clinic. Patients diagnosed with the following diagnosis were initially identified so as to cover all possible patients that could have colorectal cancer. The diagnosis included:

- **Malignant tumour cell**
- **Colon**
- **Rectal/rectum**
- **Stomach/gastric**
- **Adenocarcinoma**
- **Anal/anus**
- **Sigmoid**
- **Bowel/small bowel**
- **Caecal/caecum**
- **Abd mass**

Patients that had no diagnosis were also recorded so as to confirm what the diagnosis was. These patients would then be included/excluded depending on the final diagnosis found in the patient file. Any patients removed from the books were excluded and the final diagnosis was based on the diagnosis found on the patient file. Patients with missing information, which would exclude patients from the sample, were also noted. All patient names were only known to the researcher and remained coded for the entire period. Patient files were used to extract data as there is no electronic capturing system in place at the CMJAH for this information

2.4.1.2 Data capture from patient files

Following patient identification, the identified patient files were used to obtain basic information such as diagnosis confirmation, treatment history and current treatment as well as any relevant pathology (Appendix B). Doses and cycle lengths were also recorded. All information that was recorded in patient files was accepted to be correct and was recorded as final. All patient data was completely anonymised and coded. Only the researcher had access to the coding.

2.4.1.3 Data analysis from patient files

2.4.1.3.1 Treatment pathways for patient cohort

Data was first divided into early CRC and advanced CRC disease. This was determined from pathology results and dates of diagnosis of firstly the colorectal cancer and then the metastasis. Patients were placed into the advanced CRC group if initial diagnoses were advanced CRC or metastasis occurred during the observation period. If the patient file had no indication of metastasis then patients were classified as early CRC. Furthermore the results were stratified according to origin within the colorectal region so as to see any differences within treatment or lines of therapy. The treatment that each patient received was used to construct treatment timelines for each patient and treatments were colour coded based on the line of therapy. This was used to identify the most common treatment regimens and the number of treatment lines. Important events or notes found in the files were also included as in some instances these provided explanations for changes in treatment or for patients to be placed on Best Supportive Care (BSC). Certain medicines prescribed were also noted as these indicated if an adverse drug reaction [173] was present or had developed.

2.4.1.3.2 Demographical analysis for patient cohort

Following the advanced CRC classification of the patients, the average, median and range ages were calculated together with gender for each sub-group. Other calculations included the number of patients on each treatment line and the number of patients per site of origin of the CRC.

2.4.1.3.3 Cost analysis for patient cohort

2.4.1.3.3.1 Average costs for patient cohort

Following the entire treatment regimen and treatment line identification, the number of cycles and doses for each patient was determined. The average number of cycles and doses were then calculated for the patient cohort. These values were used in the costing model so that the costs for the patient cohort could be determined. The Time and Motion study, conducted in

section 2.3.4.4.1, was used for the administrative costs and the supportive care medicine costs were calculated in the same manner as the theoretical costs however, the type of medicines included were found in some patient files but also had to be confirmed by the pharmacy and medical staff at the clinic. The administration costs were calculated and used for both the theoretical and observed costs. The costs obtained for the patient cohort was compared to the theoretical costs. The differences and similarities were studied and possible reasons for this are discussed in later sections.

2.4.2 Private healthcare sector

2.4.2.1 Data capture from data sets

A data request was sent to a private medical scheme for all newly diagnosed CRC patients between the 2012 and 2014. Two anonymised claims data sets (A1 and A2) was obtained, the first consisting of all the medical claims and the second all non-medical claims (Table 2.3).

Table 2.3 Medical and Non-medical data set contents for the claims data

Medical data set contents (A1)	**Non-medical data set contents (A2)**
Anonymised Patient identifier	Anonymised Patient identifier
Advanced CRC status	Service date
ATC code	Advanced CRC status
NAPPI code	Quantity
Product name	Amount paid
Strength	MOB enrollment date
Dosage form	Number of months since enrollment
Quantity	Procedure ID
Amount paid	Procedure code description
MOB enrollment date	High level description
Number of months on scheme before enrollment	Practice number
Days from enrollment	Practice type description
Service date	
ATC description	
Chemotherapy	
Date of first surgery	
Days since surgical procedure	
MOB enrollment year	

The patient identifiers from each data set was coded and only known to the researchers for the entire duration of the research. The medical data set included patients enrolled prior to 2012 and after 2014 therefore patients were excluded based on the enrollment year. Furthermore

additional data was required and obtained to complete demographical information (data set A3). This included age and gender of the patients enrolled between 2012 and 2014. Patients with incomplete demographical information were excluded. This gave rise to a modified data set of A1, which was called A4. Patients were classified as advanced CRC if initially the diagnosis was advanced CRC or metastasis occurred and classified as early CRC if the patient had no indication of metastasis. If the patient's metastasis status was unknown, this was confirmed with the additional data obtained from the medical scheme (data set A3). The advanced CRC status of patients was confirmed from data set A3 but the treatment pathways for each patient finalised the advanced CRC status (section 2.4.2.2.1).

The patients that were included from the above ordering (data set A4) under went further ordering from data set A2. Patients that had received chemotherapy but were found to have had no claims in the non-medical data set A2 were excluded and this resulted in a further modification of data set A4 and A2, which was subsequently called A5 and A6. This data set was used to map treatment pathways for each patient. Following this, patients who received chemotherapy medicines not indicated for CRC were excluded (section 2.4.2.2.1). This was the final data set for the project and referred to A7 (Figure 2.9). The final non-medical database (A6) contained all the administrative costs including the global fees, facility fees and consultations. The codes used to extract information from data set A2 and the new high-level description allocated to each code can be seen in Table 2.4. The exact patient numbers can be found in section 3.2.2.1 of the results.

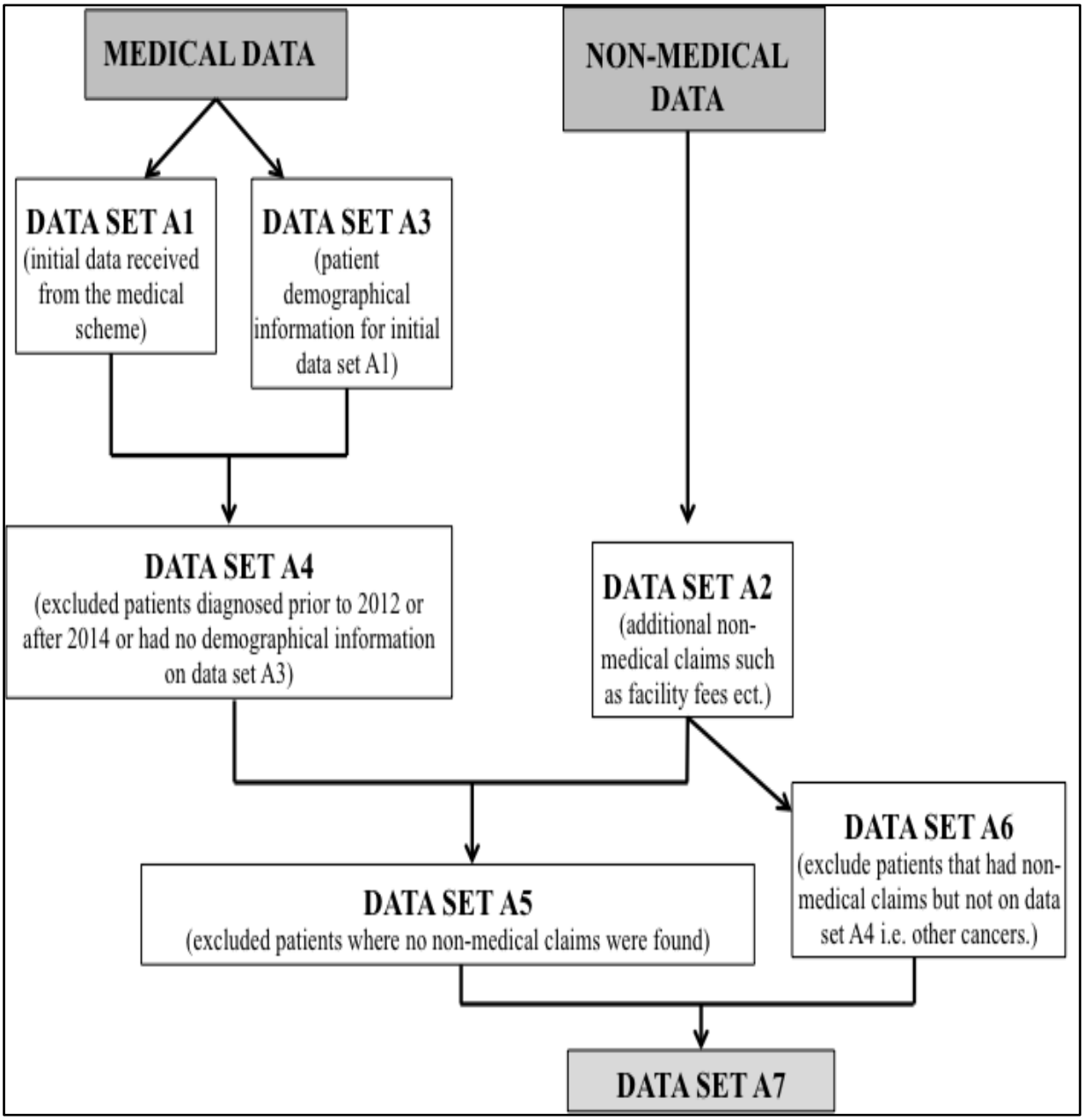


Figure 2.9 Flow diagram indicating process of elimination of patients in order to obtain final patient cohort

Table 2.4 Procedure codes used for chemotherapy administrative in the private sector

PROCEDURE ID	PROCEDURE CODE DESCRIPTION	HIGH LEVEL DESCRIPTION
5790	RA5790 - Non Infusional Chemotherapy: Global Fee for the management of and for related services delivered in the treatment of cancer with oral chemotherapy (per cycle), intramuscular, subcutaneous, intrathecal or bolus chemotherapy or oncology specific drug administration per treatment day -	Global fee-oral
5791	RA5791 - Non Infusional Chemotherapy Facility Fee: oncology medicines procured or scripted for oral chemotherapy, IM, subcutaneous, intrathecal or bolus chemotherapy or oncology specific drug administration per treatment day. Chargeable with appropriate oncology training, and others that provide the services as per the appropriate billing structure.	Facility fee-oral
5792	RA5792 - Non Infusional Chemotherapy Facility Fee: oncology meds purchased, stored and dispensed during oral chemo (per cycle), IM, subcut, intrathecal or bolus chemo or oncology specific drug administration per treatment day. Chargeable with appropriate oncology training, and by others that provide the services as per the appropriate billing structure.	Facility fee-oral
5793	RA5793 - Infusional Chemotherapy: Global fee for the management of and for services delivered during infusional chemotherapy per treatment day - for exclusive use by doctors with appropriate oncology training using recognised chemotherapy facilities(consultations to be charged separately)	Global fee
5794	RA5794 - Infusional Chemotherapy Facility Fee: oncology meds procured, stored, admixed and administered, where appropriately trained medical/nursing and support staff are in attendance. Chargeable by doctors with appropriate oncology training, and by others that provide the services as per the appropriate billing structure.	Facility fee
5795	RA5795 - Infusional Chemotherapy Facility Fee: oncology medicines purchased, stored, dispensed, admixed and administered where appropriately trained medical/nursing and support staff are in attendance. Chargeable by doctors with appropriate oncology training, and by others that provide the services as per the appropriate billing structure.	Facility fee
109	RA0109 - Hospital follow-up visit to patient in ward or nursing facility - Refer to general rule G(a) for post-operative care) (may only be charged once per day) (not to be used with items 0111, 0145, 0146, 0147 or ICU items 1204-1214)	Consultations
129	RA0129 - Prolonged face-to-face attendance to a patient: ADD to either item 0192, item 0175 or item 0169 as appropriate, for each 15-minute period only if service extends 10 minutes or more into the next 15-minute period following on the first 60 minutes	Consultations
190	RA0190 - New and established patient: Consultation/visit of new or established patient of an average duration and/or complexity. Includes counselling with the patient and/or family and co-ordination with other health care providers or liaison with third parties on behalf of the patient (for hospital consultation/visit - refer to item 0173-0175 or item 0109) - not appropriate for pre-anaesthetic assessment followed by the appropriate anaesthetics - refer to new anaesthetic structure	Consultations
191	RA0191 - New and established patient: Consultation/visit of new or established patient of a moderately above average duration and/or complexity. Includes counselling with the patient and/or family and co-ordination with other health care providers or liaison with third parties on behalf of the patient (for hospital consultation/visit - refer to item 0173-0175 or item 0109) - not appropriate for preanaesthetic assessment followed by the appropriate anaesthetics - refer to new anaesthetic structure	Consultations
192	RA0192 - New and established patient: Consultation/visit of new or established patient of long duration and/or high complexity. Includes counselling with the patient and/or family and co-ordination with other health care providers or liaison with third parties on behalf of the patient (for hospital consultation/visit - refer to item 0173-0175 or item 0109) - not appropriate for pre-anaesthetic assessment followed by the appropriate anaesthetics - refer to new anaesthetic structure	Consultations

Therefore similarly to the public sector, the data included in the final data sets for the cohort included demographical information, treatment and non-medical information (Table 2.5).

Table 2.5 Final information included in the medical and non-medical data sets for the patients enrolled between 2012 and 2014

Medical data set contents (A7)	Non-medical data set contents (A6)
Patient cohort code	Patient cohort code
Gender	Service date
Age	Advanced CRC status
Advanced CRC status	Quantity
ATC code	Amount paid
NAPPI code	MOB enrollment date
Product name	Number of months since enrollment
Strength	Procedure ID
Dosage form	Procedure code description
Quantity	High level description
Amount paid	Practice number
MOB enrollment date	Practice type description
Service date	
ATC description	
MOB enrollment year	

2.4.2.2 Data analysis from data sets

2.4.2.2.1 Treatment pathways per patient based on medical data set

Data set A7 was restructured to include an ATC classification column. This allowed each claim to be classified as administration medicines, chemotherapy, diagnostic/radiation medicines, pain management, secondary supportive medicine and supportive medicine. The medicines under each category can be seen in Appendix C.

An automatic two-dimensional pivot table was constructed in Excel for Mac (2011). All fields within the data set were selected for the pivot table and the pivot table was built so as to summarise each patient's treatment in order to establish the treatment pathways per patient (Appendix D). The treatment regimens and subsequent pathways were developed based on the service dates of the claims. Chemotherapy medicines claimed over a window period of 3 months were grouped together due to the difficulties patients may experience during chemotherapy treatment and the difficulties of claim processing. Therefore a break in claims didn't result in an automatic treatment line change. Patients that were early CRC were

changed to advanced CRC if a biological medicine was used in their 1st or 2nd line treatment or more than two lines of therapy followed by a biological medicine.

Within treatment pathway development, treatment lines were colour coded and it was assumed that a change in treatment line occurred when a change occurred between oxaliplatin and irinotecan or a biological medicine was included or changed to another biological medicine. Patients remained on the same treatment line if a medicine was dropped for a certain number of cycles, if 5-FU was changed to capecitabine or vice versa and lastly if an oxaliplatin/irinotecan-containing regimen was changed to 5-FU/capecitabine monotherapy.

2.4.2.2.2 Demographical analysis for medical data set

Following the final classification of advanced CRC status based on the treatments patients received, a new Excel workbook was opened in which the patient cohort code, age, gender, advanced CRC status and date of surgery was copied from data set A7. The duplicates were removed. This meant that every line represented a patient. The date of surgery column was changed to whether or not the patient underwent surgery. Using pivot tables, the number of patients that were early CRC and advanced CRC was calculated. For each sub-group the average, median and range of the age was calculated in addition to the number of patients that underwent surgery.

2.4.2.2.3 Cost analysis for medical data set

A two-dimensional pivot table was constructed from data set A7 in order to establish the observed claimed costs per patient for all the medical claims from enrollment to the end 2015. All fields were selected within the data set and were filtered by the advanced CRC status (Appendix D).

2.4.2.2.3.1 Cost adjustment

Cost adjustment to 2014 was performed in order to allow for comparisons between the two sectors and to the theoretical costs. All costs claimed were adjusted to the last cost claimed in 2014 for each medicine. Where quantities claimed didn't match the claimed SEP, the

quantities were adjusted to reflect the claimed prices. Medicines where no claims were found for 2014 were adjusted by the August 2014 SEP database (http://www.mpr.gov.za/PublishedDocuments.aspx). These prices corresponded to the theoretical cost calculations. Instances where 2014 prices couldn't be obtained for medicines due to registration after or withdrawal prior to August 2014, calculations were based on the last claimed price in 2012, 2013 or the first claimed price in 2015 and the annual increase for the SEP database was applied (Table 2.6). Section 21 medicines and the claims classified as "ethical nonspecific" were adjusted by the annual average Consumer Price Index (CPI) increase (http://www.inflation.eu/inflation-rates/south-africa/historic-inflation/cpi-inflation-south-africa.aspx).

Table 2.6 Annual price SEP increase calculations – The adjustment calculations accounted for the adjustment from the year the price was obtained straight up to 2014 hence 2012 is a more complex calculation as it accounts for 2012 and 2013 adjustment in one calculation where 2013 and 2015 only require adjustment by one year.

Year	SEP annual increase	Calculation
2012	5,8%	**Adjustment per Item**=((2012 Price+(2012 Price*5,8%))+(2012 Price+(2012 Price*5,8%)*5,82%)/Quantity claimed
2013	5,82%	**Adjustment per Item**=(2013 Price+(2013 Price*5,28%))/Quantity claimed
2015	7,5%	**Adjustment per Item**=(2015 Price-(2015 Price*7,5%))/Quantity claimed

If claims were from more than one of the above-mentioned years then, 2013 or 2015 was used and all adjustments were by that year.

2.4.2.2.3.2 Average costs per treatment regimen

Based on the cost adjustment data, the average costs per regimen and the average number of cycles was calculated and compared to the public healthcare sector. Using the adjusted data, a pivot table was constructed for the early CRC and advanced CRC sub-groups, in order to calculate the average costs (Appendix D). The pivot table generated the total cost per ATC classification (medicines were grouped based on the role the medicine played within treatment i.e. whether it was chemotherapy, supportive medicine etc.) as well as the number of times it was claimed. The sum of the number of cycles was calculated from a pivot table generated from the treatment lines and for a particular regimen and then filtered by regimen in order to calculate the total number of cycles (Appendix D) and the average number of cycles (Table 2.7). The average number of cycles was rounded up to a whole number due to the

nature of receiving chemotherapy. Subsequently the average cost per regimen was calculated however this was not specific to the line of therapy (Table 2.7).

Table 2.7 Calculations used to calculate the average costs per medicine and regimen together with the average number of cycles for cohort

Average cost per cycle=Sum of Total adjusted price for 2014 for regimen / Average number of cycles
Average number of cycles=Sum of the number of cycles per regimen for cohort / Number of patients that received that regimen

The average adjusted costs for the administration and supportive medicines were calculated from a pivot table generated similarly to Appendix D. These average cost is based on the total cost claimed divided by the number of claims. This is similar to the basket approach used in the public sector and the basket medicines can be seen in Appendix E. The average costs were multiplied by the number of cycles calculated for the regimens and added to the chemotherapy regimens.

2.4.2.2.4 Cost analysis of non-medical (administrative) data set

Observed claimed costs per patient for all the administrative costs from enrollment to the end 2015 were established. All fields were filtered by the advanced CRC status similarly to the medical data set (Appendix D). The biggest difference within the pivot tables is that the non-medical dataset doesn't include ATC descriptions but rather high level descriptions, namely global fee; global fee-oral; facility fee and facility fee-oral.

2.4.2.2.4.1 Cost adjustment

Cost adjustment was in line with the medical database in that the last claimed cost for 2014 was used. No other sources of data were required for the global and facility fees.

2.4.2.2.4.2 Average costs per treatment regimen

Based on the cost adjustment data, the average administrative costs per regimen were calculated and compared to the public healthcare sector. The administrative costs include the

global fee and facility fee. For simplification, the global and facility fees were averaged for an oral and I.V regimen. The costs per cycle and the total adjusted costs were calculated based on the average number of cycles per regimen calculated in section 2.4.2.2.3.2. Early CRC and advanced CRC filters weren't required as the administrative costs aren't dependent on this.

2.4.2.2.5 Average costs for patient cohort

The total average costs for the patient cohort was calculated according to Table 2.8.

Table 2.8 Calculations for average costs for patient cohort

Total cost for regimen per cycle=chemotherapy regimen cost + administration cost + supportive medicine cost + administrative cost
Total cost for x cycles=Total cost for regimen per cycle x average number of cycles for that regimen

These average costs were compared to the theoretical costs for the relevant regimens.

2.4.2.2.5.1 Average chemotherapy dosages for patient cohort

The average chemotherapy dose for each chemotherapy medicine was calculated based on the average cost per medicine and the cost per vial or tablets for the medicine with the lowest SEP (Figure 2.10). The lowest SEP price was selected to allow for comparison between the public and private healthcare sectors.

Average dosages for cohort					
Chemotherapy medicine	Medicine 1	Medicine 2	Medicine 3	...	Medicine x
Average cost per claim (adjusted data)	Calculated based on patient cohort claims				
Medicine price/vial	Theoretical calculations (lowest SEP)				
No. of vials	Average cost per claim/medicine price/vial(tabs)				
Vial size/tab	SEP database for the respective vial/tabs				
Dose per cycle (mg)	Vial size/tabs x number of vials				

Figure 2.10 Average dose calculations for the cohort

2.4.2.2.5.2 Average number of cycles per regimen for patient cohort

For each chemotherapeutic regimen noted in the sub-groups, the average number of cycles was calculated by firstly tallying the total number of cycles for that regimen and the number of patients receiving that regimen. The average was therefore total number of cycles divided by number of patients. The cycles were rounded off to the nearest whole number if need be.

2.5 Sensitivity Analysis

A one-way sensitivity analysis was carried out to assess the impact that changes of the input variables would have on the costs of receiving chemotherapy per regimen in the costing model based on the theoretical costs. The input variables included chemotherapy cost, administrative costs, supportive care medicine costs, administration costs and the number of cycles and were all varied separately to test the sensitivity. This analysis was used so as to determine which variables the costing model is most sensitive to. These variables were changed by (+/-) 50% and (+/-) 20% (Figure 2.11). Changes greater than R1000 in the total cost were noted and it was concluded that these were the variables most likely to affect the model.

Sensitivity analysis					
Cost variables	Regimen				
	Baseline	Half (-50%)	-20%	20%	Double (+50%)
Chemotherapy costs					
Administration costs					
Supportive care medicine costs					
Administrative costs					
Total cost per cycle					
Number of cycles					
Total cost for x cycles					

Figure 2.11 Sensitivity analysis table used to test the robustness of the costing model

2.6 Ethical Approval

This study was approved by the University of the Witwatersrand Human Research Ethics Committee (Medical). Clearance Certificate number: MP140809 (Appendix R).

2.7 Acknowledgement of Research Support

The University of the Witwatersrand, Faculty of Health Sciences Research Grant for funding the study however had no involvement in the study design, collection, analysis or interpretation of the data and writing of the dissertation.

3. CHAPTER THREE - RESULTS

3.1 Treatment pathways

3.1.1 Literature search

The results of the literature search using PubMed can be seen in Figure 3.1.

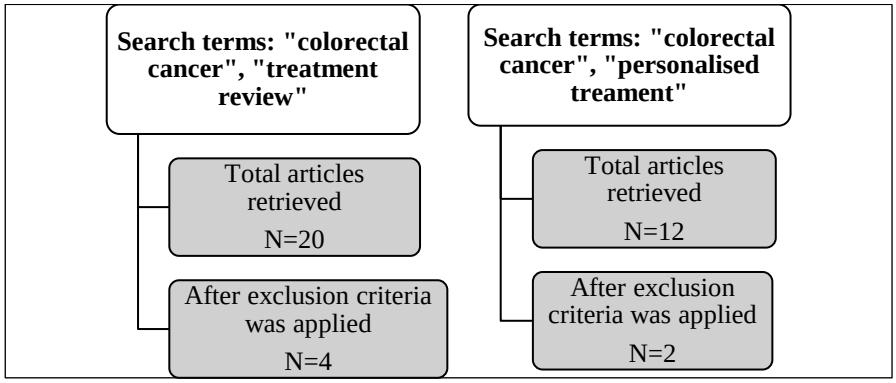


Figure 3.1 Results for the literature search on PubMed

The literature search on SCOPUS produced fewer new results, as three of the four articles were already acquired on PubMed. The search using the second search term produced no new results at all (Figure 3.2). From both literature searches, seven articles where used to identify the relevant medicines and clinical trials. Of the seven, two articles addressed the treatment of geriatric patients. The articles used can be found in Appendix F.

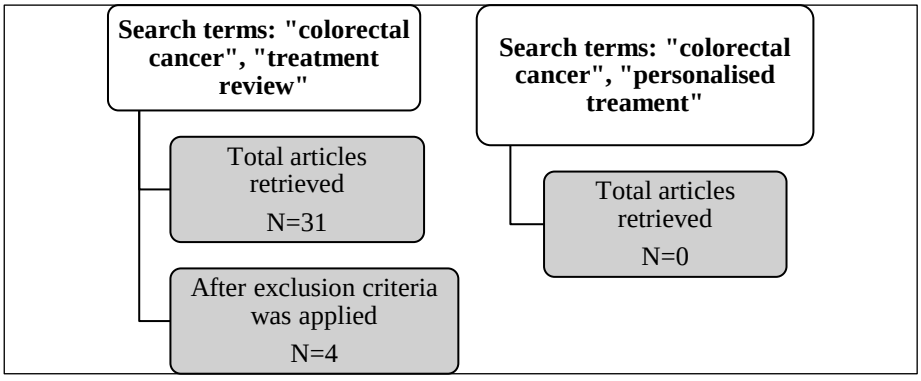


Figure 3.2 Results for the literature search on SCOPUS

3.1.1.1 Clinical Trials identified from literature search

The review literature identified the pivotal clinical trials, which provide evidence that a treatment is adequate enough to be used in clinical practice. The results of this search through the review articles are shown in Table 3.1.

Table 3.1 Relevant clinical trials found from a search of review articles

Review article	Relevant phase 3 clinical trial authors and date	Treatment line	Regimen	Number of citations in review articles	UpToDate® (Yes or No)	Results
Golfinopoulos *et al.*, 2006* [174] Tol and Punt, 2010 [175] Edwards *et al.*, 2012 [176] Heinemann *et al.*, 2013 [177] Kordatou *et al.*, 2014* [178] Bekaii-Saab and Wu, 2014 [179] Fakih, 2015 [180]	Douillard *et al.*, 2000 [181]	First	FU + LV/ FOLFIRI	2	Yes	Inc. RR, PFS, OS and longer QoL
	Saltz *et al.*, 2000 [49]	First	FU + LV/ FOLFIRI	2	Yes	Inc. PFS and OS
	De Gramont *et al.*, 2000** [48]	First	FU + LV/ FOLFOX	4	Yes	Inc. PFS and maintenance of QoL
	Hurwitz *et al.*, 2004** [67]	First	IFL/ IFL + BEV	6	Yes	OS benefit
	Cunningham *et al.*, 2004** [78]	Irinotecan refractory	Irinotecan + CET/ CET monotherapy	3	Yes	Clinical benefit of adding CET to Irinotecan even in irinotecan refractory cancer
	Goldberg *et al.*, 2004 [182]	First	IFL/ FOLFOX/ IROX	3	Yes	Inc. PFS, RR and median OS
	Tournigand *et al.*, 2004 [51]	First or Second depending on sequence	FOLFIRI → FOLFOX6/ FOLFOX6 → FOLFIRI	1	Yes	Similar OS, RR and PFS
	Colucci *et al.*, 2005 [183]	First	FOLFIRI/ FOLFOX4	1	Yes	No difference in OS, ORR or TPP
	Van Cutsem *et al.*, 2007 [92]	Chemo. refractory	BSC alone/ BSC + PANIT	3	Yes	Significant improvement in PFS
	Giantonio *et al.*, 2007 [69]	Fluoropyrimidine and irinotecan resistant	FOLFOX alone/ FOLFOX + BEV/ BEV alone	4	Yes	Combination Improves survival duration (Inc. PFS and ORR)
	Jonker *et al.*, 2007 [184]	Chemot. refractory	BSC alone/ BSC + CET	4	Yes	CET improves OS, PFS and QoL measures
	Saltz *et al.*, 2008 [68]	First	FOLFOX or CAPOX/ FOLFOX or CAPOX + BEV	5	Yes	Improved PFS but no OS benefit
	Sobrero *et al.*, 2008 [185]	Second (following fluoropyrimidine and oxaliplatin failure)	Irinotecan alone/ Irinotecan + CET	3	Yes	Improved PFS and RR, better QOL
	Van Cutsem *et al.*, 2008 [80]	Chemo. refractory	BSC/ BSC + PANIT		Yes	Significant improvement in PFS
	Karapetis *et al.*, 2008 [91]		BSC/ BSC + CET	3	Yes	Wild-type KRAS is required for efficacy
	Amado *et al.*, 2008 [167]		BSC/ PANIT	3	Yes	Wild-type KRAS is required for efficacy

	Hurwitz *et al.*, 2009 [186]	First	IFL/ IFL + BEV	1		Clinical benefit regardless of KRAS status
	Van Cutsem *et al.*, 2009 [187]	First	FOLFIRI alone/ FOLFIRI + CET	4	Yes	Inc. PFS Beneficial for wild-type KRAS. OS benefit on subsequent analysis
	Bokemeyer *et al.*, 2009 [188]	First	FOLFOX alone/ FOLFOX + CET	2	Yes	Inc. ORR, PFS for wild-type KRAS
	Kim *et al.*, 2009 [189]	Second (5-FU refractory)	FOLFOX4/ Irinotecan	1	Yes	OS is not significantly different, FOLFOX4 has higher RR and longer TPP when started before irinotecan
	Douillard *et al.*, 2010 and 2013 [81, 190]	First	FOLFOX4 alone/ FOLFOX4 + PANIT	4	Yes	Significant improvement in PFS for wild-type KRAS. Subsequent data showed improved PFS as well as OS benefit in RAS WT.
	Peeters *et al.*, 2010 [83]	Second	FOLFIRI alone/ FOLFIRI + PANIT	4	Yes	Improved PFS for wild-type KRAS
	Maughan *et al.*, 2011 [191]	First	FOLFOX or CAPOX/ FOLFOX or CAPOX + CET	3	Yes	Inc. RR, no benefit in PFS or OS for KRAS wild-type
	Van Cutsem *et al.*, 2011 [90]	First	FOLFIRI/ FOLFIRI + CET	3	Yes	Improved survival for wild-type KRAS
	Van Cutsem *et al.*, 2012 [73]	Previously treated with oxaliplatin	FOLFIRI/ FOLFIRI + Aflibercept	2	Yes	Inc. survival benefit
	Tveit *et al.*, 2012 [192]	First	Nordic FLOX/ Nordic FLOX + CET	3	Yes	No, CET did not add any benefit
	Bennouna *et al.*, 2013 [193]	Second	Standard Chemo/ Standard Chemo + BEV	2	Yes	Clinical benefit to continue BEV passed disease progression
	Cunningham *et al.*, 2013 [70]	First line for elderly patients	Capecitabine/ Capecitabine + BEV	2		Inc. PFS
	Grothery *et al.*, 2013 [85]	Second/ Third	BSC/ BSC + Regorafenib	2	Yes	Inc. PFS, OS and disease control
	Heinemann *et al.*, 2014 [194]	First	FOLFIRI + CET/ FOLFIRI + BEV	1	Yes	OS benefit. FOLFIRI + CET are preferred in wild-type KRAS. Subsequent analysis showed further OS improvement in RAS WT patients.

* Treatment review for geriatric patients; ** Also referenced from geriatric paper

3.1.2 Theoretical developed treatment pathways

Based on the definition of a clinical pathway, South Africa does not have well-defined pathways for oncology [126-129] therefore review of the literature and consultations with oncologists at the CMJAH confirmed that once the cancer is advanced CRC, the origin of the cancer i.e. colon or rectum, is irrelevant thus treatment is the same. Stage 2 colorectal cancer was excluded as there is no consensus as to whether or not chemotherapy treatment is necessary. Early-staged colorectal cancer is however, treated with adjuvant chemotherapy. The main difference between colon and rectum is that early-staged rectum cancer will also be treated with radiation. The treatment pathways for early-staged adjuvant CRC can be seen in Figure 3.3 and Figure 3.4.

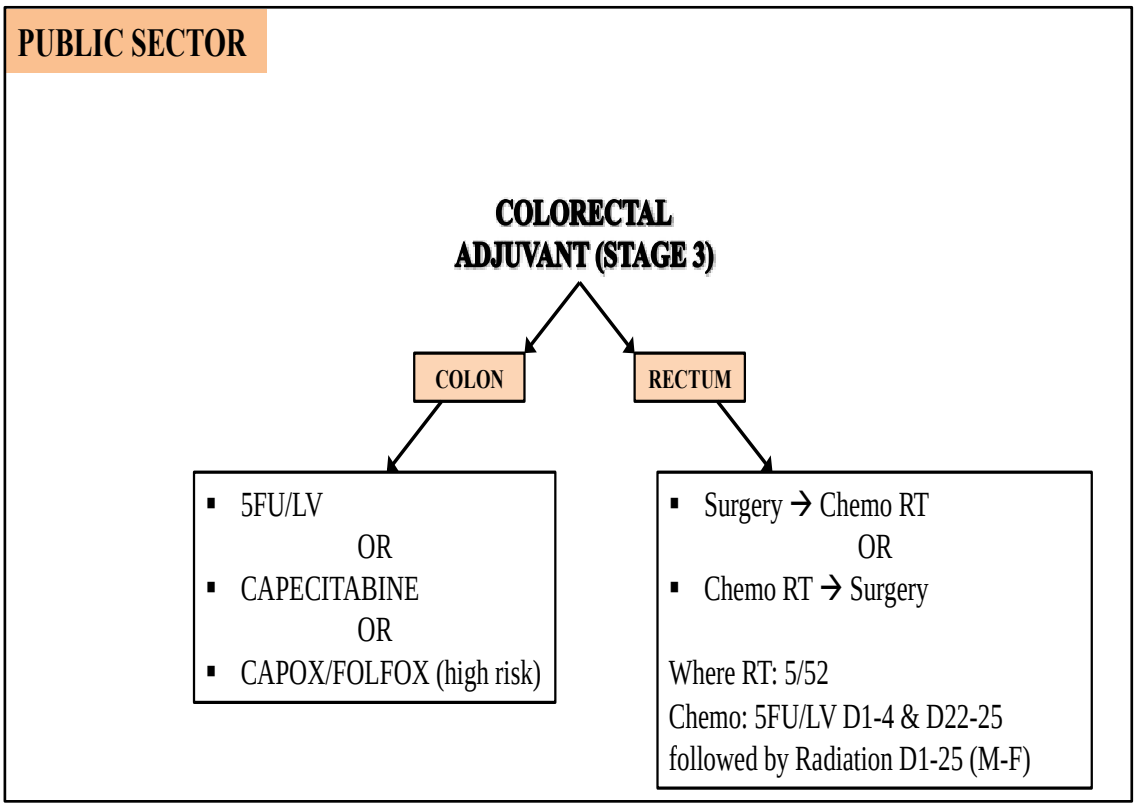


Figure 3.3 Treatment pathway for early adjuvant colorectal cancer in the public healthcare sector for South Africa – 5FU/LV is 5-fluorouracil and folinic acid, CAPOX – capecitabine and oxaliplatin, FOLFOX - 5-fluorouracil, folinic acid and oxaliplatin. RT – radiation therapy, Chemotherapy D1-4: days 1 to 4 and D22-25: days 22 to 25. Radiation D1-25: days 1 to 25, Monday to Friday.

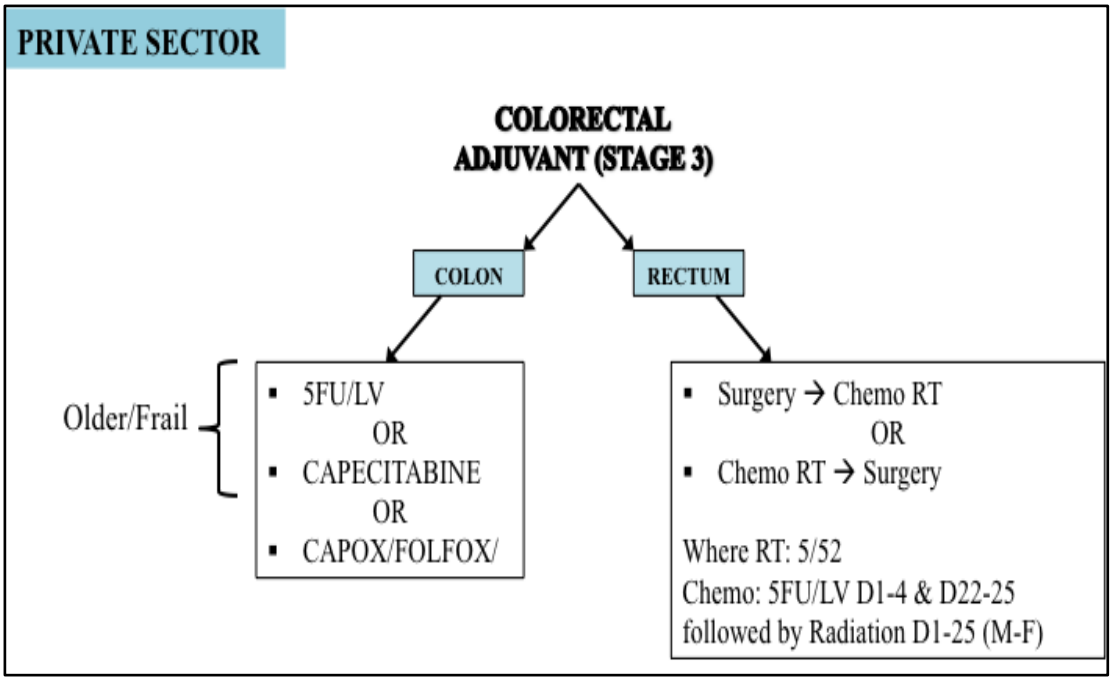


Figure 3.4 Treatment pathway for early adjuvant colorectal cancer in the private healthcare sector for South Africa - 5FU/LV is 5-fluorouracil and folinic acid, CAPOX – capecitabine and oxaliplatin, FOLFOX - 5-fluorouracil, folinic acid and oxaliplatin. RT – radiation therapy, Chemotherapy D1-4: days 1 to 4 and D22-25: days 22 to 25. Radiation D1-25: days 1 to 25, Monday to Friday.

Most notably the differences between the early adjuvant CRC treatment pathways that 5FU/LV and capecitabine are usually reserved for older and frail patients. This is not necessarily the case in the public sector as the CAPOX and FOLFOX regimens are reserved for high risk patients. Figure 3.5 and Figure 3. show the treatment pathways for advanced CRC for each sector respectively.

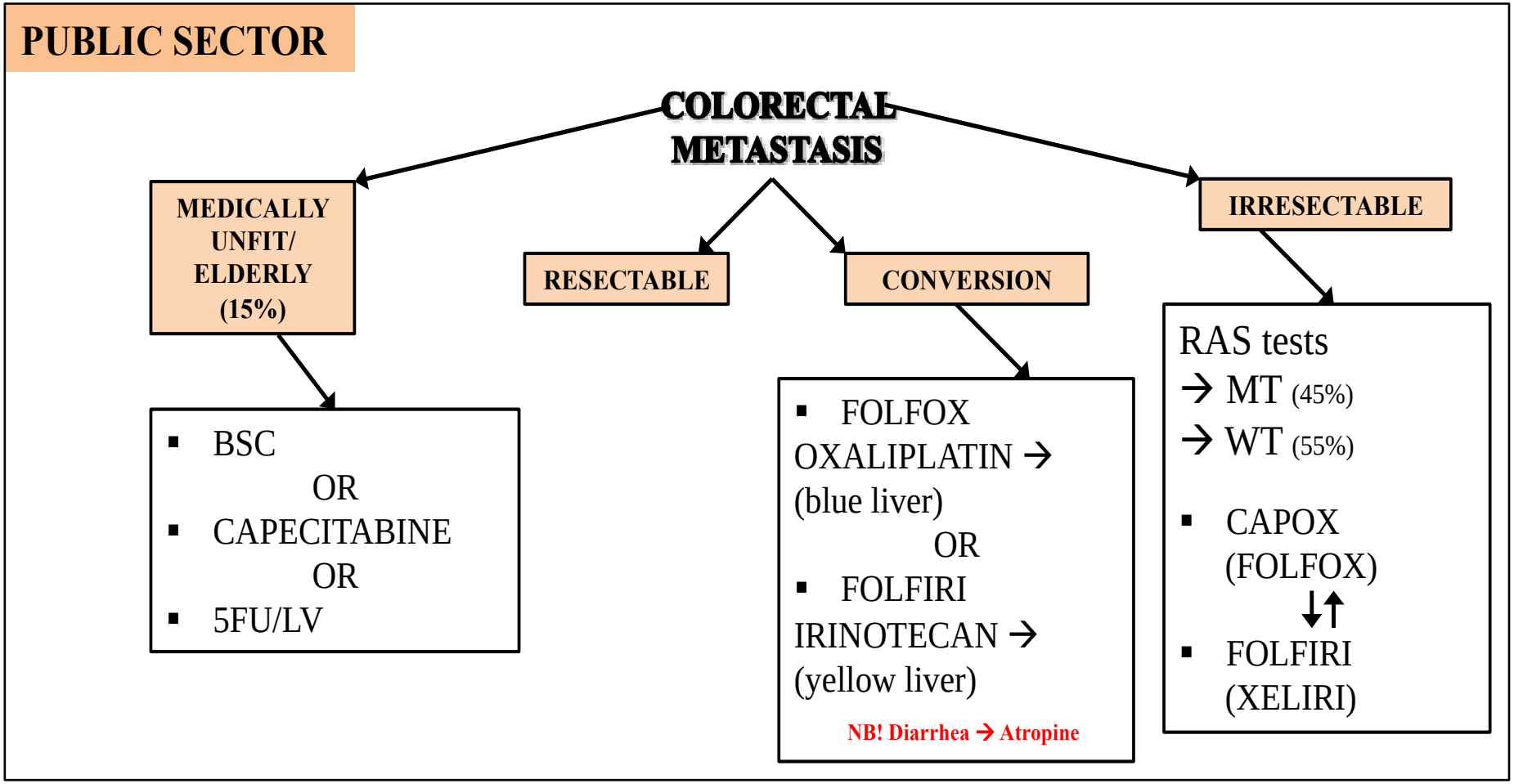


Figure 3.5 Treatment pathway for advanced CRC colorectal cancer in the public healthcare sector for South Africa - 5FU/LV is 5-fluorouracil and folinic acid, CAPOX – capecitabine and oxaliplatin, FOLFOX - 5-fluorouracil, folinic acid and oxaliplatin. XELIRI – capecitabine and irinotecan, FOLFIRI – 5-fluorouracil, folinic acid and irinotecan. RAS tests – MT: Mutant type; RAS, WT: Wildtype RAS.

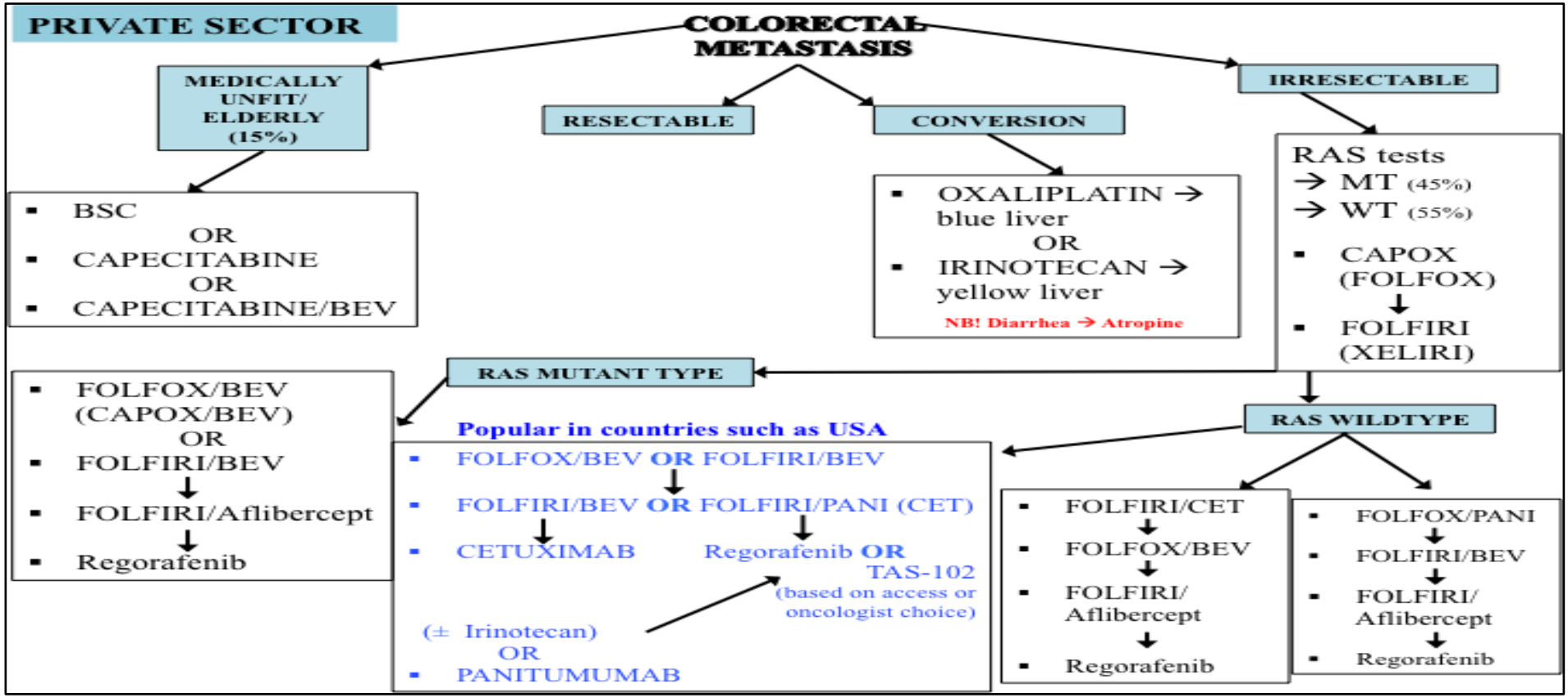


Figure 3.6 Treatment pathway for advanced CRC colorectal cancer in the private healthcare sector for South Africa – medicines such as Panitumumab, Aflibercept, Ramucirumab and Regorafenib were not commercially available in South Africa at the time of this research, therefore, the combinations could only be prescribed under a Section 21 application. **Aflibercept was however available on an Expanded Access Programme (EAP).** Panitumumab has since been approved (2016). 5FU/LV is 5-fluorouracil and folinic acid, CAPOX – capecitabine and oxaliplatin, FOLFOX - 5-fluorouracil, folinic acid and oxaliplatin. XELIRI – capecitabine and irinotecan, FOLFIRI – 5-fluorouracil, folinic acid and irinotecan, Bev – bevacizumab, Pani – panitumumab, CET – cetuximab. *Pathway in blue is used in the USA and EU: – Tipiracil + Trifluridine, Aflibercept and Ramucirumab are new medicines and not available to South African patients. Ramucirumab can be used in combination with FOLFIRI in place of Aflibercept.*

Comparing the developed public and private sector pathways indicates a big difference in the number of medicines available to patients for advanced CRC disease. The developed private sector pathways are comparable to the local South African guidelines however the public sector has fewer medicines available to patients [126, 127]. The most notable difference is the availability of biological agents to patients in the private sector and not the public sector. Although irinotecan is found on the public sector pathways, it has only recently become available in the sector with patients who received irinotecan in this sector previously having to purchase this medicine themselves.

When comparing the private sectors pathways, the availability of medicines is more comparable to international guidelines such as American Cancer Society (ACS – United States of America), National Comprehensive Cancer Network (NCCN – United States of America) and National Cancer Institute (NCI – United States of America) as well as National Institute for Health and Care Excellence (NICE – United Kingdom) and European Society for Medical Oncology (ESMO – Switzerland based for Europe) [25, 26, 156-162]. Patients have a greater access to newer therapies and early-staged patients do have access to regimens such as CAPOX and FOLFOX, which is independent of their risk unlike in the public sector.

Panitumumab is absent when comparing pathways in the United States of America although it has recently been registered in South Africa. Aflibercept was not commercially available to all patients, Section 21 applications provided access to patients on an Expanded Access Program.

Medicines such as ramucirumab and combinational treatment containing trifluridine and tipiracil are newly FDA and EMA approved agents used in advanced CRC although they are not yet registered in South Africa. Ramicurumab is used in combination with FOLFIRI as a 2nd line therapy following failure of treatment with FOLFOX + bevacizumab. Trifluridine and tipiracil (TAS-102) is used for third line treatment of advanced CRC similarly to regorafenib. Although it is not registered in South Africa, it may be obtained with MCC approval via Section 21 of Medicines and Related Substances Act 101 of 1965 via the expanded access program in both the public and private healthcare sectors [195]. At this stage the choice between the two agents appears to be dependent on patient access (funding) and oncologist choice.

3.1.2.1 Supportive care medicines relevant to the treatment regimen

The relevant supportive care medicines which were identified and refined to reflect the availability in each sector are shown in Table 3.2.

Table 3.2 Table of supportive care medicines relevant to the regimen for which they are indicated (http://0-www.uptodate.com.innopac.wits.ac.za/contents/search).

Chemotherapy medicines	*Emetogenic Potential	Supportive care medicines for Public Sector	Supportive care medicines for Private Sector
5-FU (+ LV)	Low	Corticosteriod (CS) + Metoclopramide	Metoclopramide
Capecitabine	Low	Metoclopramide	Metoclopramide
Oxaliplatin	Moderate	$5HT_3$ antagonist + CS +/- Metoclopramide	$5HT_3$ antagonist + CS +/- Aprepitant
Irinotecan	Moderate	$5HT_3$ antagonist + CS +/- Metoclopramide + Atropine	$5HT_3$ antagonist + CS +/- Aprepitant + Atropine
		Not applicable to patients in this sector.	
Bevacizumab	Minimal		Cyclizine
Aflibercept	Low		Cyclizine
Regorafenib	Minimal		N/A
Cetuximab	Minimal		Cyclizine
Panitumumab	Low		Cyclizine
Ramucirumab	Low		Cyclizine
TAS-102 (Trifluridine + Tipiracil)	Low		N/A

* Key: frequency of emesis (%) - **Minimal <10, Low 10-30, Moderate (MEC) 30-90, High >90**

Medicines with minimal effect do not contribute to emesis thus there is clinically no need to prescribe antiemetics. With combination treatment regimens, emesis is treated with the medicines from highest tier of frequency. Combination regimens may have a higher emetic risk than single medicines but none of the currently available colorectal cancer regimens have a high emetogenic risk [196, 197].

3.1.3 Public healthcare sector observed treatment pathways

3.1.3.1 Observed treatment pathways for early CRC disease

Figure 3.7 reveals that although most patients seek treatment however, ~15% of patients don't receive treatment at all. Capecitabine is used extensively in early CRC treatment regimens

regardless of the site of origin of the cancer. There are a low number of patients that change to an alternative regimen (approx. 3%). A change in regimen was considered as a change in the fluoropyrimidine and/or the addition of a non-standard adjuvant medicine such as mitomycin. The number of chemotherapy cycles and dosages for each patient (Table 3.3) was used in order to calculate the average number of chemotherapy cycles and dosages for each regimen. The averages seen in Table 3.3 were used to calculate the total cost of chemotherapy in the costing model (section 2.3.4.1). The observed treatment pathways per patient can be found in Appendix G.

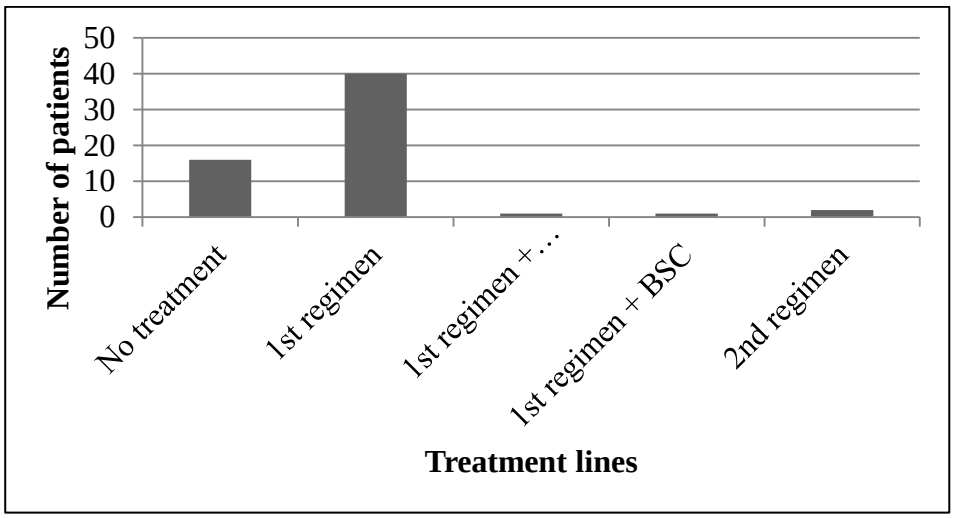


Figure 3.7 The number of early CRC patients per the number of treatment regimens used in the public healthcare sector

Table 3.3 Average number of cycles of chemotherapy treatment for early CRC in the public healthcare sector

Chemotherapy Regimens - colon	**5-FU + LV**	**CAPECITABINE**	**CAPOX**
Averages (Rounded off to nearest whole number)	**6**	**4**	**6**
Chemotherapy Regimens - rectal	**5-FU + LV**	**CAPECITABINE**	**CAPOX**
Averages (Rounded off to nearest whole number)	**3**	**2**	**5**

When compared to the theoretical number of cycles seen in Table 3.14 capecitabine use is less than the 8 cycles found in literature but oxaliplatin use is restricted due to suspected neuropathy development therefore 6 cycles of CAPOX is more likely to be administered in clinical practice. FOLFOX is not used at all in this patient cohort and is largely related to the easier administration of CAPOX. Rectal cancer patients received less active treatment than

colon cancer patients, this is not unexpected as literature does indicate fewer cycles of treatment.

3.1.3.2 Observed treatment pathways for advanced CRC disease

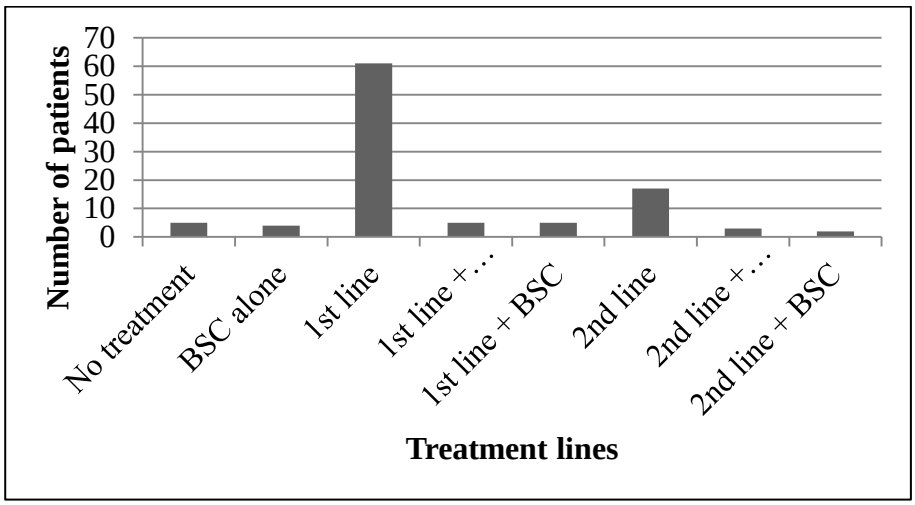


Figure 3.8 The number of advanced CRC patients per treatment line in the public healthcare sector

The advanced CRC sub-group of patients had more patients receiving treatment in comparison to the early CRC sub-group. In addition, a few patients only received best supportive care and no active chemotherapy. Similarly to the early CRC sub-group, capecitabine was extensively administered in 1st line treatment but more patients did receive 2nd line treatment. Most of the 2nd line treatments contained irinotecan-containing regimens Interestingly 76% of patients between 60 and 70 years received oxaliplatin however, it can't be determined if these patients are high-risk or not. In addition, more patients were placed onto maintenance therapy with capecitabine although this doesn't seem to be standard practice for CRC (Figure 3.8). The observed treatment pathways per patient can be found in

Appendix H.

Table 3.4 Average number of cycles of chemotherapy treatment for advanced CRC in the public healthcare sector

Chemotherapy Regimens	**5-FU + LV**	**CAPE (1ST)**	**CAPOX**	**CAPOX (2ND)**	**XELIRI**	**XELIRI (2ND)**	**Cape-Mito**	**CAPE (2ND)**
Averages (Rounded off to nearest whole number)	**6**	**3**	**6**	**6**	**1**	**4**	**2**	**3**
Chemotherapy Regimens	**FOLFOX**		**OXALI**	**FOLFIRI**	**FOLFIRI (2ND)**		**CAPE (MAINT)**	
Averages (Rounded off to nearest whole number)	**6**		**6**	**7**	**7**		**14**	

Although capecitabine is widely administered, the average number of cycles is lower for the patient cohort where capecitabine is combined with oxaliplatin. Oxaliplatin toxicity is a problem thus 8 cycles as found in literature is probably higher than used in clinical practice. FOLFOX is used for advanced CRC treatment and is used at the prescribed number of cycles.

Table 3.5 Average dosages for each treatment cycle for advanced CRC disease in the public healthcare sector

Chemo. Regimen	5-FU + LV		Cape (1st line)	CAPOX		CAPOX (2nd line)		XELIRI		XELIRI (2nd line)	
Medicine composition for the regimen	5-FU	LV	Cape	Cape	Oxaliplatin	Cape	Oxaliplatin	Cape	Irinotecan	Cape	Irinotecan
Average dose (mg) per cycle	**3600**	**180**	**43960**	**42896**	**208**	**38164**	**207**	**32200**	**350**	**42728**	**370**

Chemo. Regimen	Cape-Mito		Cape (2nd line)	FOLFOX			Oxal.	FOLFIRI			FOLFIRI (2nd line)		
Medicine composition for the regimen	Cape	Mito	Cape	5-FU	LV	Oxaliplatin	Oxaliplatin	5-FU	LV	Irinotecan	5-FU	LV	Irinotecan
Average dose (mg) per cycle	**37492**	**11**	**44800**	**5440**	**640**	**160**	**260**	**4700**	**700**	**300**	**4680**	**680**	**300**

Chemo. Regimen	Cape (maint)	
Medicine composition for the regimen	Cape	
Average dose (mg) per cycle	**37240**	

When used in FOLFOX or FOLFIRI, the doses are however, much higher and closer to the theoretical doses. Capecitabine also falls within the prescribed range expect when administered with irinotecan. This regimen has a lower capecitabine dose but higher irinotecan dose than the theoretical doses based on the average BSA for a cancer patient. The maintenance capecitabine dose is nevertheless, expected to be lower than active treatment doses. For this group of patients the 2nd line treatment doses are not necessarily higher as seen with FOLFIRI and CAPOX. This could be due to patient cohort characteristics and tolerability after much 1st line treatment.

3.1.4 Private healthcare sector

3.1.4.1 Observed treatment pathways for early CRC disease

Majority (69%) of early CRC patients received one regimen or didn't change their regimen notably, the number of patients changing their regimens is lower however, a noteworthy number of patients only received best supportive care (9%) and 11% didn't receive any treatment (Figure 3.9). A change in regimen was noted if the fluoropyramidine changed or the patient switched between irinotecan and oxaliplatin or the addition of a non-standard medicine was observed. Maintenance therapy was not often recorded (0,36%) similarly with 3rd and 4th treatment regimen changes. Of all the early CRC patients that received no treatment (93 in total), 78,5% underwent surgery. In addition, 56% of these patients were male. The observed treatment pathways per patient can be found in Appendix I.

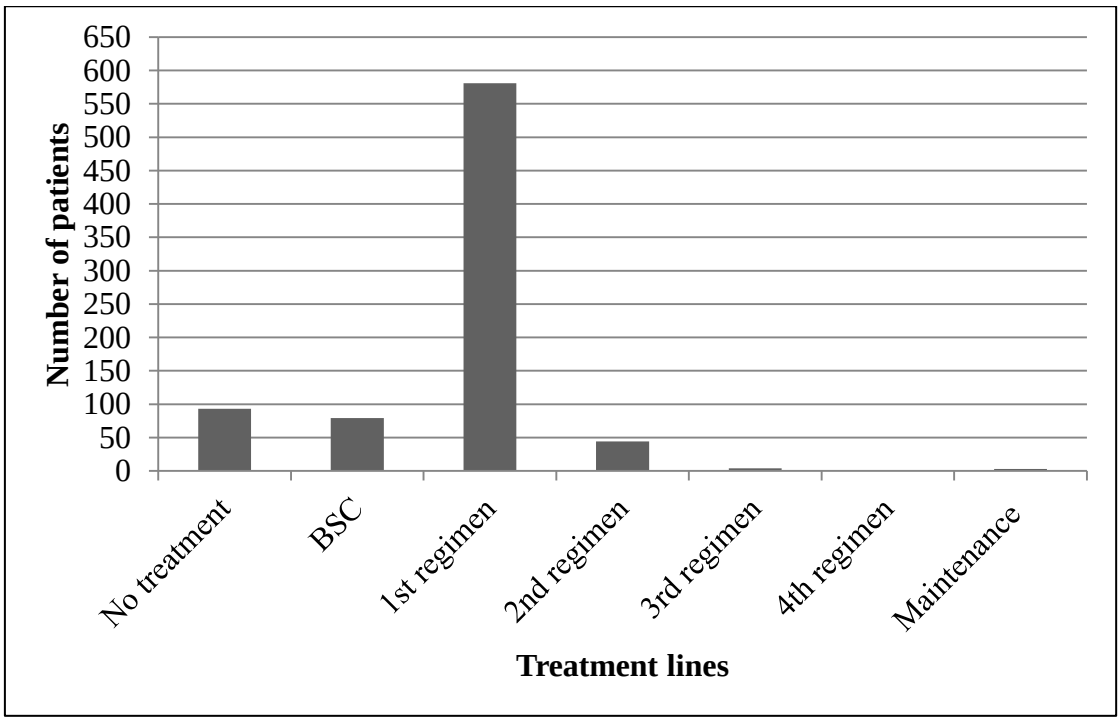


Figure 3.9 The number of early CRC patients per treatment line in the private healthcare sector

The average number of cycles per regimen was calculated from the treatment pathways whereby the same regimen for the group of early CRC patients was summed and an average calculated for the number of patients that received that regimen (Table 3.6).

Table 3.6 The average number of cycles per conventional CRC regimen for the early CRC group of patients in the private healthcare sector

Chemotherapy regimens	Total no. of cycles	No. of patients per regimen	Average no. of cycles	Rounding
5FU	684	135	5,07	5
Capecitabine	1376	306	4,50	5
Oxaliplatin	62	31	2	2
FOLFOX	1395	186	7,50	8
CAPOX	1007	201	5,01	5

Based on the theoretical costing model, the average dosages for the patient cohort were calculated. The lowest SEP prices were used and were only calculated for the conventional CRC medicines as the theoretical costing model only comprised of these medicines (Table 3.7).

Table 3.7 The average dose (mg) per conventional CRC chemotherapy medicine for the early CRC group in the private healthcare sector– the doses are regardless of monotherapy or combined in a regimen

Chemotherapy	5-FU	LV	Capecitabine	Oxaliplatin
Average cost per claim	R232,94	R840,92	R3 513,10	R2 862,09
Medicine price/vial	R15,66	R184,00	R12,40	R974,13
		R552,00	R41,71	R1 948,26
No. of vials	15	2	84	1
		2		1
Vial size/tab	500mg	100mg, 300mg	150mg, 500mg	50mg, 100mg
Dose per cycle (mg)	**7437**	**623**	**42113**	**194**

3.1.4.2 Observed treatment pathways for advanced CRC disease

Majority (65%) of advanced CRC patients received 1st line treatment, the number of patients receiving 2nd line treatments are greater than the early CRC group. Fewer patients received best supportive care (1,5%) and few patients didn't receive any treatment (1,3%) (Figure 3.10). Maintenance therapy was not often recorded (0,7%) similarly with 3rd and 4th line treatments however, there was one patient that received 6 lines of therapy. Although a small number of advanced CRC patients received no treatment (6 in total), 66,7% or two-thirds

underwent surgery for colorectal cancer. In addition, all of these patients were male. The observed treatment pathways per patient can be found in Appendix J.

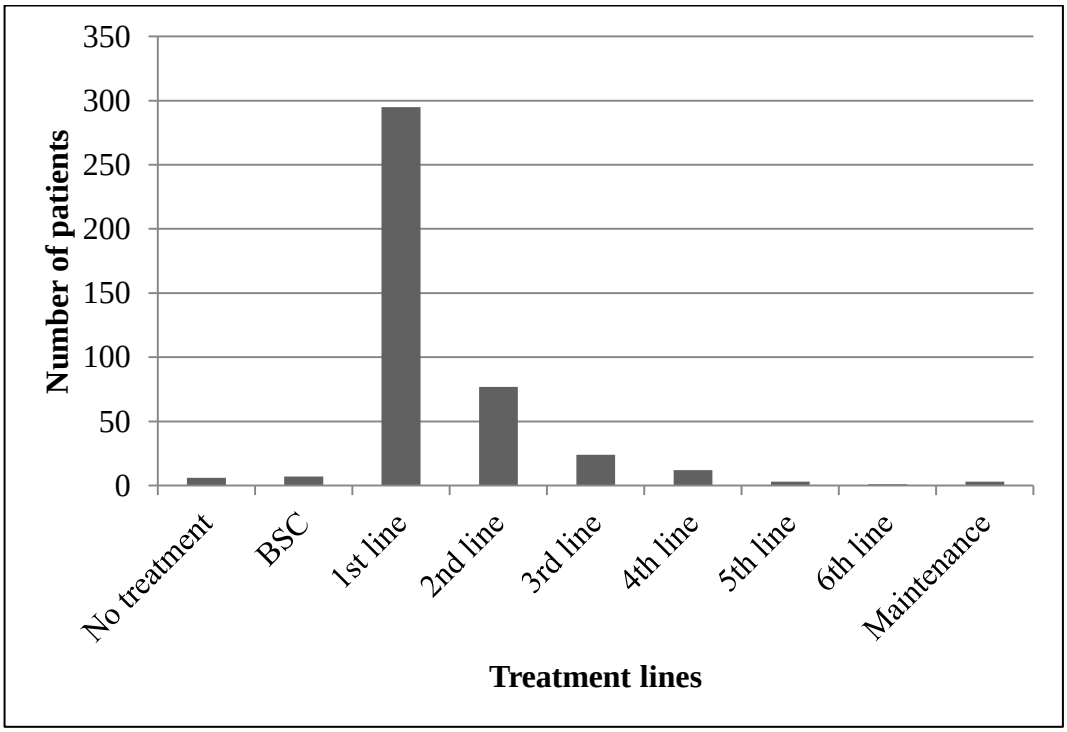


Figure 3.10 The number of advanced CRC patients per treatment line in the private healthcare sector

The average number of cycles for the advanced CRC group was calculated (Table 3.8) in addition to the average doses per chemotherapy medicine (Table 3.9).

Table 3.8 The average number of cycles per conventional CRC regimen for the advanced CRC group of patients in the private healthcare sector

Chemotherapy regimens	Total no. of cycles	No. of patients per regimen	Average no. of cycles	Rounding
5-FU	346	74	4,68	5
Capecitabine	551	133	4,14	4
Irinotecan	105	33	3,18	3
Oxaliplatin	60	36	1,67	2
FOLFOX	1112	170	6,54	7
FOLFIRI	772	131	5,89	6
CAPOX	512	118	4,34	4
XELIRI	180	36	5	
FOLFOXIRI	30	4	7,50	8
Bev	135	47	2,87	3
5-FU+Bev	70	20	3,5	4
Capecitabine+Bev	201	42	4,79	5
Oxaliplatin+Bev	43	16	2,69	3
Irinotecan+Bev	49	9	5,44	6
FOLFOX + Bev	737	108	6,82	7
FOLFIRI+Bev	496	77	6,44	6
FOLFOXIRI+Bev	1	1	1	
CAPOX+Bev	314	64	4,91	5
XELIRI+Bev	93	16	5,81	6
Cet	141	30	4,70	5
5-FU+Cet	20	7	2,86	3
Capecitabine+Cet	1	1	1	
Irinotecan+Cet	105	22	4,77	5
FOLFOX + Cet	114	24	4,75	5
FOLFIRI+Cet	356	57	6,25	6
CAPOX+Cet	12	3	4	
XELIRI+Cet	8	2	4	
Regorafenib	34	15	2,27	2

Table 3.9 The average dose (mg) per conventional CRC chemotherapy medicine for the advanced CRC group in the private healthcare sector – the doses are regardless of monotherapy or combined in a regimen and cetuximab includes the loading dose

Chemo/ Biological	5-FU	LV	Capecitabine	Oxaliplatin	Irinotecan	Bevacizumab	Cetuximab	Regorafenib
Average cost per claim	R272,31	R962,29	R3 470,76	R2 966,24	R2 325,89	R11 683,80	R19 335,34	R50 374,15
Medicine price/vial	R15,66	R184,00	R12,40	R974,13	R370,50	R3 682,56	R2 897,69	R628,37
		R552,00	R41,71	R1 948,26	R934,80	R14 730,25		
No. of vials/tablets	17	2	83	2	2	1	7	80 tablets
		2		1	4			
Vial size/tab	500mg	100mg, 300mg	150mg, 500mg	50mg, 100mg	20mg, 100mg	100mg, 400mg	100mg	Flat dose (4x400mg)
Dose per cycle (mg)	**8694**	**843**	**41606**	**205**	**324**	**317**	**667**	**3207**

3.2 Retrospective Drug Utilisation Review – patient cohort demographics

3.2.1 Public healthcare sector

3.2.1.1 Patient identification from "new case" books

Table 3.10 Number of patients identified from "new case" books for 3 year period starting in 2012

Year	Number of patients identified	Number of patients with missing diagnosis	Number of patient files captured
2012	151	18	**74**
2013	103*	7	**62**
2014	89*	37	**26**
TOTAL	343	62	**162**

* Patients could not be identified for the entire year as "new case" books were missing from the clinic.

Patients that were excluded as the missing diagnosis was not colorectal or diagnosis were in fact stomach, small bowel or anal cancer. Anal cancer was only included if the origin was adenocarcinoma and not squamous cell or neuroendocrine origin.

3.2.1.2 Patient cohort

The patient cohort consisted of 162 patients of whom 73 were females and 89 males. The average age at which the patients presented at the clinic was approximately 57 years (s.d +/- 13) (median 58 years, range 67 years). Although more males presented at the clinic, the advanced CRC data indicates a similar number for the genders.

Table 3.11 Colorectal cancer incidences per age group for CMJAH between 2012 and 2014

Age group	Males		Females	
	Number	Percentage	Number	Percentage
0 – 49	20	23	24	33
50 – 79	62	72	45	63
80^{+}	4	5	3	4
Total	***86**	**100**	***72**	**100**

*Totals exclude the patients where age couldn't be determined

Table 3.12 Colorectal cancer incidences per colorectal site for CMJAH between 2012 and 2014

Tumour location [198]	All		Males		Females	
	Number	Percentage	Number	Percentage	Number	Percentage
Right-sided	23	14	14	16	9	12
Left-sided	61	38	39	44	22	30
Rectum	50	31	26	29	24	33
Colon - unspecified	21	13	8	9	13	18
Synchronous tumours	7	4	2	2	5	7
Total	***162**	**100**	***89**	**100**	***73**	**100**

*Totals include patients where age couldn't be determined

Table 3.11 and Table 3.12 illustrate the spread of data between age groups and primary tumour location within the colorectal region. Most patients presented at the clinic were over 50 years of age and more distal colon cancer and rectal cancer were treated for this cohort.

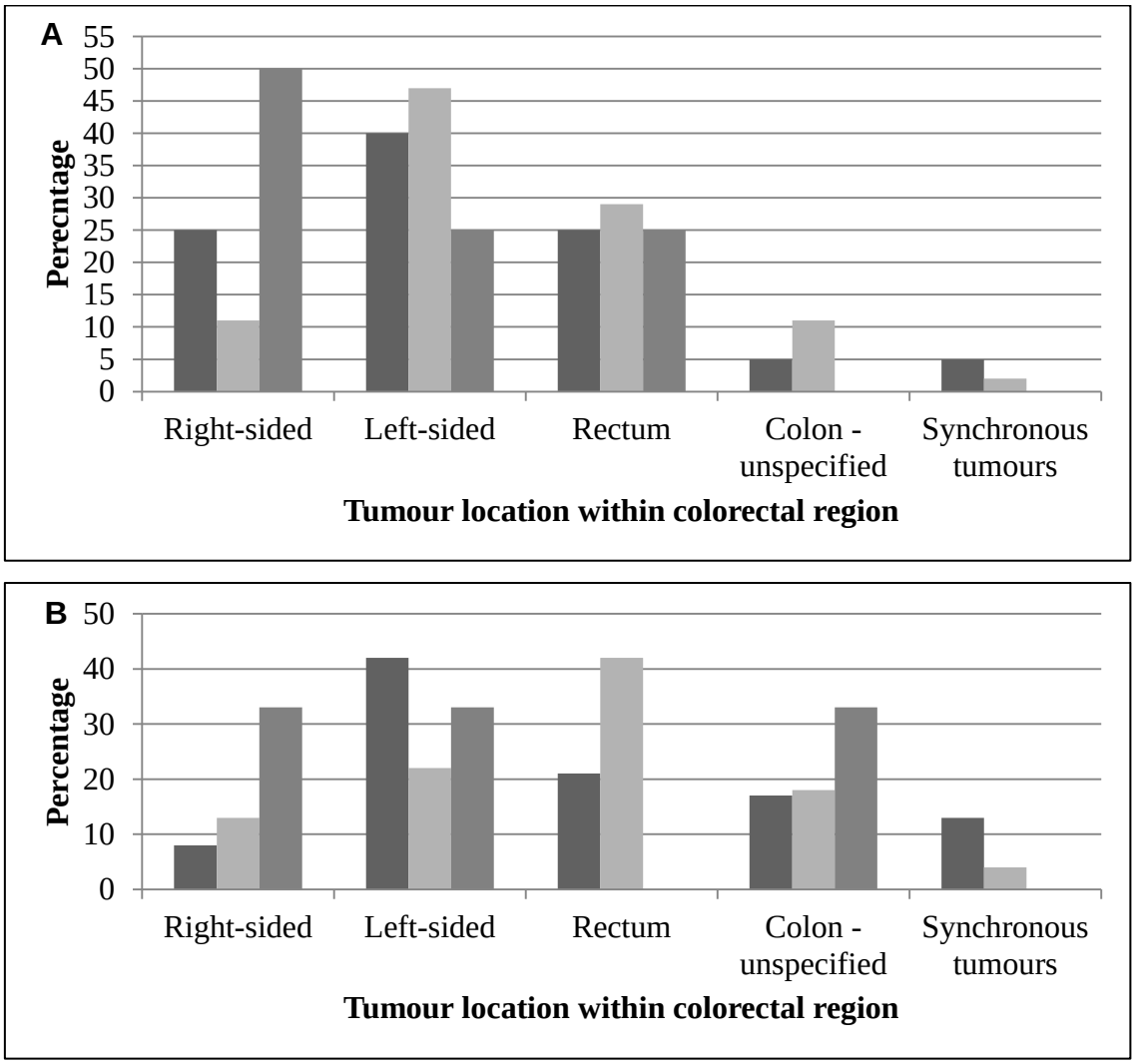


Figure 3.11 Distribution of colorectal cancer tumour location by age and sex for CMJAH patient cohort between 2012 and 2014 for males (A) and females (B) – Dark grey (0-49 years), Light grey (50-79 years); Medium grey (80+ years)

3.2.1.2.1 Early CRC disease

60 patients were identified with early CRC disease and accounts for slightly more than a third (37%) of the total identified patient population. Within the early CRC group, majority (82%) had left-sided colorectal cancer (Figure 3.12). This includes rectal cancer patients as the rectum is anatomically on the left side of the colon.

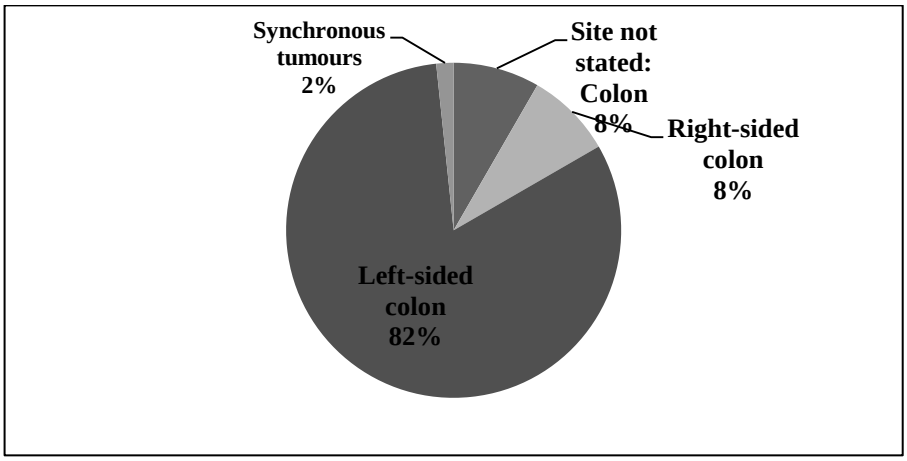


Figure 3.12 Percentage of CRC cases based on diagnosed site of origin for early CRC patients at CMJAH

None of the patients had cancer of the transverse colon however, 8% of the patient cases were non-specific to the site of origin. With regard to gender and age, more males were diagnosed with early CRC disease (62%) and the highest number of cases occurred between the ages of 40 and 60 years (Figure 3.13).

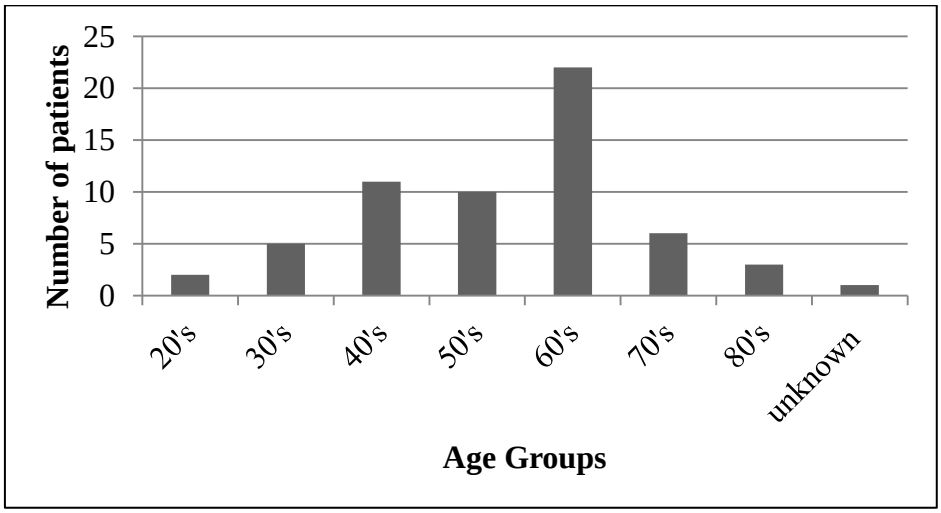


Figure 3.13 Number of early CRC disease patients for each age group based on the age at which patients presented at CMJAH

3.2.1.2.2 Advanced CRC disease

Of the 162 patients identified, approximately 64% were diagnosed with advanced CRC disease. Similarly to the early CRC patient group, left-sided colorectal cancer was more common and nearly 60% had rectal cancer as the primary site of origin (Figure 3.14). Colorectal cancer of transverse origin is once again a small percentage but there are also a higher number of patients with synchronous tumours, which could include the transverse colon. The percentage of patients with a diagnosis of only colon cancer is double when compared to the early CRC group therefore there may very well be more cases of right-sided and transverse colon origins as well.

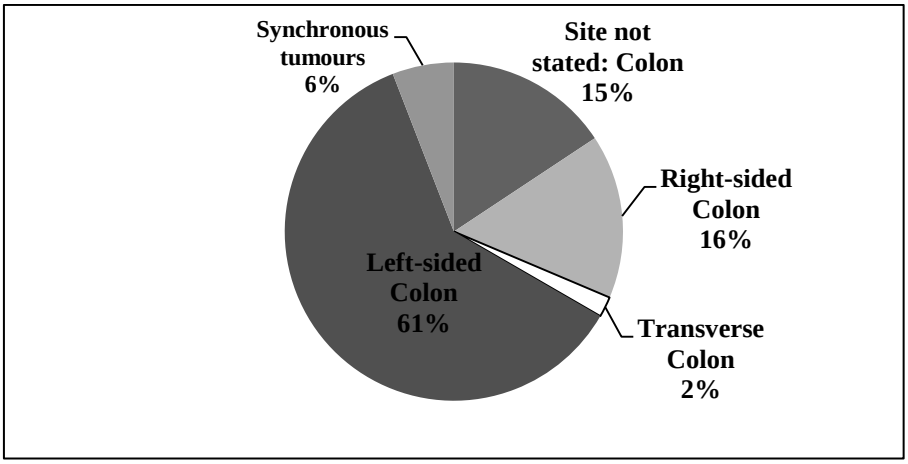


Figure 3.14 Percentage of CRC cases based on diagnosed site of origin for advanced CRC patients at CMJAH

In comparison to the early CRC sub-group, the number of cases based on gender is similar for the advanced CRC group, 51% male patients and 49% female patients. From this result it can be said that CRC is not gender specific particularly for advanced CRC disease diagnosis. In terms of age groups, it is similar to the early CRC sub-group in that the ages most likely to present at the clinic was between the ages of 40 and 60 years (Figure 3.15).

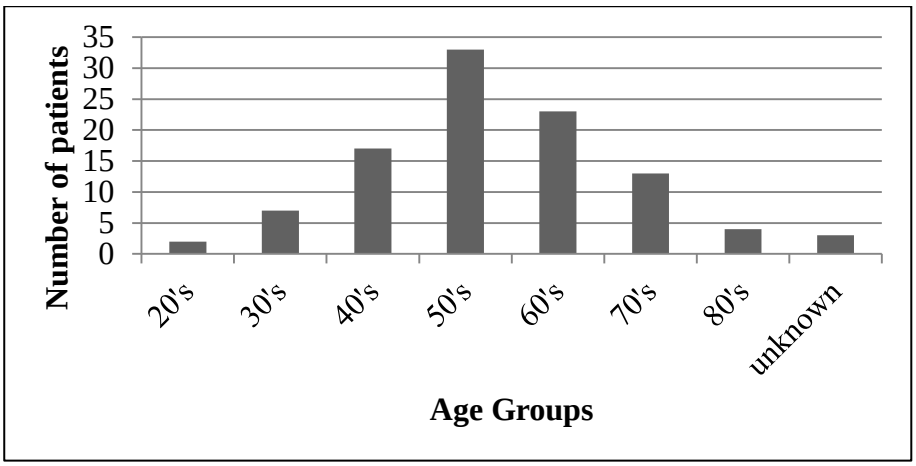


Figure 3.15 Number of advanced CRC disease patients for each age group based on the age at which patients presented at CMJAH

3.2.2 Private healthcare sector

3.2.2.1 Data capture from data sets

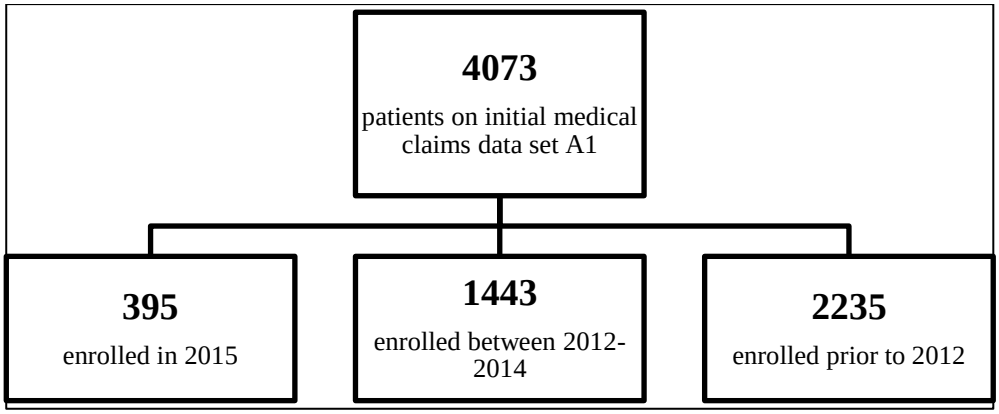


Figure 3.16 Patient enrollment numbers per year from data set A1

The final number of patients included in data set A7 following the subsequent exclusions was 1297 (Figure 3.17).

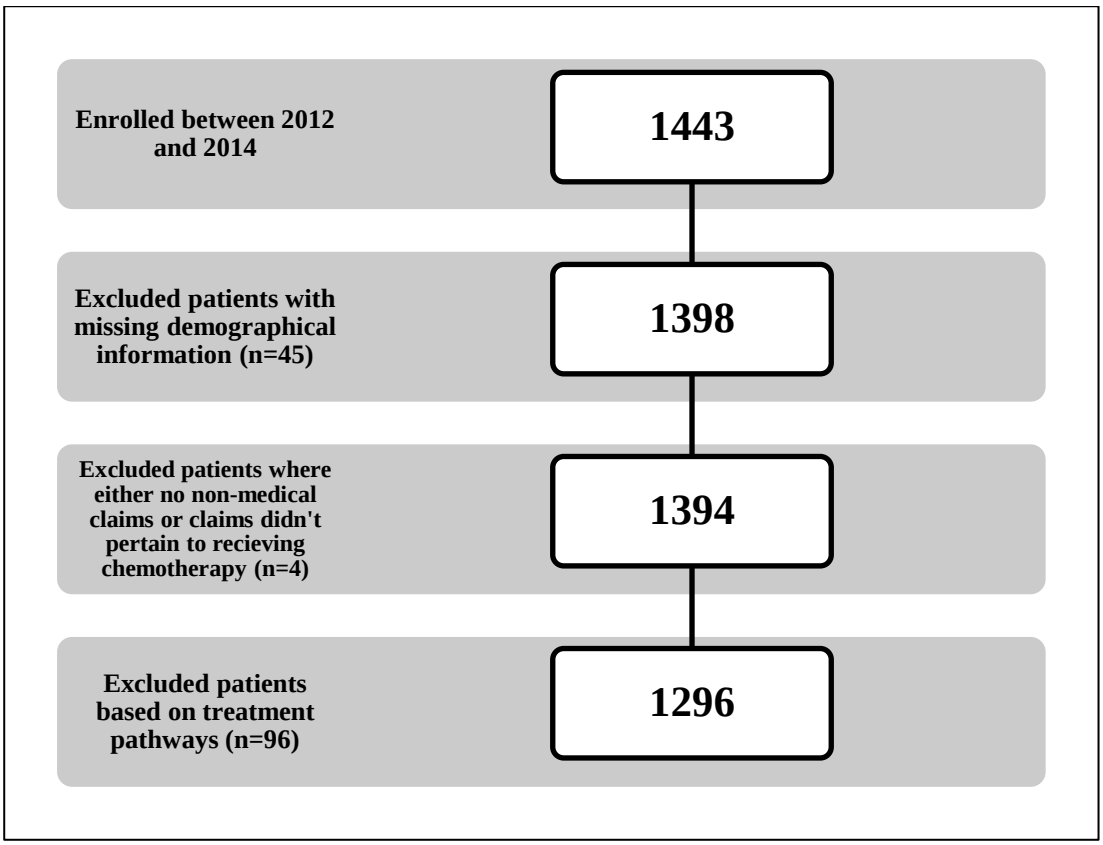


Figure 3.17 Total number of patients included in the private healthcare sector cohort prior to treatment pathway development

3.2.2.2 Patient cohort

Table 3.13 Colorectal cancer incidences per age group for a South African medical scheme between 2012 and 2014

Age group	Male		Female	
	Number	%	Number	%
20-59	248	53	218	47
60-79	435	59	302	41
80+	46	49	47	51
Total	**729**	**56**	**567**	**44**

The patient cohort comprise of 729 males and 567 females (Table 3.13). The average age, both advanced CRC and early CRC, was calculated to be 63 years (s.d +/- 12). The average age for the advanced CRC sub-group was lower than for the overall cohort at 61 years (s.d +/- 12). The median and range of the ages for the total cohort was calculated to be 68 and 64 years respectively. 84% of the cohort underwent surgery but most of these patients were early CRC (Figure 3.18).

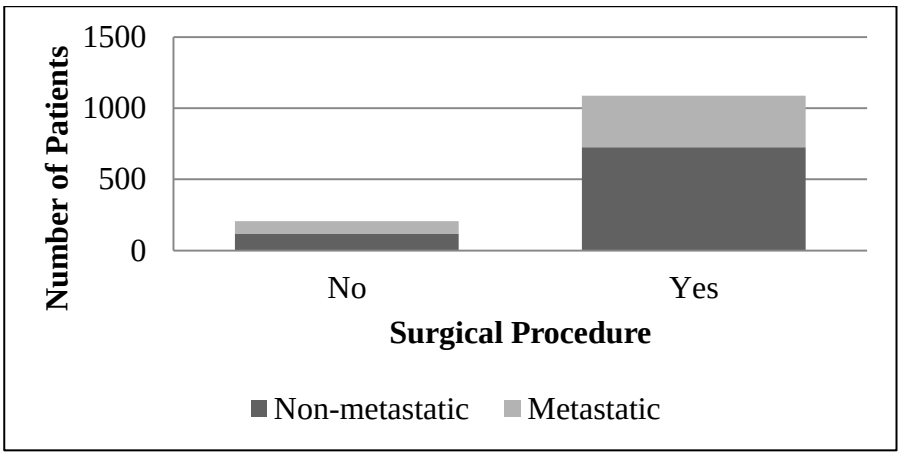


Figure 3.18 The number of patients that underwent definitive surgery for colorectal cancer based on their advanced CRC status for patients enrolled onto the medical scheme– the type of definitive surgery was not specified in the anonymised data

Due to the nature in which the medical scheme dataset is captured, it is unclear the specific site of disease within the colorectal region.

3.2.2.2.1 Early CRC disease

Just less than two-thirds of the cohort was diagnosed with early CRC disease (65%) of which more males (55%) was diagnosed than females (45%). The average age for the early CRC group was calculated to be 64 years (s.d +/- 13) with a range and median of 65 years and 68 years respectively. The most frequently recorded age group on the database with 32% was patients in their 60s. Patients in their 20s and 90s were recorded, albeit less than 1% each (Figure 3.19).

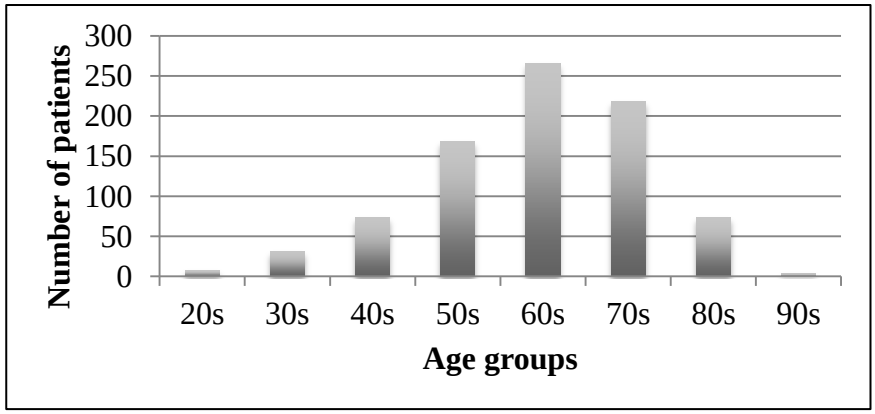


Figure 3.19 Number of early CRC disease patients for each age group based on the age recorded on the South African medical scheme

3.2.2.2.2 Advanced CRC disease

Slightly more than one-third of the cohort was diagnosed with advanced CRC disease or where disease progression occurred to an advanced stage (35%). Similarly to the early CRC group, more males (58%) were diagnosed than females (42%). The average age for the advanced CRC group was calculated to be 61 years (s.d +/- 12) with a range and median of 61 years and 62 years respectively. These demographics are lower than the early CRC group. The most frequently recorded age group on the database with 35% was patients in their 60s. Patients in their 20s were recorded, albeit less than 1%. There were no patients older than 90 years of age (Figure 3.20).

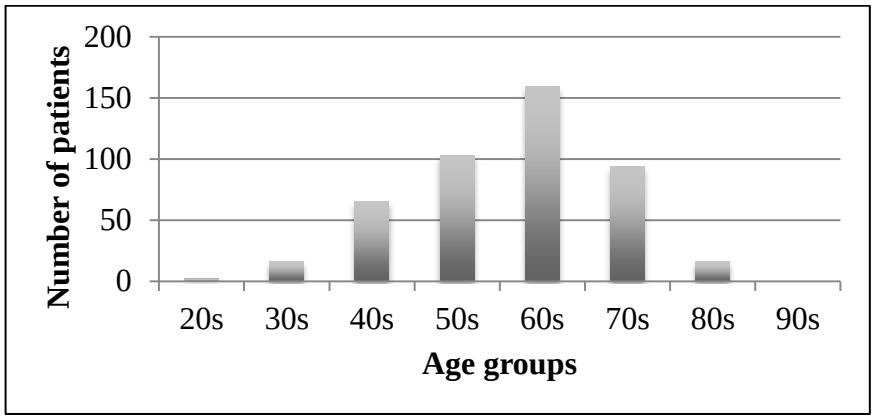


Figure 3.20 Number of early CRC disease patients for each age group based on the age recorded on the South African medical scheme

3.3 Treatment costs

Treatment costs were calculated (theoretical costs, public healthcare sector and private healthcare sector) using the costing model developed in section 2.3.4. Each component of the total cost is presented below.

3.3.1 Total cost for CRC treatment

3.3.1.1 Theoretical treatment pathway costs for the public healthcare sector

3.3.1.1.1 Early CRC disease

The total theoretical costs for early CRC adjuvant treatment was calculated based on dosages in Table 2.1 and the average body surface area and ideal body weight as noted in Section 2.3.4.1. Figure 3.21 shows the cost per cycle of the regimens as determined by the treatment pathways in Figure 3.3 whereas Table 3.14 shows the total theoretical cost based on the recommended number of cycles found in the essential clinical trial data (Table 3.1), international guidelines from the American Cancer Society (ACS – United States of America), National Comprehensive Cancer Network (NCCN – United States of America) and National Cancer Institute (NCI – United States of America) as well as National Institute for Health and Care Excellence (NICE – United Kingdom) and European Society for Medical Oncology (ESMO – Switzerland based for Europe) [25, 26, 156-162] and local guidelines from the South African Oncology Consortium (SAOC) and the Independent Clinical Oncology Network (ICON) [127, 155].

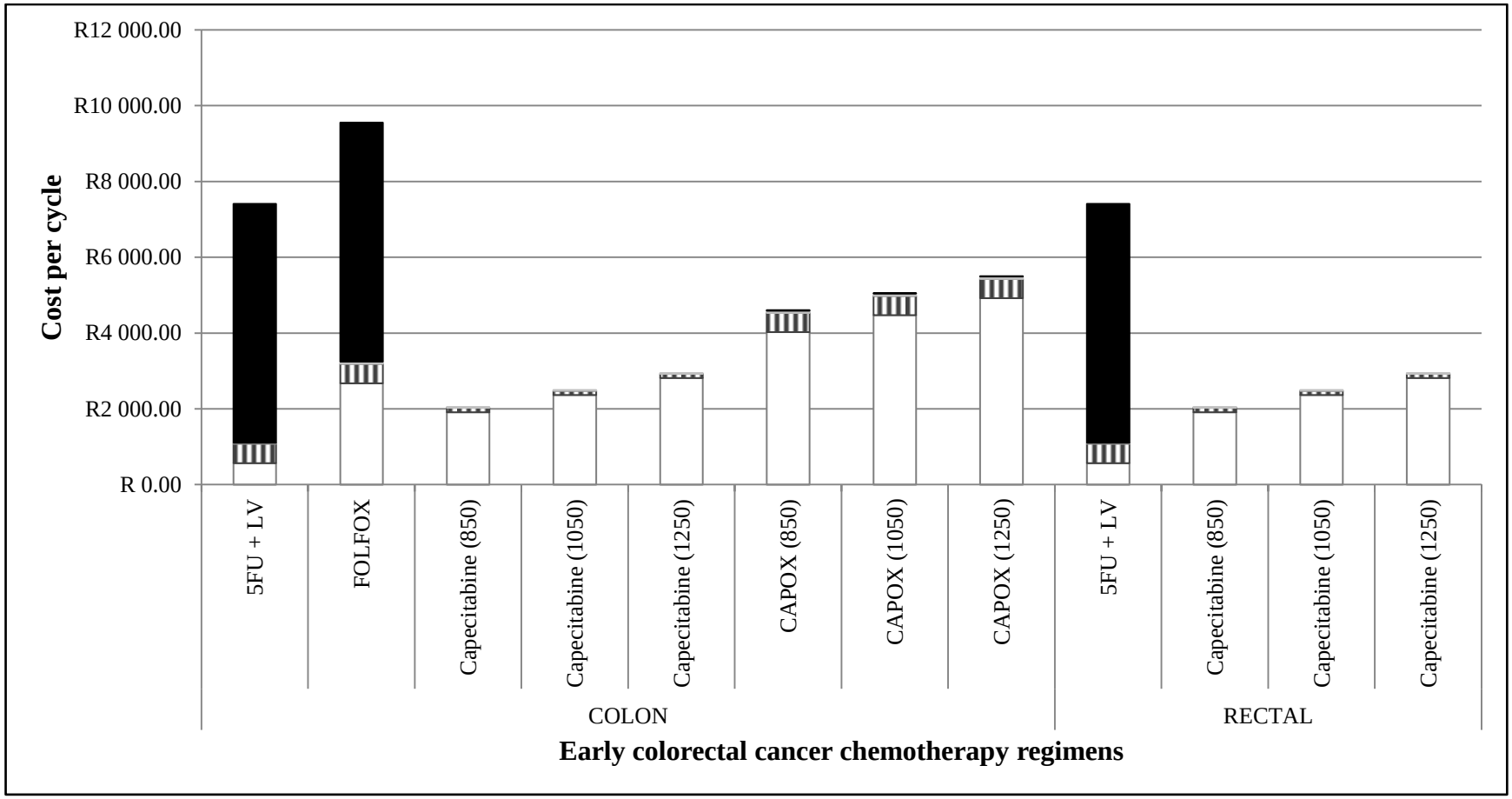


Figure 3.21 Theoretical cost per cycle for early CRC treatment regimens in the public healthcare sector – The cost per treatment regimen comprises of the chemotherapy cost, administrative cost (grey stripe), supportive care medicine costs (grey) and administration costs (black).

Table 3.14 Total theoretical costs per treatment regimen for early CRC in the public healthcare sector - The number of cycles is based on the recommended total number of cycles from literature and the total cost is calculated by multiplying the cost per cycle with the number of cycles.

	COLON							
	5FU + LV	**FOLFOX**	**Capecitabine (850)**	**Capecitabine (1050)**	**Capecitabine (1250)**	**CAPOX (850)**	**CAPOX (1050)**	**CAPOX (1250)**
Total treatment costs per cycle	R7 409,18	R9 555,79	R2 052,21	R2 502,23	R2 949,73	R4 602,59	R5 052,61	R5 500,11
Number of cycles	6	12	8	8	8	8	8	8
Treatment costs per x cycles	**R 44 455,09**	**R 114 669,45**	**R 16 417,70**	**R 20 017,86**	**R 23 597,86**	**R 36 820,70**	**R40 420,86**	**R44 000,86**
Total costs for pathway	**FOR EARLY CRC TREATMENT IS EITHER/OR I.E. NOT ONE FOLLOWING OTHER**							

	RECTAL			
	5-FU + LV	**Capecitabine (850)**	**Capecitabine (1050)**	**Capecitabine (1250)**
Total treatment costs per cycle	R7 409,18	R2 052,21	R2 502,23	R2 949,73
Number of cycles	4	4	4	4
Treatment costs per x cycles	**R29 636,73**	**R8 208,85**	**R10 008,93**	**R11 798,93**
Total costs for pathway	**FOR EARLY CRC TREATMENT IS EITHER/OR I.E. NOT ONE FOLLOWING OTHER**			

3.3.1.1.2 Advanced CRC disease

From the theoretical costs, 5-FU-containing regimens have greater costs per cycle than capecitabine-containing regimens for either stage of CRC (Figure 3.4). This is due to higher administration costs for intravenous therapy as opposed to oral therapy despite the cheaper chemotherapy cost for 5-FU than capecitabine. For regimens where oxaliplatin is also prescribed, FOLFOX and CAPOX, the difference between the same regimen without oxaliplatin (5-FU or capecitabine) is greater for capecitabine-containing regimens as administration costs are then included (Figure 3.21). The theoretical costs for capecitabine-containing regimens are dose dependent and treatments range between 850 to 1250 mg. Therefore the lowest, highest and mid-point doses were used to calculate the range of capecitabine-containing regimens. The trend for the cost per cycles is similar between early and advanced CRC. The total cost per treatment regimen differs only by the number of theoretical cycles a patient will receive (Table 3.14, Table 3.15). This is the only difference between early colon and rectal cancer, advanced CRC is one theoretical cost per regimen. The total costs are reflective of the pathways as treatment is based on an either/or situation and not more than one defined line of therapy.

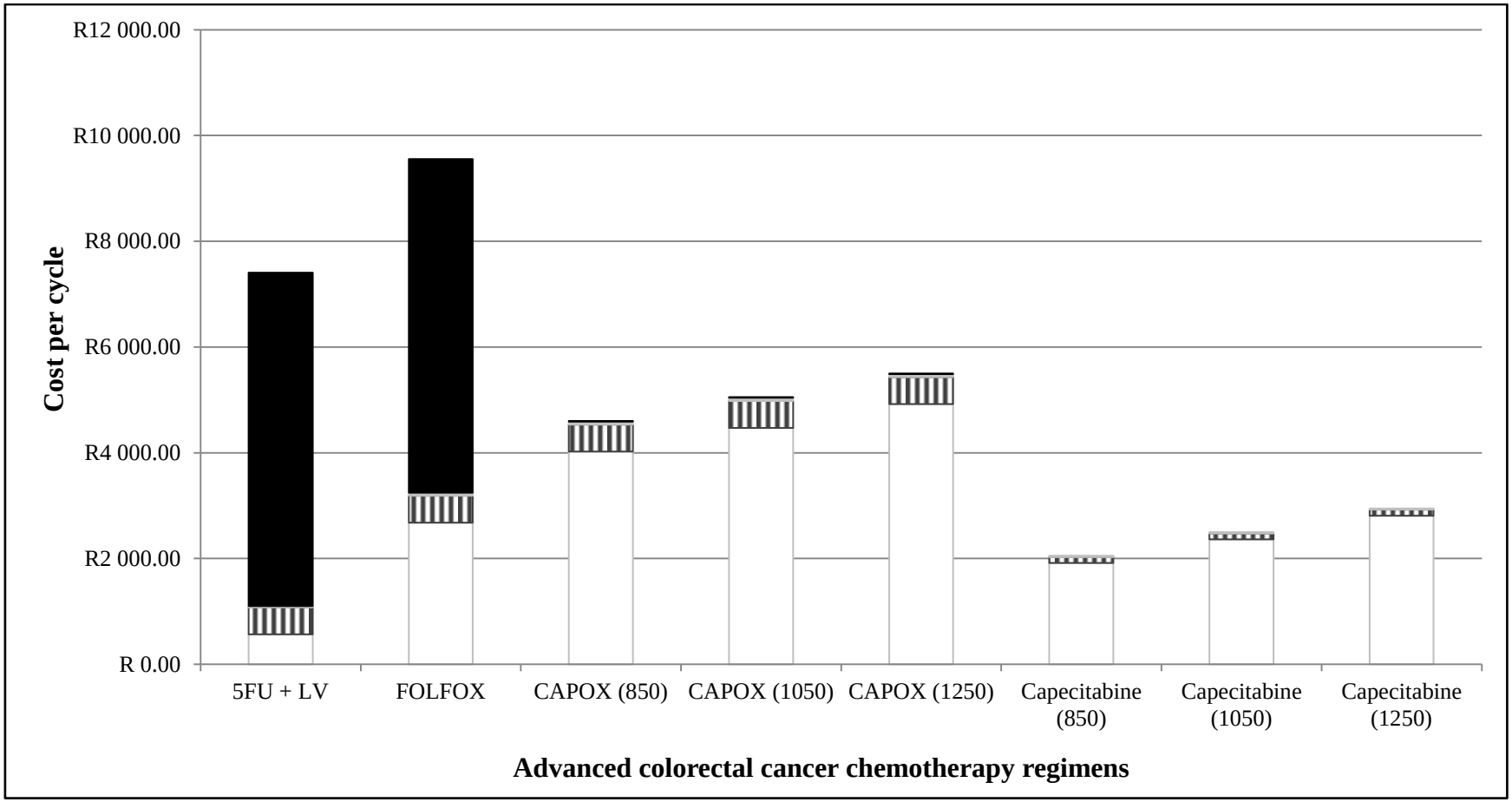


Figure 3.22 Theoretical cost per cycle for advanced CRC treatment regimens in the public healthcare sector – The cost per treatment regimen comprises of the chemotherapy cost, administrative cost (grey stripe), supportive care medicine costs (grey) and administration costs (black).

Table 3.15 Total theoretical costs per treatment regimen for advanced CRC in the public healthcare sector - The number of cycles is based on the recommended total number of cycles from literature and the total cost is calculated by multiplying the cost per cycle with the number of cycles.

	Advanced CRC								
	5-FU + LV	**FOLFOX**	**CAPOX (850)**	**CAPOX (1050)**	**CAPOX (1250)**	**Capecitabine (850)**	**Capecitabine (1050)**	**Capecitabine (1250)**	**FOLFOX (10 cycles)**
Total treatment costs per cycle	R7 409,18	R9 555,79	R4 602,59	R5 052,61	R5 500,11	R2 052,21	R2 502,23	R2 949,73	R9 555,79
Number of cycles	6	6	8	8	8	8	8	8	10
Treatment costs per x cycles	**R 44 455,09**	**R 57 334,72**	**R 36 820,70**	**R40 420,86**	**R44 000,86**	**R16 417,70**	**R20 017,86**	**R23 597,86**	**R 95 557,87**
Total costs for pathway	**FOR advanced CRC TREATMENT IS EITHER/OR I.E. NOT ONE FOLLOWING OTHER**								

3.3.1.2 Theoretical treatment pathway costs for private healthcare sector

3.3.1.2.1 Early CRC disease

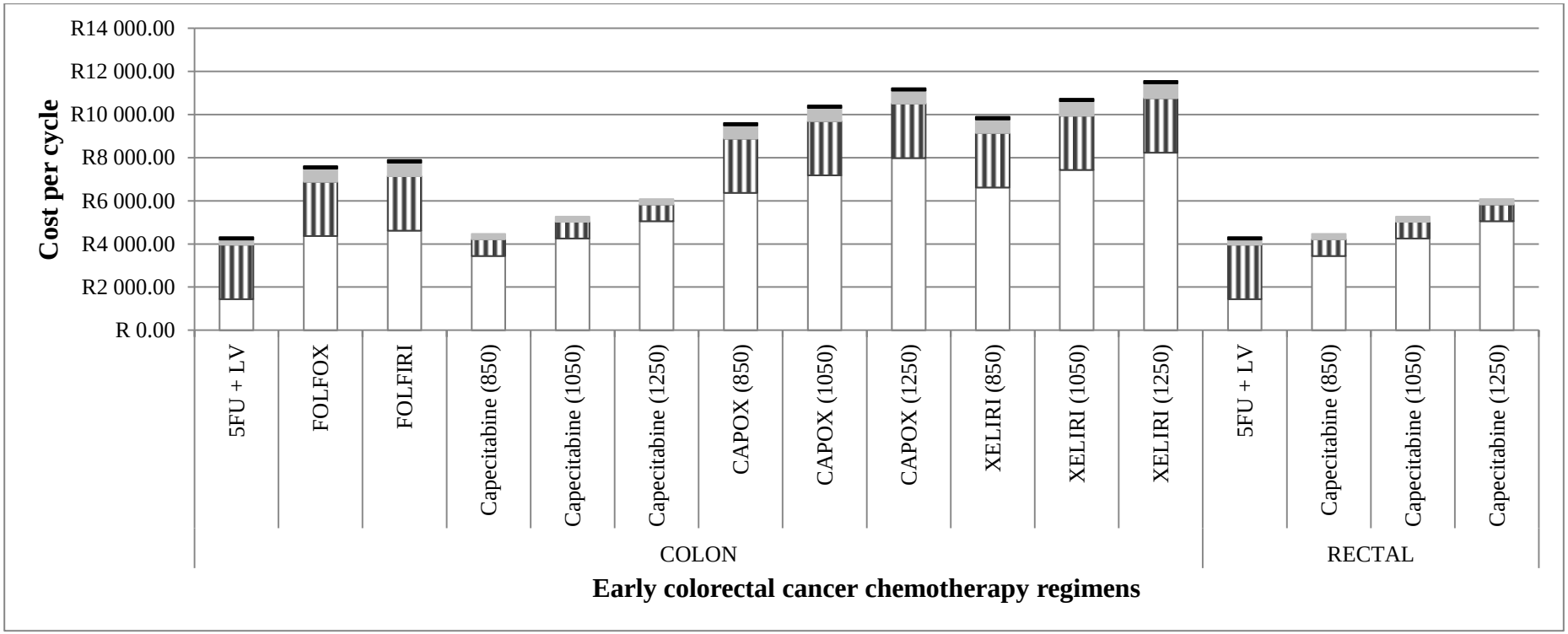


Figure 3.23 Theoretical cost per cycle for early CRC treatment regimens in the private sector – The cost per treatment regimen comprises of the chemotherapy cost, administrative cost (grey stripe), supportive care medicine costs (grey) and administration costs (black). The administrative costs are the average for the two types of facilities, the administration costs include admixtures calculated from the DUR for this sector.

Table 3.16 Total theoretical costs per treatment regimen for early CRC in the private sector - The number of cycles is based on the recommended total number of cycles from literature and the total cost is calculated by multiplying the cost per cycle with the number of cycles.

	COLON										
	5FU + LV	**FOLFOX**	**Capecitabine (850)**	**Capecitabine (1050)**	**Capecitabine (1250)**	**CAPOX (850)**	**CAPOX (1050)**	**CAPOX (1250)**	**XELIRI (850)**	**XELIRI (1050)**	**XELIRI (1250)**
Total treatment costs per cycle	R4 321,15	R7 607,65	R4 463,65	R5 273,05	R6 077,94	R9 608,06	R10 417,46	R11 222,35	R9 890,21	R10 729,25	R11 563,78
Number of cycles	6	12	8	8	8	8	8	8	8	8	8
Treatment costs per x cycles	**R25 926,89**	**R91 291,84**	**R35 709,16**	**R42 184,36**	**R48 623,48**	**R76 864,48**	**R83 339,68**	**R89 778,80**	**R79 121,68**	**R85 834,00**	**R92 510,24**
Total costs for pathway	**FOR EARLY CRC TREATMENT IS EITHER/OR I.E. NOT ONE FOLLOWING OTHER**										

	RECTAL			
	5-FU + LV	**Capecitabine (850)**	**Capecitabine (1050)**	**Capecitabine (1250)**
Total treatment costs per cycle	R4 321,15	R4 463,65	R5 273,05	R6 077,94
Number of cycles	4	4	4	4
Treatment costs per x cycles	**R17 284,60**	**R17 854,58**	**R21 092,18**	**R24 311,74**
Total costs for pathway	**FOR EARLY CRC TREATMENT IS EITHER/OR I.E. NOT ONE FOLLOWING OTHER**			

3.3.1.2.2 Advanced CRC disease

The theoretical costs in the private sector are higher than the public sector (Table 3.14, Table 3.15, Table 3.16 and Table 3.17). For both stages of CRC, the chemotherapy costs are the largest cost contributor. Biological agents are particularly expensive and increase the cost by more than 50% in certain instances. An interesting cost trend occurs in that as disease progression occurs, the cost per regimen prescribed increases. This is clearly illustrated in the cost of Regorafenib, a 3rd line therapy. Figure 3.23 and Figure 3.24 show that intravenous regimens have greater costs in comparison to the equivalent oral regimen, more over oxaliplatin and irinotecan-containing regimens are very similar in cost and is most noticeably absent in the public healthcare sector. The contribution of the administrative costs to newer advanced CRC regimens appears much lower due to the high chemotherapy costs. The number of cycles of treatment differs not only between early colon and rectum cancer but also between the lines of therapy of the regimens used in advanced CRC (Table 3.16, Table 3.17). There are definite pathways for advanced CRC in the private sector thus the cost of treatment is expected to be higher.

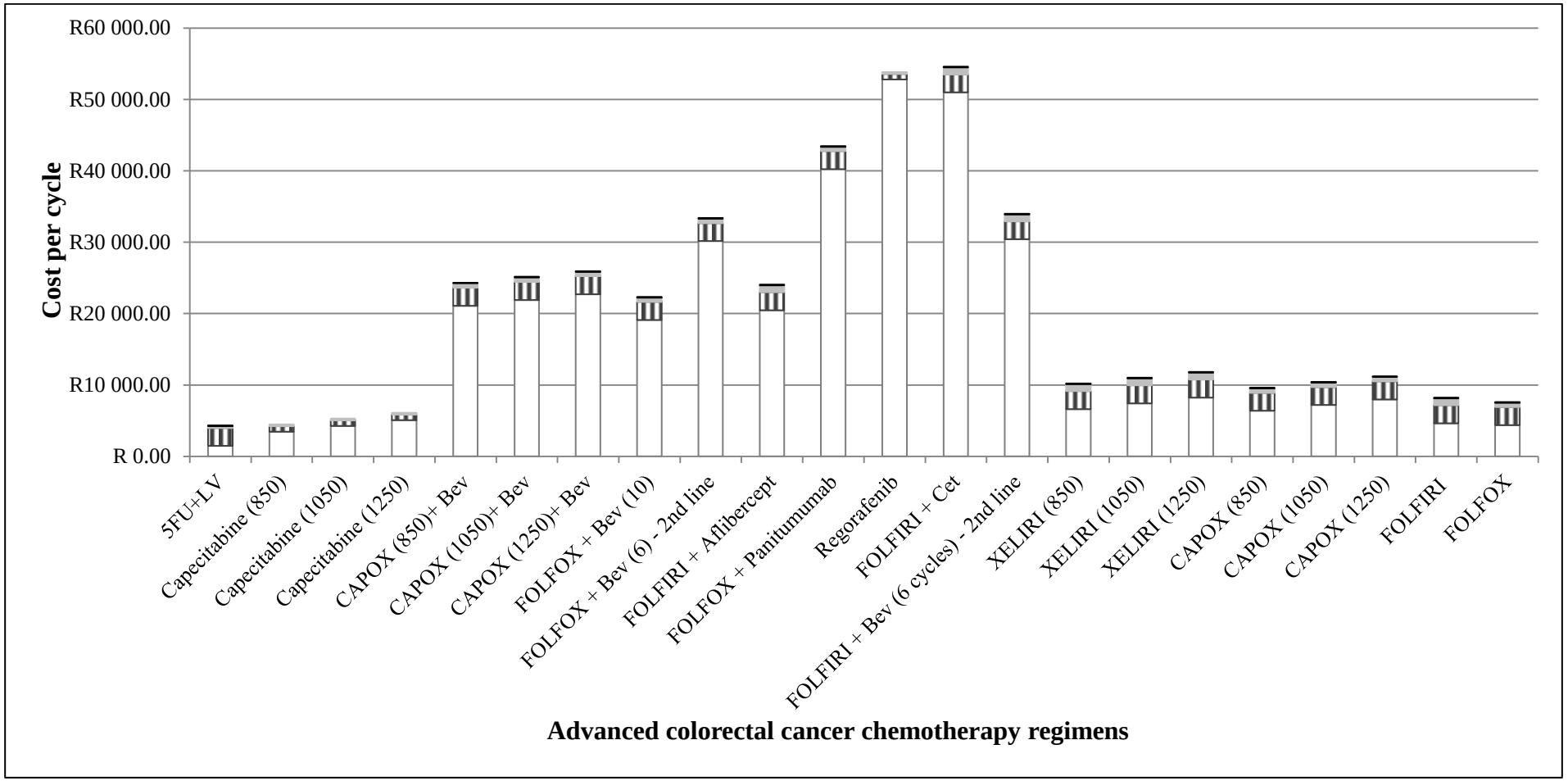


Figure 3.24 Theoretical cost per cycle for advanced CRC treatment regimens the private sector – The cost per treatment regimen comprises of the chemotherapy cost, administrative cost (grey stripe), supportive care medicine costs (grey) and administration costs (black). The administrative costs are the average for the two types of facilities, the administration costs include admixtures calculated from the DUR for this sector. Bev – bevacizumab, Cet – cetuximab.

Table 3.17 Total theoretical costs per treatment regimen for advanced CRC in the private sector - The number of cycles is based on the recommended total number of cycles from literature and the total cost is calculated by multiplying the cost per cycle with the number of cycles.

	5-FU+LV	FOLFIRI	FOLFOX	Cape. (850)	Cape. (1050)	Cape. (1250)	XELIRI (850)	XELIRI (1050)	XELIRI (1250)	CAPOX (850)	CAPOX (1050)
Total treatment costs per cycle	R4 315,12	R8 105,42	R7 493,59	R4 463,65	R5 273,05	R6 077,94	R10 105,83	R10 915,23	R11 720,12	R9 494,00	R10 303,40
Number of cycles	6	12	12	8	8	8	8	8	8	8	8
Treatment costs per x cycles	**R25 890,71**	**R97 265,08**	**R89 923,12**	**R35 709,16**	**R42 184,36**	**R48 623,48**	**R80 846,64**	**R87 321,84**	**R93 760,96**	**R75 952,00**	**R82 427,20**

	CAPOX (1250)	FOLFIRI + Cet	FOLFIRI + Bev (6 cycles)	FOLFIRI + Aflibercept	FOLFOX + Bev (10)	FOLFOX + Bev (6)	FOLFOX + Panitumumab	CAPOX (850)+ Bev	CAPOX (1050)+ Bev	CAPOX (1250)+ Bev	Regorafenib
Total treatment costs per cycle	R11 108,29	R54 468,46	R33 883,36	R23 946,35	R22 223,84	R33 271,53	R43 348,44	R24 224,25	R25 033,65	R25 838,54	R53 801,43
Number of cycles	8	12	6	9	10	6	8	10	10	10	3
Treatment costs per x cycles	**R88 866,32**	**R653 621,56**	**R203 300,18**	**R215 517,18**	**R222 238,43**	**R199 629,20**	**R346 787,55**	**R242 242,49**	**R250 336,49**	**R258 385,39**	**R161 404,29**

3.3.1.2.2.1 Medically unfit patients

Medically unfit patients, according to the treatment pathways seen in Figure 3., will receive one treatment regimen as opposed to several regimens, which follow on. The cost of these can be seen in Table 3.17. Medically unfit patients will receive treatment similar to an early CRC patient even though they have advanced CRC disease.

3.3.1.2.2.2 RAS mutant type patients

The total theoretical costs (lowest, highest and average costs) for advanced CRC *RAS mutant* type patients are based on the theoretical pathways patients should follow through treatment as disease progression occurs (Figure 3.25 and Figure 3.26). The full range of costs for all capecitabine-containing regimen doses can be seen in Appendix M.

3.3.1.2.2.3 RAS wildtype patients

The total theoretical costs (lowest, highest and average costs) for advanced CRC *RAS mutant* type patients are based on the theoretical pathways patients should follow through treatment as disease progression occurs (Figure 3.27 and Figure 3.28). The full range of costs for all capecitabine-containing regimen doses can be seen in Appendix N.

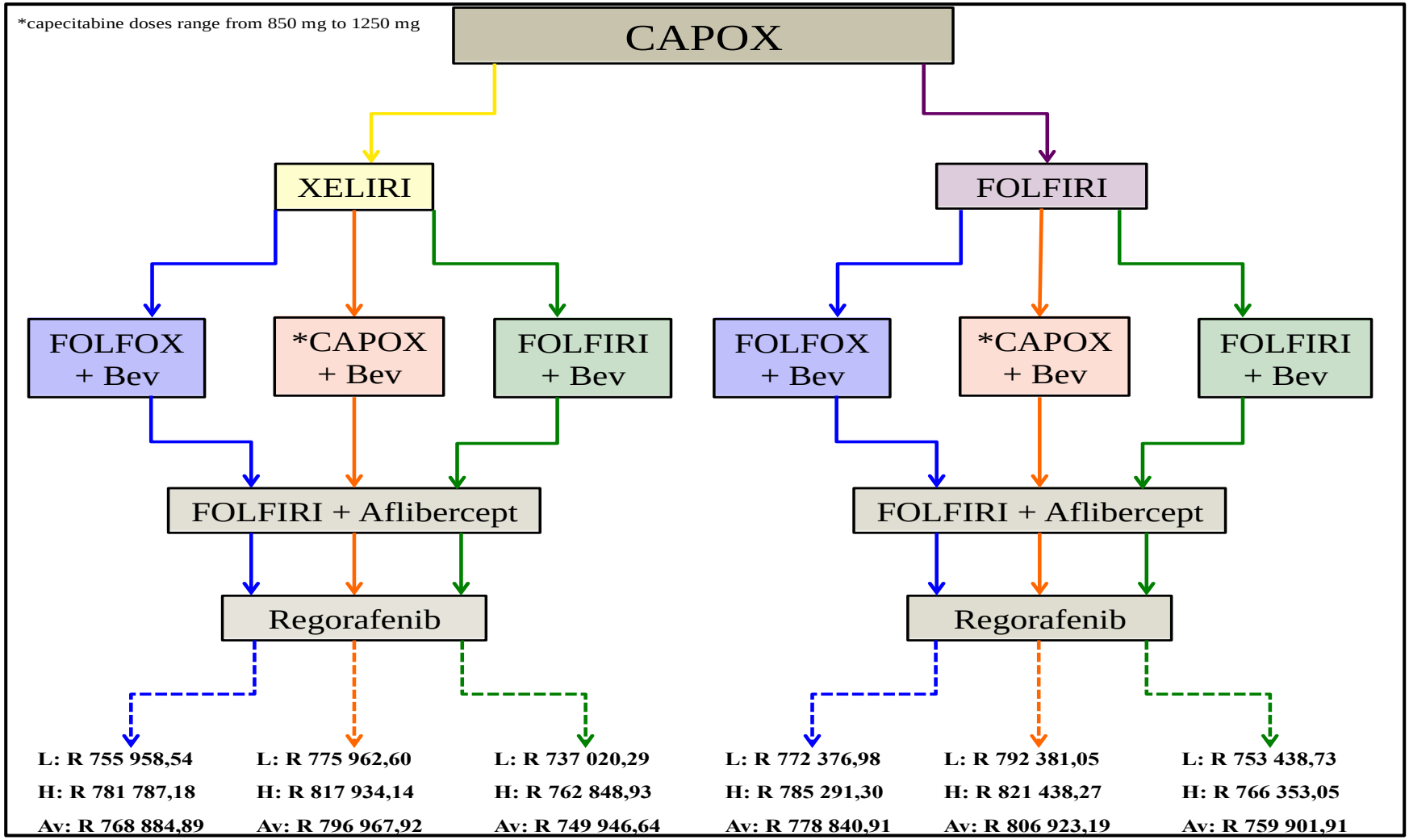


Figure 3.25 Total theoretical pathway costs for advanced CRC RAS mutant type patients starting treatment with CAPOX – Bev: Bevacizumab

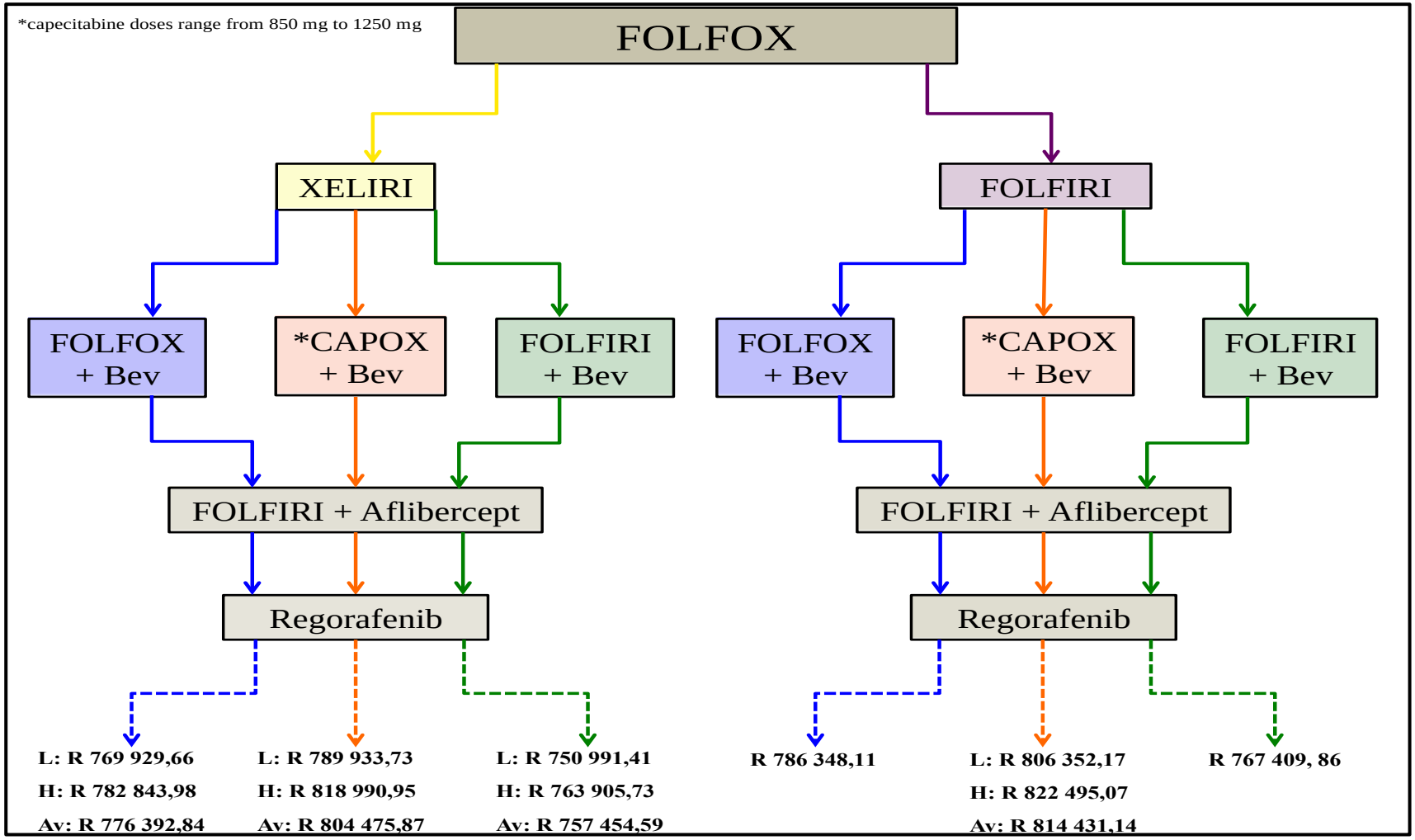


Figure 3.26 Total theoretical pathway costs for advanced CRC RAS mutant type patients starting treatment with FOLFOX - Bev: Bevacizumab

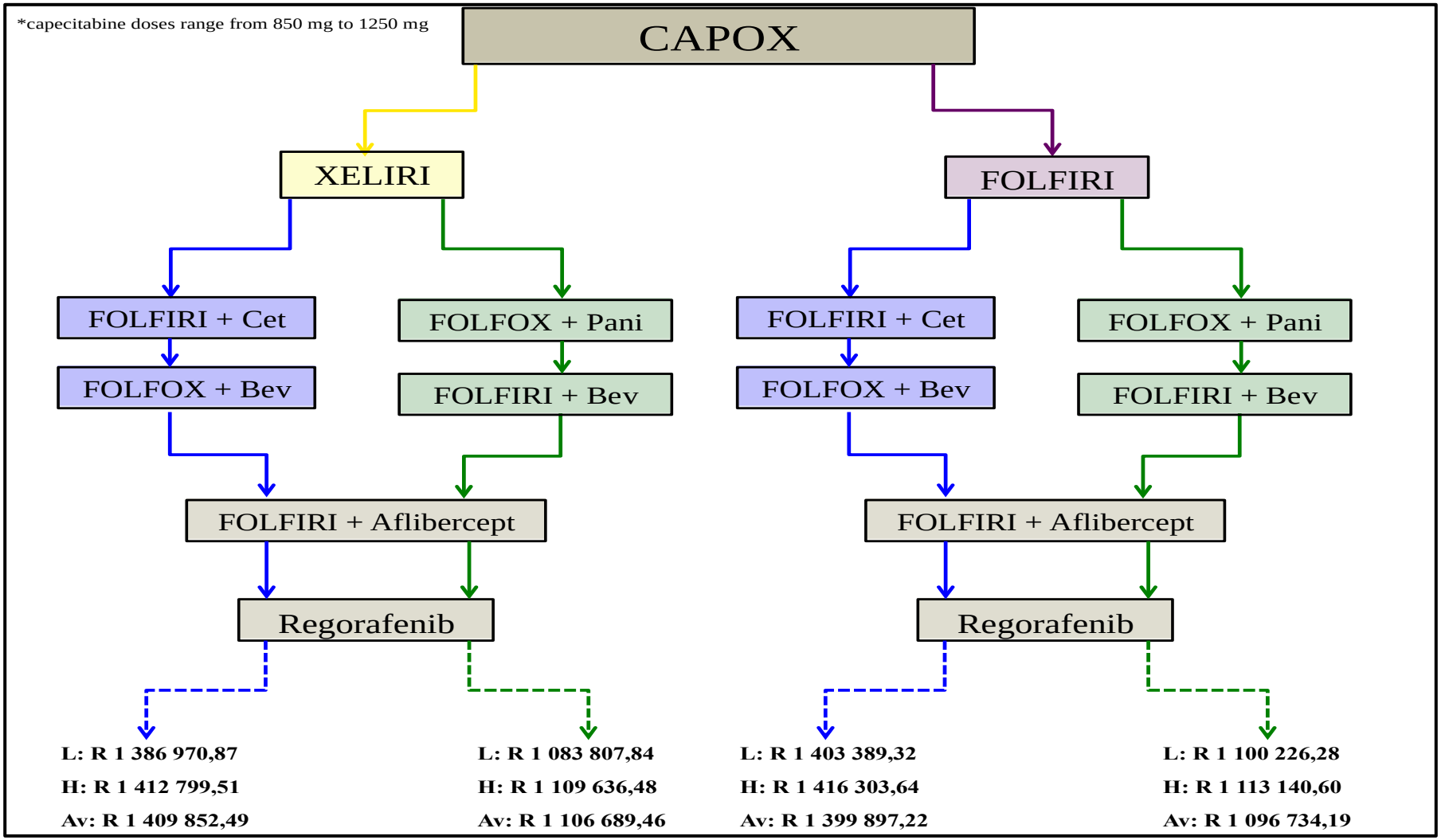


Figure 3.27 Total theoretical pathway costs for advanced CRC RAS wildtype patients starting treatment with CAPOX - Bev: Bevacizumab, Cet: Cetuximab, Pani: Panitumumab

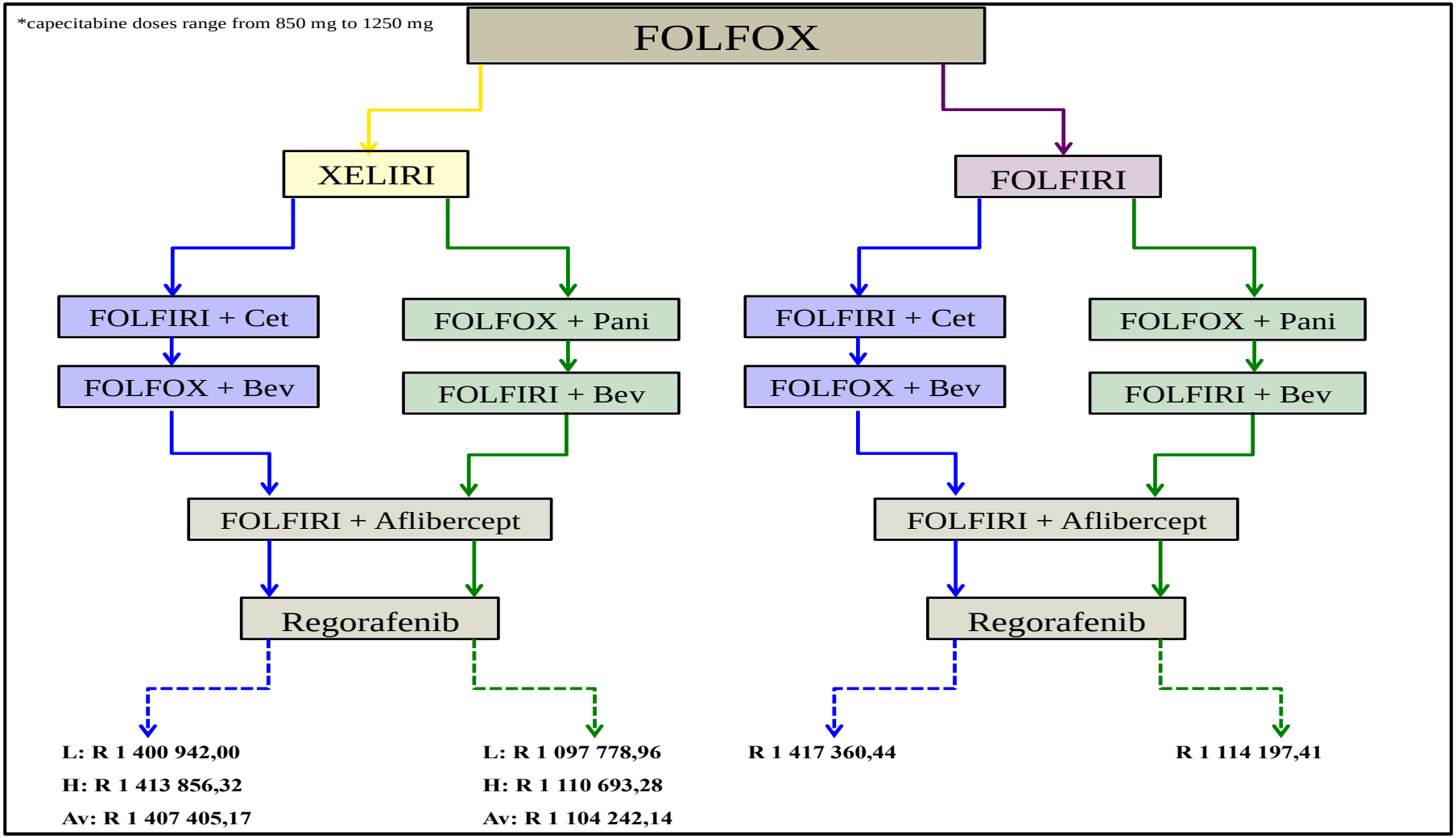


Figure 3.28 Total theoretical pathway costs for advanced CRC RAS wildtype patients starting treatment with FOLFOX - Bev: Bevacizumab, Cet: Cetuximab, Pani: Panitumumab

3.3.1.3 Observed treatment pathways for the public healthcare sector

3.3.1.3.1 Early CRC disease

3.3.1.3.1.1 Total costs per cycle

The cost per cycle is the same for a regimen provided the dosages are the same for either early CRC colon or rectal cancer (Figure 3.29). For this patient cohort, all calculated average dosages are the same as the recorded dosages per rectal cancer patient showed little variation to colon cancer patients thus it was decided to include the two groups to calculate one average dose per regimen which results in the same cost per cycle.

Chemotherapy costs have the largest contribution to the total costs and are expected particularly for regimens containing capecitabine however; supportive medicines don't appear to affect cost much. It is an unexpected result as it was thought that greater costs would be seen with supportive medicines but upon closer inspection, all these medicines are older medicines and prices per tablet are cheaper. The use of irinotecan and mitomycin-C was unexpected as these medicines have found to have no role in the adjuvant setting for the treatment of early CRC (Figure 3.29). This result is furthermore seen in Figure 3.30 where irinotecan and mitomycin-C have no theoretical costs therefore no comparison could be made.

The administrative fees calculated from the time and motion study (section 3.3.1.5.4.1.2) indicate a fair contribution for intravenously administrated regimens and is a large portion of regimens such as 5-FU + LV as these chemotherapy medicines are older and cheaper.

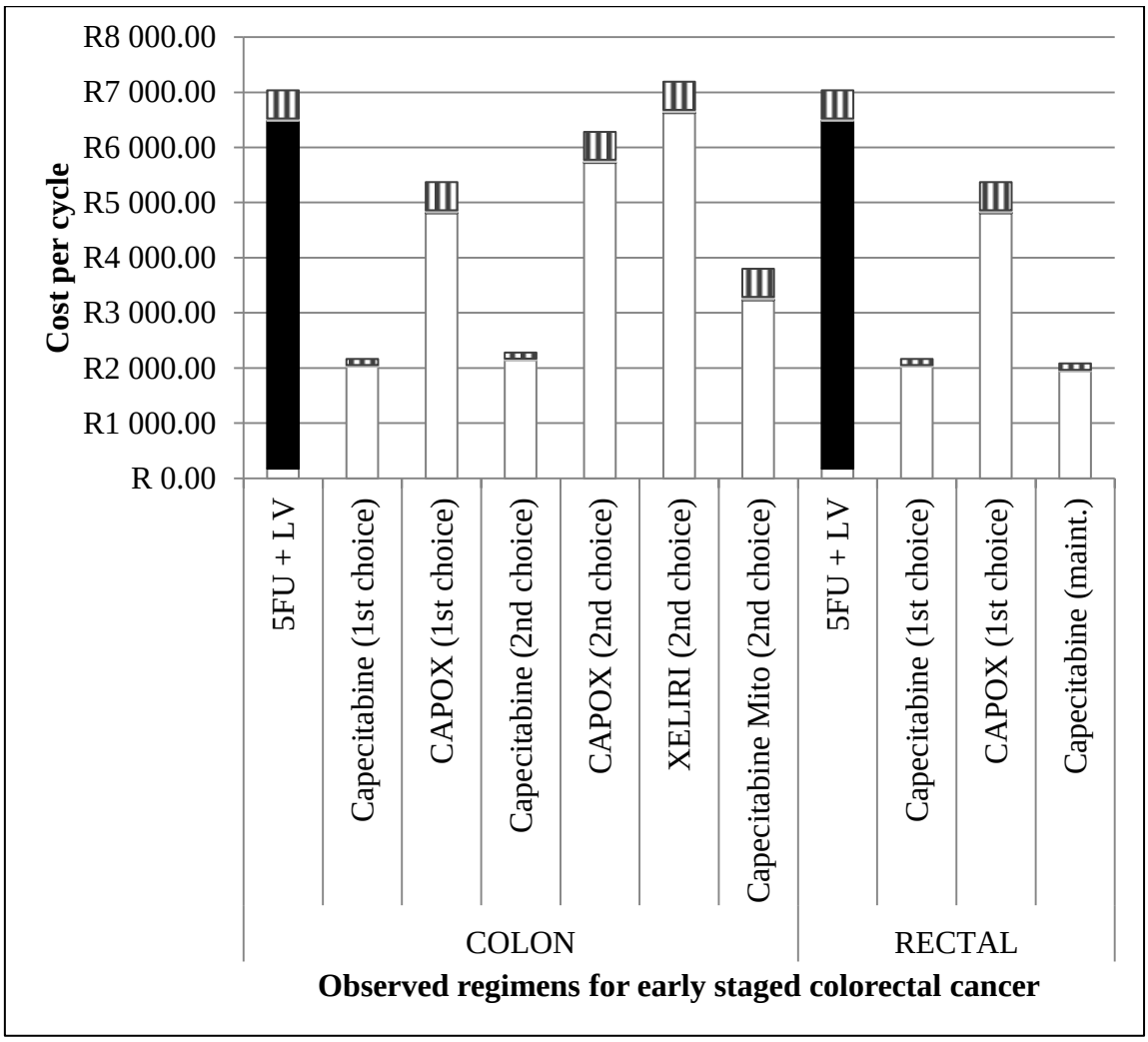


Figure 3.29 Cost per cycle for each chemotherapy regimen for early CRC colorectal cancer in the public healthcare sector- The cost per treatment regimen comprises of the comprises of the chemotherapy cost, administrative cost (grey stripe), supportive care medicine costs (grey) and administration costs (black). The total costs will not be less than this. The 1st and 2nd choices were based on a definite change in the patient's treatment regimen.

The greatest difference was observed in the number of cycles a regimen was administered and rectal cancer patients received fewer cycles therefore a lower total cost is expected as seen in Figure 3.30. Interestingly, not all the regimens used for colon cancer are used for rectal cancer and from this patient cohort; only colon cancer patients appear to be prescribed a 2nd choice treatment regimen. Capecitabine maintenance therapy was only administered for rectal cancer. Treatment regimens such as 5-FU + LV and capecitabine, given as a first regimen for treatment, are double the cost for colon cancer as opposed to rectal cancer. This is due to colon cancer patients in this cohort receiving double the number of cycles compared to rectal cancer patients. CAPOX prescribed as a first regimen however doesn't follow this trend and is much closer in cost. Reserved for high-risk patients, many patients were treated with CAPOX (section 3.2.1.2.1) and could account for the one cycle difference.

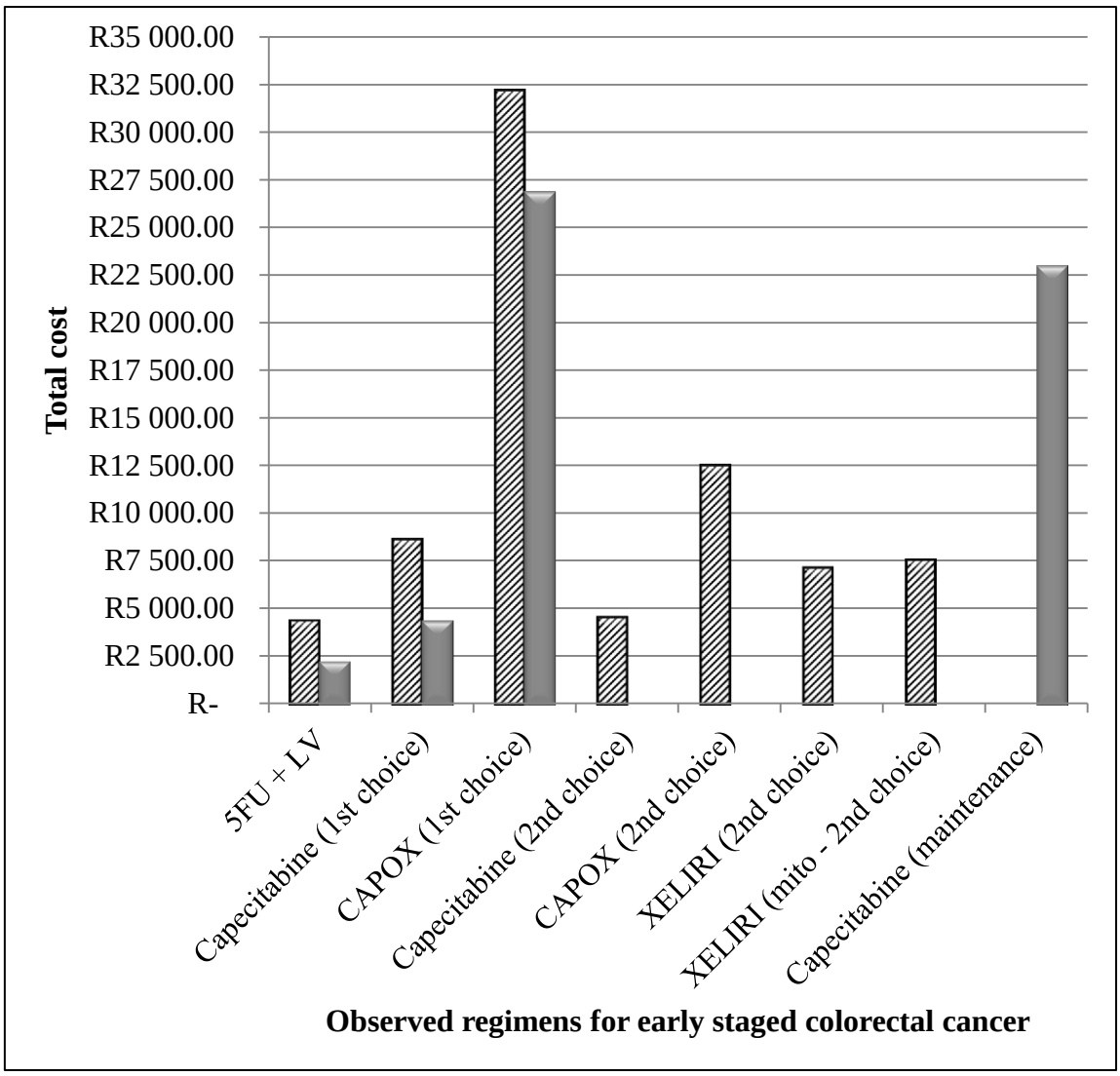


Figure 3.30 Total cost comparison per regimen for early CRC disease in the public healthcare sector – Early CRC colon cancer (black and white stripe) and early CRC rectal cancer (grey). The 1st and 2nd choices were based on a definite change in the patient's treatment regimen.

Table 3.18 Total observed costs per treatment regimen for early CRC in the public healthcare sector - The number of cycles is based on the average calculated from the patient cohort and the total cost is calculated by multiplying the cost per cycle with the number of cycles.

	COLON						
	5-FU + LV	**Capecitabine (1st choice)**	**CAPOX (1st choice)**	**Capecitabine (2nd choice)**	**CAPOX (2nd choice)**	**XELIRI (2nd choice)**	**Capecitabine Mito (2nd choice)**
Total treatment costs per cycle	R7 038,25	R2 168,25	R5 375,01	R2 284,20	R6 286,40	R7 192,28	R3 800,71
Number of cycles	6	4	6	2	2	1	2
Treatment costs per x cycles	**R 42 229,50**	**R 8 673,00**	**R 32 250,06**	**R 4 568,40**	**R 12 572,80**	**R 7 192,28**	**R7 601,42**

	RECTAL			
	5-FU + LV	**Capecitabine (1st choice)**	**CAPOX (1st choice)**	**Capecitabine (maint.)**
Total treatment costs per cycle	R7 038,25	R2 168,25	R5 375,01	R2 084,90
Number of cycles	3	2	5	11
Treatment costs per x cycles	**R21 114,75**	**R 4 336,50**	**R 26 875,05**	**R 22 933,90**

3.3.1.3.2 Advanced CRC disease

3.3.1.3.2.1 Total cost per cycle

Similarly to early CRC, most of the cost for majority of the regimens can be attributed to chemotherapy. In addition supportive medicines have less of an impact on the cost and the administrative fees are the same as for early CRC as per the time and motion study (section 3.3.1.5.4.1.2). Regimens that are the same as early CRC have higher chemotherapy costs per cycle and are attributed to an increase in observed chemotherapy dosages. This in turn increases the average dosage used in the calculations (Figure 3.31).

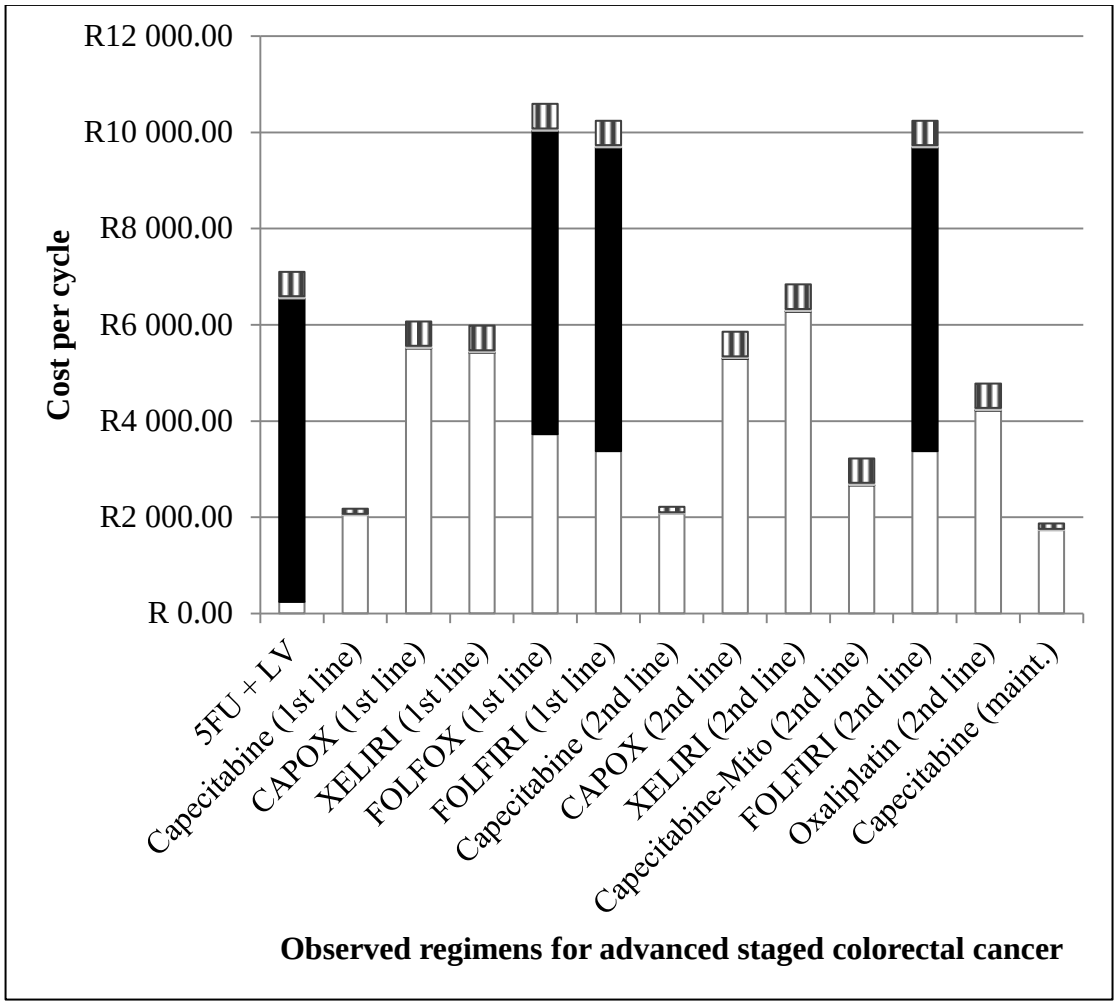


Figure 3.31 Cost per cycle for each chemotherapy regimen for advanced CRC patient group in the public healthcare sector- The cost per treatment regimen comprises of the comprises of the chemotherapy cost, administrative cost (grey stripe), supportive care medicine costs (grey) and administration costs (black). The costs used for irinotecan and mitomycin C are the lowest cost SEP as these were unavailable on the EML at the time. The total costs will not be less than this.

The total costs for advanced CRC disease per regimen are not always higher than early CRC disease as seen with 1st line capecitabine therapy for the advanced CRC sub-group when compared to 1st choice capecitabine regimens for early CRC. Other regimens such as 2nd line CAPOX are more than double the cost for advanced CRC when compared to patients receiving CAPOX as a 2nd choice regimen in early CRC (Table 3.19). Although XELIRI 2nd line also has a great increase, patients will pay for the irinotecan according to SEP therefore it is not unexpected to see an increase as much as 280%.

Table 3.19 Total costs per regimen for the public healthcare sector patient cohort for early CRC and advanced CRC disease with percentage change – shaded blocks indicate no regimen administered for that disease state. A negative percentage change (blue) indicates advanced CRC regimen is cheaper and changes greater than 100% are marked red.

Regimen	Early Colon Cancer	Early Rectum Cancer	Advanced CRC	% change - colon to Advanced CRC	% change - rectum to Advanced CRC
5-FU + LV	R4 403,88	R2 201,94	R4 764,48	8%	116%
Capecitabine (1st line/choice)	R8 673,00	R4 336,50	R6 532,98	-25%	51%
CAPOX (1st line/choice)	R32 193,54	R26 827,95	R36 353,16	13%	36%
FOLFOX (1st line)			R26 679,46		
FOLFIRI (1st line)			R27 512,10		
XELIRI (1st line)			R5 969,24		
Capecitabine (2nd line/choice)	R4 568,40		R6 643,89	45%	
CAPOX (2nd line/choice)	R12 553,96		R35 059,56	179%	
FOLFIRI (2nd line)			R27 512,10		
XELIRI (2nd line/choice)	R7 182,86		R27 306,92	280%	
XELIRI-mito (2nd line/choice)	R7 582,58		R6 421,42	-15%	
Oxaliplatin (2nd line)			R28 618,20		
Capecitabine (maintenance)		R22 933,90	R26 134,92		14%

Table 3.20 Total observed costs per treatment regimen for advanced CRC in the public healthcare sector - The number of cycles is based on the average calculated from the patient cohort and the total cost is calculated by multiplying the cost per cycle with the number of cycles.

	Advanced CRC					
	5-FU + LV	**Capecitabine (1st line)**	**CAPOX (1st line)**	**XELIRI (1st line)**	**FOLFOX (1st line)**	**FOLFIRI (1st line)**
Total treatment costs per cycle	R7 098,35	R2 177,66	R6 068,28	R5 978,66	R10 587,39	R10 237,78
Number of cycles	6	3	6	1	6	7
Treatment costs per x cycles	**R 42 590,10**	**R 6 532,98**	**R 36 409,68**	**R 5 978,66**	**R 63 524,34**	**R 71 664,46**

	Advanced CRC						
	Capecitabine (2nd line)	**CAPOX (2nd line)**	**XELIRI (2nd line)**	**Capecitabine-Mito (2nd line)**	**FOLFIRI (2nd line)**	**Oxaliplatin (2nd line)**	**Capecitabine (maint.)**
Total treatment costs per cycle	R2 214,63	R5 852,68	R6 836,15	R3 220,13	R10 237,78	R4 779,12	R1 866,78
Number of cycles	3	6	4	2	7	6	14
Treatment costs per x cycles	**R 6 643,89**	**R 35 116,08**	**R 27 344,60**	**R6 440,26**	**R71 664,46**	**R 28 674,72**	**R 26 134,92**

Table 3.21 Total costs per regimen for the public healthcare sector patient cohort and theoretical costs for early CRC and advanced CRC disease with percentage change – shaded blocks indicate no regimen administered for that disease state. A negative percentage change (blue) indicates advanced CRC regimen is cheaper and changes greater than 100% are marked red.

Regimen	Early Colon Cancer Cohort	Early Colon Cancer Theoretical	% change	Early Rectum Cancer Cohort	Early Rectum Cancer Theoretical	% change	Advanced CRC Cohort	Advanced CRC Theoretical	% change
5-FU + LV	R4 403,88	R6 629,47	51%	R2 201,94	R4 419,65	101%	R4 764,48	R6 629,47	39%
Capecitabine (1st line/choice)*	R8 673,00	R16 417,70	89%	R4 336,50			R6 532,98		
CAPOX (1st line/choice)*	R32 193,54	R36 745,34	14%	R26 827,95			R36 353,16	R36 745,34	1%
FOLFOX (1st line/choice)		R38 979,69					R26 679,46	R19 489,84	-27%
FOLFIRI (1st line)							R27 512,10		
XELIRI (1st line)							R5 969,24		
Capecitabine (2nd line/choice)*	R4 568,40	R16 417,70	259%				R6 643,89		
CAPOX (2nd line/choice)*	R12 553,96	R36 745,34	193%				R35 059,56	R36 745,34	5%
FOLFOX (2nd line)								R32 483,07	
FOLFIRI (2nd line)							R27 512,10		
XELIRI (2nd line/choice)	R7 182,86						R27 306,92		
XELIRI-mito (2nd line/choice)	R7 582,58						R6 421,42		
Oxaliplatin (2nd line)							R28 618,20		
Capecitabine (maintenance)*				R22 933,90			R26 134,92		

*lowest theoretical dose of capecitabine

3.3.1.4 Observed treatment pathways for the private healthcare sector

3.3.1.4.1 Early CRC disease

The cost per cycle for the observed regimens (Figure 3.32) indicates that the largest component of the cost per cycle is due to the chemotherapy particularly for multiple medicine regimens.

Although all the regimens in Figure 3.32 are for early CRC disease, the classification of patients by origin (colon or rectum) was not known thus the cost per cycle in the private sector differs to the public sector for early staged disease. In addition a number of unproven treatments were prescribed. These include 5-azacitadine which is commonly used in the treatment of Myelodysplastic Syndromes (MDS) or fludarabine which is mainly indicated for treatment of Chronic Lymphocytic Leukaemia (CLL) (all these regimens are highlighted in Table 3.22) (Figure 3.32; Table 3.22). This may be due to the presence of a second cancer or off-label use.

The lowest contributors to the cost include the supportive medicines. Although the supportive medicines only included classes of medicines available in the public sector, there were many additional medicines claimed. Most notably was the costs attributed to pain management. The regimens with the highest costs are the regimens where unproven colorectal cancer chemotherapy was prescribed. The total costs for the early CRC patient group can be seen in Table 3.22.

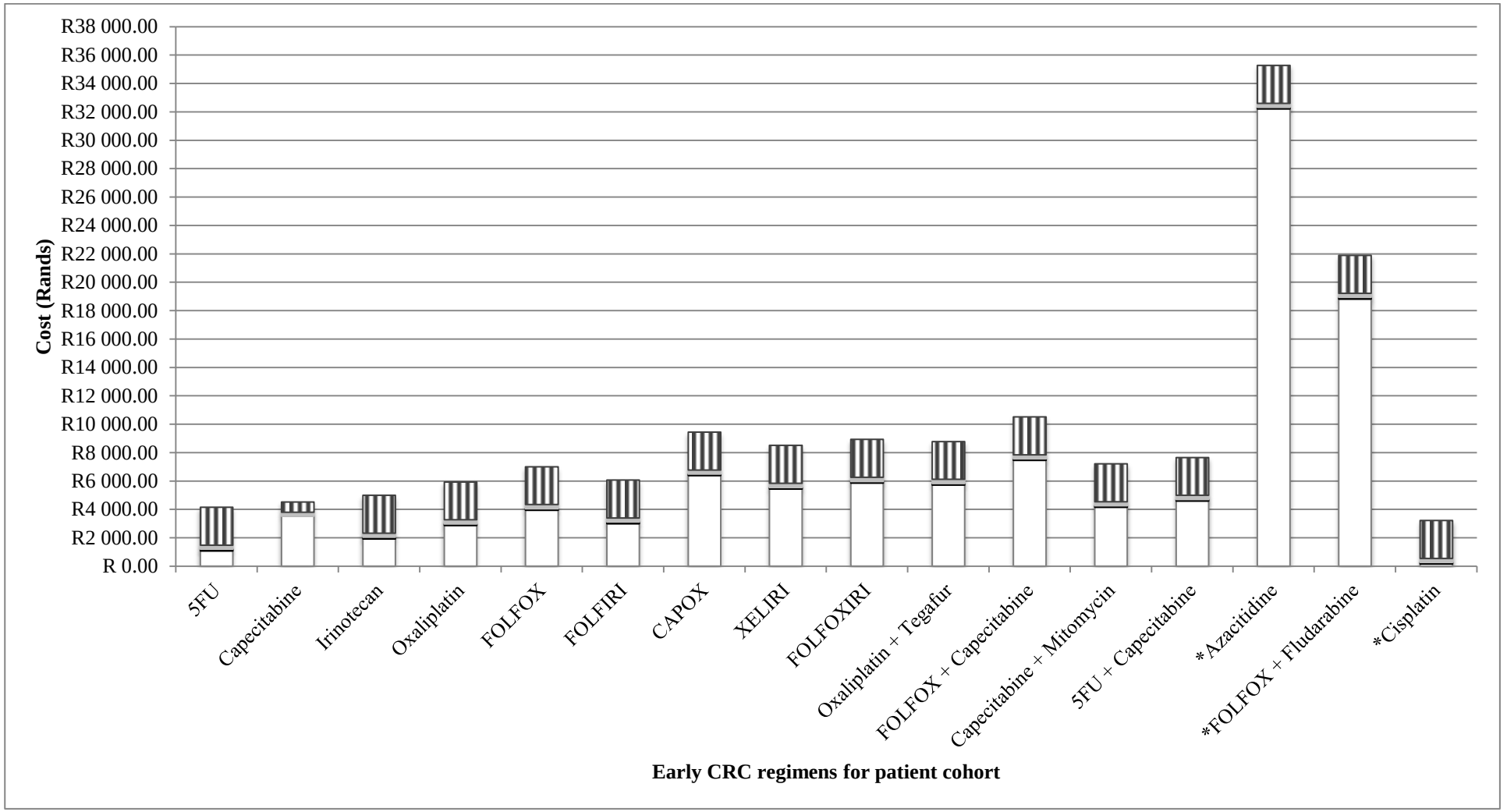


Figure 3.32 Cost per cycle of each early CRC regimen observed in the private healthcare sector – Chemotherapy costs; Administration costs (black); supportive care medicines (light grey) and administrative costs (dark grey stripe); *unconventional CRC treatment

Table 3.22 Total cost per chemotherapy regimen for early CRC patient group – regimens highlighted in grey are not conventional CRC treatments

Chemotherapy regimens	Cost per cycle	Number of cycles	Total cost
5-FU	R4 140,13	5	**R20 700,64**
Capecitabine	R4 523,06	5	**R22 615,31**
Irinotecan	R4 989,28	3	**R14 967,85**
Oxaliplatin	R5 928,36	2	**R11 856,72**
FOLFOX	R7 002,21	8	**R56 017,71**
FOLFIRI	R6 063,14	8	**R48 505,12**
CAPOX	R9 441,45	5	**R47 207,27**
XELIRI	R8 502,38	5	**R42 511,90**
FOLFOXIRI	R8 925,23	1	**R8 925,23**
Oxaliplatin + Tegafur	R8 775,77	7	**R61 430,41**
FOLFOX + Capecitabine	R10 515,31	1	**R10 515,31**
Capecitabine + Mitomycin	R7 209,11	2	**R14 418,21**
5-FU + Capecitabine	R7 653,22	1	**R7 653,22**
Azacitidine	R35 269,17	4	**R141 076,69**
FOLFOX + Fludarabine	R21 887,05	1	**R21 887,05**
Cisplatin	R3 218,31	4	**R12 873,25**

1.1.1.1.2 Advanced CRC disease

Similarly to the early CRC group of patients, the cost per cycle for the observed advanced CRC regimens (Figure 3.33) indicates the large component chemotherapy contributes to the cycle cost.

Similarly to the early CRC disease observations, patients were found to receive treatments not indicated for CRC. These include tretinion+idarubicin for the treatment of Acute Promyelocytic Leukemia (APL), carboplatin+paclitaxel for non-small cell lung cancer and ovarian cancer; cisplatin+gemcitabine for relapsed breast cancer and biliary tract cancer to name a few. This again indicates that patients either were treated for a secondary cancer or the treatment was off-label (Figure 3.33; Table 3.23).

The total costs in Table 3.23 are lower for certain regimens when compared to the early CRC group however, there are more regimens observed. The total costs are lower than the early CRC group as patients with advanced disease were observed to experience treatment changes before the same number of cycles for a specific regimen was reached. This is most likely due to disease progression due to lack of response to by the specific regimen thereby requiring a change in treatment regimen. Biological medicines such as bevacizumab and cetuximab are

also included indicating patients move through multiple regimens quicker and this does increase cost.

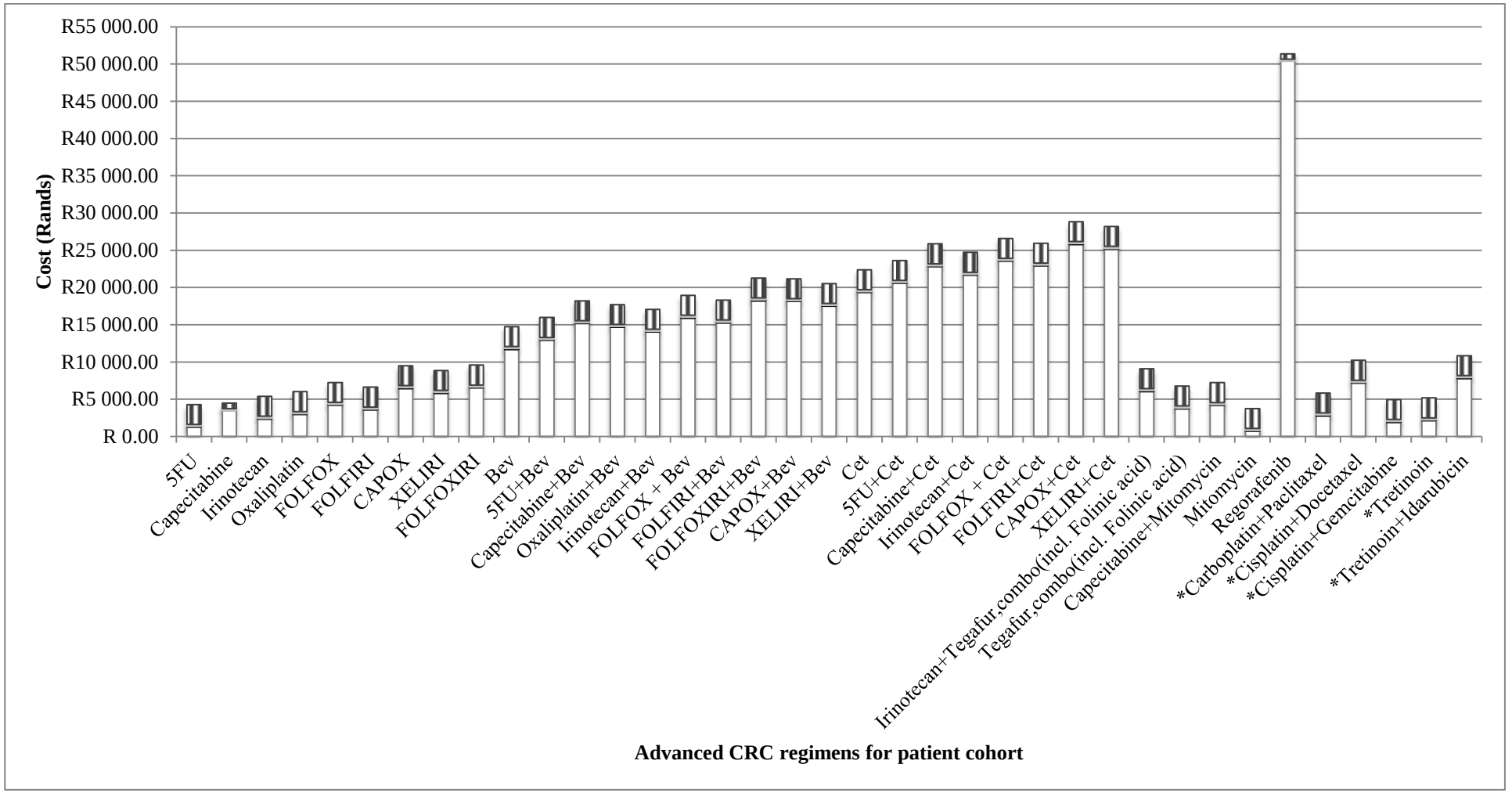


Figure 3.33 Cost per cycle of each advanced CRC regimen observed in the private sector – Chemotherapy costs; Administration costs (black); supportive care medicines (light grey) and administrative costs (dark grey stripe) *unconventional CRC treatment

3.3.1.4.1.1 Total costs

Table 3.23 Total cost per chemotherapy regimen for advanced CRC patient group – regimens highlighted in grey are not conventional CRC treatments

Chemotherapy regimens	Cost per cycle	Number of cycles	Total cost
5-FU	R4 278,53	5	**R21 392,64**
Capecitabine	R4 464,41	4	**R17 857,64**
Irinotecan	R5 375,09	3	**R16 125,26**
Oxaliplatin	R6 010,16	2	**R12 020,33**
FOLFOX	R7 244,77	7	**R50 713,38**
FOLFIRI	R6 609,69	6	**R39 658,15**
CAPOX	R9 480,93	4	**R37 923,71**
XELIRI	R8 845,85	5	**R44 229,24**
FOLFOXIRI	R9 575,93	8	**R76 607,46**
Bev	R14 727,73	3	**R44 183,18**
5-FU+Bev	R15 962,33	4	**R63 849,32**
Capecitabine+Bev	R18 198,49	5	**R90 992,44**
Oxaliplatin+Bev	R17 693,97	3	**R53 081,90**
Irinotecan+Bev	R17 058,89	5	**R85 294,44**
FOLFOX + Bev	R18 928,57	7	**R132 500,01**
FOLFIRI+Bev	R18 293,49	6	**R109 760,97**
FOLFOXIRI+Bev	R21 259,74	1	**R21 259,74**
CAPOX+Bev	R21 164,73	5	**R105 823,65**
XELIRI+Bev	R20 529,65	6	**R123 177,91**
Cet	R22 379,26	5	**R111 896,30**
5-FU+Cet	R23 613,87	3	**R70 841,60**
Capecitabine+Cet	R25 850,02	1	**R25 850,02**
Irinotecan+Cet	R24 710,42	5	**R123 552,12**
FOLFOX + Cet	R26 580,11	5	**R132 900,54**
FOLFIRI+Cet	R25 945,03	6	**R155 670,18**
CAPOX+Cet	R28 816,26	4	**R115 265,06**
XELIRI+Cet	R28 181,19	4	**R112 724,75**
Irinotecan+Tegafur,combo (incl. Folinic acid)	R9 084,37	2	**R18 168,73**
Tegafur,combo (incl. Folinic acid)	R6 753,20	1	**R6 753,20**
Capecitabine+Mitomycin	R7 217,26	3	**R21 651,77**
Mitomycin	R3 746,49	2	**R7 492,99**
Regorafenib	R51 367,81	2	**R102 735,63**
Carboplatin+Paclitaxel	R5 818,07	4	**R23 272,29**
Cisplatin+Docetaxel	R10 214,65	4	**R40 858,62**
Cisplatin+Gemcitabine	R4 942,29	1	**R4 942,29**
Tretinoin	R5 163,77	6	**R30 982,62**
Tretinoin+Idarubicin	R10 823,98	2	**R21 647,97**

Table 3.24 Total costs per regimen for the private sector patient cohort for early CRC and advanced CRC disease with percentage change – shaded blocks indicate no regimen administered for that disease state. A negative percentage change (blue) indicates advanced CRC regimen is cheaper and changes greater than 100% are marked red. The percentage change is an indication that the cost differences, between regimens prescribed for either early or advanced CRC, is a result of the difference in dose or the number of cycles received.

Regimen	Early CRC	Advanced CRC	% change	Regimen	Early CRC	Advanced CRC	% change
5-FU	R20 700,64	R21 392,64	3,34%	**FOLFIRI+Bev**		R109 760,97	
Capecitabine	R22 615,31	R17 857,64	-21,04%	**FOLFOXIRI+Bev**		R21 259,74	
Azacitidine	R141 076,69			**CAPOX+Bev**		R105 823,65	
Irinotecan	R14 967,85	R16 125,26	7,73%	**XELIRI+Bev**		R123 177,91	
Oxaliplatin	R11 856,72	R12 020,33	1,38%	**Cet**		R111 896,30	
FOLFOX	R56 017,71	R50 713,38	-9,47%	**5-FU+Cet**		R70 841,60	
FOLFIRI	R48 505,12	R39 658,15	-18,24%	**Capecitabine+Cet**		R25 850,02	
CAPOX	R47 207,27	R37 923,71	-19,67%	**Irinotecan+Cet**		R123 552,12	
XELIRI	R42 511,90	R44 229,24	4,04%	**FOLFOX + Cet**		R132 900,54	
FOLFOXIRI	R8 925,23	R76 607,46	758,33%	**FOLFIRI+Cet**		R155 670,18	
Oxaliplatin + Tegafur	R61 430,41			**CAPOX+Cet**		R115 265,06	
FOLFOX + Fludarabine	R21 887,05			**XELIRI+Cet**		R112 724,75	
FOLFOX + Capecitabine	R10 515,31			**Carboplatin+Paclitaxel**		R23 272,29	
Capecitabine + Mitomycin	R14 418,21	R21 651,77	50,17%	**Cisplatin+Docetaxel**		R40 858,62	
Cisplatin	R12 873,25			**Cisplatin+Gemcitabine**		R4 942,29	
5-FU + Capecitabine	R7 653,22			**Irinotecan+Tegafur,**		R18 168,73	
Bev		R44 183,18		**Tegafur,combo**		R6 753,20	
5-FU+Bev		R63 849,32		**Tretinoin**		R30 982,62	
Capecitabine+Bev		R90 992,44		**Tretinoin+Idarubicin**		R21 647,97	
Oxaliplatin+Bev		R53 081,90		**Mitomycin**		R7 492,99	
Irinotecan+Bev		R85 294,44		**Regorafenib**		R102 735,63	
FOLFOX + Bev		R132 500,01					

Table 3.25 Total costs per regimen for the private sector patient cohort and theoretical costs for early CRC and advanced CRC disease with percentage change – shaded blocks indicate no regimen administered for that disease state. A negative percentage change (blue) indicates cohort regimen is cheaper and changes greater than 100% are marked red. The percentage change is an indication that the cost differences, between regimens prescribed in the cohort and the theoretical calculations, is a result of the dose or the number of cycles received. This is also an indication that patients often receive less treatment than the literature states due to individual response to treatment.

Regimen	Early CRC Cohort	Early CRC Theoretical[1]	% change	Advanced CRC Cohort	Advanced Theoretical[1]	% change
5-FU	R20 700,64	R25 242,54	21,94%	R21 392,64	R25 242,54	18,00%
Capecitabine*	R22 615,31	R35 709,18	57,90%	R17 857,64	R35 709,16	99,97%
Azacitidine	R141 076,69					
Irinotecan	R14 967,85			R16 125,26		
Oxaliplatin	R11 856,72			R12 020,33		
FOLFOX	R56 017,71	R89 923,10	60,53%	R50 713,38	R89 923,10	77,32%
FOLFIRI	R48 505,12			R39 658,15	R97 265,06	145,26%
CAPOX*	R47 207,27	R75 952,00	60,89%	R37 923,71	R75 952,00	100,28%
XELIRI*	R42 511,90	R80 846,64	90,17%	R44 229,24	R80 846,64	82,79%
FOLFOXIRI	R8 925,23			R76 607,46		
Oxaliplatin + Tegafur	R61 430,41					
FOLFOX + Fludarabine	R21 887,05					
FOLFOX + Capecitabine	R10 515,31					
Capecitabine + Mitomycin	R14 418,21			R21 651,77		
Cisplatin	R12 873,25					
5-FU + Capecitabine	R7 653,22					
Bev				R44 183,18		
5-FU+Bev				R63 849,32		
Capecitabine+Bev				R90 992,44		
Oxaliplatin+Bev				R53 081,90		
Irinotecan+Bev				R85 294,44		
FOLFOX + Bev				R132 500,01	R222 238,43	67,73%

FOLFIRI+Bev				R109 760,97	R203 300,18	85,22%
FOLFOXIRI+Bev				R21 259,74		
CAPOX+Bev*				R105 823,65	R242 242,49	128,91%
XELIRI+Bev				R123 177,91		
Cet				R111 896,30		
5-FU+Cet				R70 841,60		
Capecitabine+Cet				R25 850,02		
Irinotecan+Cet				R123 552,12		
FOLFOX + Cet				R132 900,54		
FOLFIRI+Cet				R155 670,18	R653 621,56	319,88%
CAPOX+Cet				R115 265,06		
XELIRI+Cet				R112 724,75		
Carboplatin+Paclitaxel				R23 272,29		
Cisplatin+Docetaxel				R40 858,62		
Cisplatin+Gemcitabine				R4 942,29		
Irinotecan+Tegafur				R18 168,73		
Tegafur,combo				R6 753,20		
Tretinoin				R30 982,62		
Tretinoin+Idarubicin				R21 647,97		
Mitomycin				R7 492,99		
Regorafenib				R102 735,63	R161 404,29	57,11%

1 average cost for both types of facilities
* Lowest theoretical dose of capecitabine

3.3.1.5 Cost components used in cost calculations

3.3.1.5.1 Chemotherapy costs

Table 3.26 indicates the costs (Rands) that were used in the calculations for the theoretical and observed costs for each healthcare sector. In the costing model the lowest cost SEP (private sector) was compared to the EML (public sector) cost. Using the model for the chemotherapy costs (section 2.3.4.1), the total costs for the chemotherapy medicine per cycle can be seen in Appendix O.

Table 3.26 Chemotherapy costs per pack size for the public sector (EML, Feb 2014) and the private sector (SEP, Aug 2014) - Ramucirumab and trifluridine/tipiracil are unavailable in South Africa, *only originators available and therefore one price for both sectors**.**

Chemotherapy (vial size/pack size)	Cost for the Public Sector	Cost for the Private Sector		
		Lowest	Highest	Average
5-FU (10ml)	R15,05	R15,66	R28,30	R21,98
*Bevacizumab				
(4ml)	N/A			R3 682,56
(16ml)				R14 730,25
*Capecitabine				
(150mg 60 tabs)	R413,54			R743,93
(500mg 120 tabs)	R2 782,42			R5 005,51
*Cetuximab (20ml)	N/A			2 897,69
Irinotecan				
(20mg/ml)	N/A	R370,50	R370,50	R370,50
(100mg/5ml)		R934,80	R2 563,58	R1 194,13
Folinic acid				
(30ml)	R180,00			R552,00
(10ml)	N/A			R184,00
(50mg/vial)	R30,00			N/A
Oxaliplatin				
(10ml)	R702,68	R974,13	R1 794,62	R1 418,11
(20ml)	R1 405,34	R1 948,26	R3 589,22	R3 228,19
*Panitumumab (5ml)	N/A			R7 170,97
*Regorafenib (40mg 28 tabs)	N/A			R52 782,91
*Aflibercept				
(100mg)	N/A			R5 280,31
(200mg)				R10 560,62

3.3.1.5.2 Supportive care medicine costs

Table 3.27 indicates the supportive care medicine costs that were used in the calculations for each sector. In the costing model the average lowest cost SEP (private sector) was compared to the average EML (public sector) cost due to the number of combination possibilities. Using the model for the supportive care medicine costs (section 2.3.4.3), the average costs for supportive care medicines for both sectors can be seen in Table 3.28. The private sector costs are based on the lowest SEP costs in order for comparisons to be made. The supportive care medicine costs per cycle are the same no matter the stage of the cancer and are represented by regimen (Table 3.28).

Table 3.27 Theoretical supportive care medicine costs per pack size for the public sector (EML, Feb 2014) and the private sector (SEP, Aug 2014) - the observed costs were obtained from the respective patient cohorts.

Supportive care medicine (vial size/*pack size)	**Cost for the Public Sector**	**Cost for the Private Sector**		
		Lowest	**Highest**	**Average**
Ondansetron				
(4mg vial)	R4,45	R51,30	R247,08	R178,24
(8mg vial)	R7,15	R102,60	R494,16	R321,97
(4mg 5 tabs)	N/A	R96,19	R150,43	R123,31
(4mg 10 tabs)	R15,38	R144,72	R182,02	R159,97
(4mg 15 tabs)	N/A	R451,30	R665,66	R558,48
(4mg 30 tabs)	N/A	R192,39	R192,39	R192,39
(8mg 5 tabs)	N/A	R192,33	R192,33	R192,33
(8mg 10 tabs)	R16,90	R289,47	R364,03	R319,94
(8mg 15 tabs)	N/A	R709,74	R1 050,65	R880,19
(8mg 30 tabs)	N/A	R384,66	R384,66	R384,66
Granisetron				
(1mg vial)	N/A	R151,62	R425,53	R225,26
(3mg vial)	R63,28	R545,63	R854,78	R635,31
(1mg 10 tabs)	N/A	R178,84	R779,24	R389,03
(2mg 5 tabs)	N/A	R291,01	R799,75	R456,59
Palonosetron (50mcg/ml)	N/A			R465,14
Dexamethasone (4mg vial)	R4,01	R76,00	R441,38	R173,59
Prednisone				
(5mg 100 tabs)	R10,51			
(5mg 40 tabs)	R4,00			N/A
(5mg 500 tabs)	R41,53			
(5mg 5000 tabs)	R410,11			
Metoclopramide				
(10mg/2ml vial)	N/A	R25,35	R92,94	R54,94
(10mg 20 tabs)	N/A	R3,34	R42,47	R16,80
(10mg 100 tabs)	R6,63	R16,71	R212,28	R114,50
(10mg 500 tabs)	R19,45	R44,97	R143,48	R74,62
(10mg 1000 tabs)	N/A	R131,81	R131,81	R131,81
Prochlorperazine				
(12,5mg/ml vial)	N/A	R129,32	R129,32	R129,32
(5mg 25 tabs)		R70,68	R70,68	R70,68
(5mg 250 tabs)		R169,53	R617,88	R393,71
(5mg 500 tabs)		R82,46	R82,46	R82,46
Aprepitant (COMBO PACK)	N/A			R714,71

* Pack sizes were used to calculate the cost per tablet and subsequently lowest, highest and average cost per tab. These costs were then used in the costing model; [1] Not currently used

Table 3.28 Average theoretical supportive medicine costs per cycle for each sector – the observed costs were obtained from the respective patient cohorts

Public sector average supportive medicine costs	
Regimen	*Average cost*
5-FU + LV or Capecitabine	R25,21
FOLFOX or CAPOX	R60,59
Private sector average lowest SEP supportive medicine costs	
Regimen	*Average cost*
5-FU + LV or Capecitabine or Regorafenib	R242,23
FOLFOX or CAPOX*	R606,34
FOLFIRI or XELIRI*	R965,66

* Same cost if a biologic is included in the regimen

The average supportive medicine costs per cycle are more costly in the private sector than the public sector for the same regimens. This is largely due to the medicine procurement in the public sector, as explained in section 1.5.7.1.3 and the medicine selection in the private sector as explained in section 0.

3.3.1.5.3 Administration costs

The administration costs used for the theoretical and observed pathways were based on the drug utilisation data obtained from each healthcare sector. The administration costs or the public healthcare sector included administration items such as ports, syringes and needles etc. and the admixtures and flush for intravenous administration (Table 3.29). The private sector costs differed in that it only included admixture and flush costs as the data only accounted for medicine costs. The costs for syringes and needles, swabs and cotton wool as well as dressing are included in the facility fees that patients will be charged for. The average costs per cycle for administration can be seen in Table 3.30.

Table 3.29 Total administration cost in the public healthcare sector

Total administration cost						
	5FU+LV	**Capecitabine**	**FOLFOX**	**CAPOX**	**FOLFIRI**	**XELIRI**
Administration component	R6 251,75	NA	R 6 251,75	R 6,21	R 6 251,75	R 6,21
Admixtures + Flush	R52,52		R55,73	R3,21	R55,73	R3,21
Total cost per cycle	**R6 304,27**		**R 6 307,48**	**R 9,42**	**R 6 307,48**	**R 9,42**

Table 3.30 Total administration cost per cycle for the private healthcare sector

Total administration cost per cycle	
Early CRC disease regimens	R 114,06
Advanced CRC disease regimens	R108,03

3.3.1.5.4 Administrative costs

3.3.1.5.4.1 Time and Motion Study for the public healthcare sector

3.3.1.5.4.1.1 Work flow diagram for CMJAH

Following clinical observations, the final workflow diagram was drawn up and includes 8 steps (includes laboratory processes) performed by 4 different professionals (Figure 3.34). The workflow diagram shows the processes the clinic has in place in which a patient will follow in order to receive their chemotherapy. Patients, who are on oral chemotherapy regimens, will not follow the last two steps in the procedure.

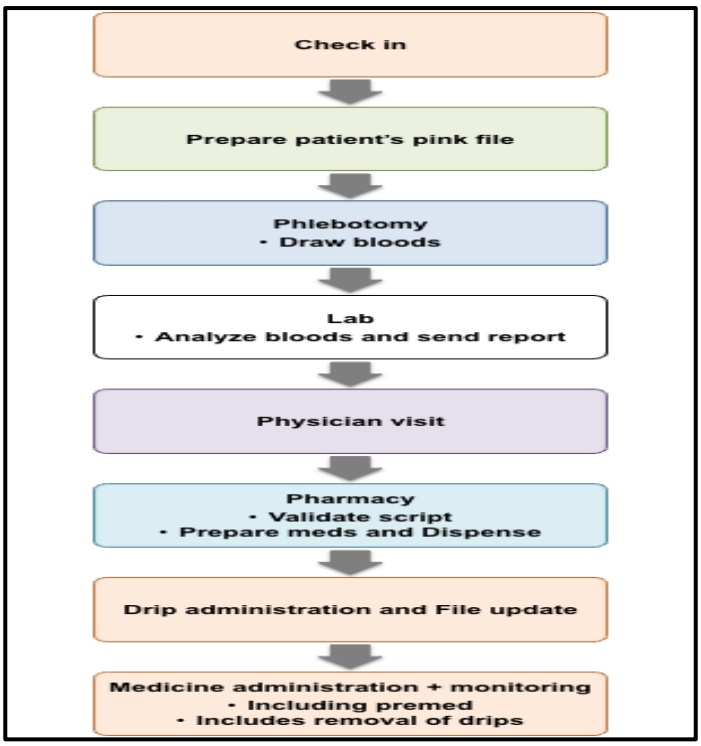


Figure 3.34 Workflow diagram for CMJAH Oncology Clinic – Orange: Oncology Nurse, Green: Administrative clerk, Blue: NHLS Nurse, Purple: Oncologist, Turquoise: Pharmacist. The laboratory work is excluded (this entails the analysis of the blood obtained from phlebotomy), as this does not form part of the duty of the oncology clinic.

3.3.1.5.4.1.2 Calculated costs

Table 3.31 shows the overall average time (minutes) and costs (Rands). The initial readings and salary calculations can be found in Appendix P.

Table 3.31 Average time (minutes) with the associated costs (Rands) - Orange: Oncology Nurse, Green: Administrative clerk, Blue: NHLS Nurse, Purple: Oncologist, Turquoise: Pharmacist. The *laboratory work is excluded as this does not form part of the duty of the oncology clinic however the blood results take on average 2:15:00. This average time was provided by the oncology nurses and physicians at the clinic.

Task	Overall Ave.	Std. Dev.	Final Ave.	Cost (Rands)	Total Costs
Check-in	00:01:38	00:00:38	00:02:00	R5, 27	**R111, 64 (Oral script)**
Pink file	00:01:08	00:00:14	00:01:00	R1, 16	
Phlebotomy	00:04:01	00:01:07	00:04:00	R10, 54	
***Lab**	02:15:00	N/A	02:15:00	N/A	
Physician visit	00:09:43	00:06:48	00:10:00	R80, 09	**R509, 20 (IV script)**
Pharmacy → oral	00:02:54	00:01:21	00:03:00	R14, 59	
Pharmacy → mixing	00:10:24	00:01:21	00:10:00	R48, 62	
Drip admin. + File update	00:03:26	00:00:53	00:03:00	R7, 90	
Administration + Monitoring	02:15:00	N/A	02:15:00	R355, 63	

Due to the number of different chemotherapy regimens administered and monitored at the same time within the clinic and taking into consideration the ethical approval obtained for the study, it was difficult to obtain the exact time for colorectal cancer patients. Thus a midpoint was taken for the period in which chemotherapy is usually administered and monitored for various cancers and this information was provided by the oncology nurses at the clinic.

3.3.1.5.4.2 The NRPL-HS Costs for the private healthcare sector

For accredited facilities, the administrative costs are comprised of a global fee and a facility fee. The global fee refers to whether the chemotherapy is administered orally or intravenously whereas the facility fee refers to the facility setting where the medicines are administered. These fees are industry based and not medical scheme specific,

Table 2.2 shows the full tariff guideline for the medical scheme industry used in this research. The total administrative costs are calculated by adding the global fee to the relevant facility fee. There are two costs per type of chemotherapy due to a variation in facility fees as calculated from the full NRPL-HS tariff guideline (Table 3.32).

Table 3.32 Administrative costs for the private sector based on the NRPL-HS tariff guidelines for the selected medical scheme

Oral chemotherapy			
NRPL 5790 + NRPL 5791 (Oral facility type A)	**R 742,70**	NRPL 5790 + NRPL 5792 (Oral facility type B)	**R 810,10**
Intravenous chemotherapy			
NRPL 5793 + NRPL 5794 (IV facility type A)	**R 2 396,30**	NRPL 5793 + NRPL 5795 (IV facility type B)	**R 2 644,20**

3.4 Sensitivity analysis

The sensitivity analysis indicated that chemotherapy costs and the number of cycles of treatment greatly affect the total cost of treatment for both sectors and each stage of CRC. An example of how the chemotherapy cost impacts the total cost of treatment can be seen in Figure 3.35 for the public healthcare sector and Figure 3.36 for the private healthcare sector. The chemotherapy costs are related to dosages thus the dosages prescribed will impact costs. The administrative costs had less of an impact on the model when the sensitivity analysis was performed however, had the effect was greater in the private sector than the public sector (Figure 3.37). Supportive care medicine costs did not appear to have a large effect except where additional medication, such as, atropine was used in regimens containing irinotecan. This once again pertains to the private sector however, where patients are prescribed the medication in the public sector, it will most likely show an effect. Using the percentage variations of +/- 50 % and +/- 20% while varying each cost component individually, the total cost variations ranged from less than R 1 000, when using 20%, to well over R 10 000, when using 50%. The sensitivity analysis tables can be found in Appendix Q.

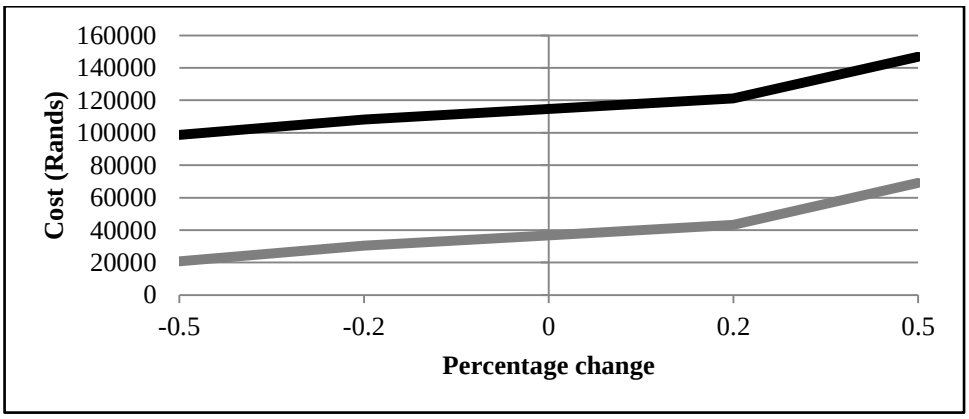


Figure 3.35 The impact the cost of chemotherapy has on the total cost of CRC treatment for two treatment regimens (FOLFOX – black and CAPOX - grey) **used in the public healthcare sector**

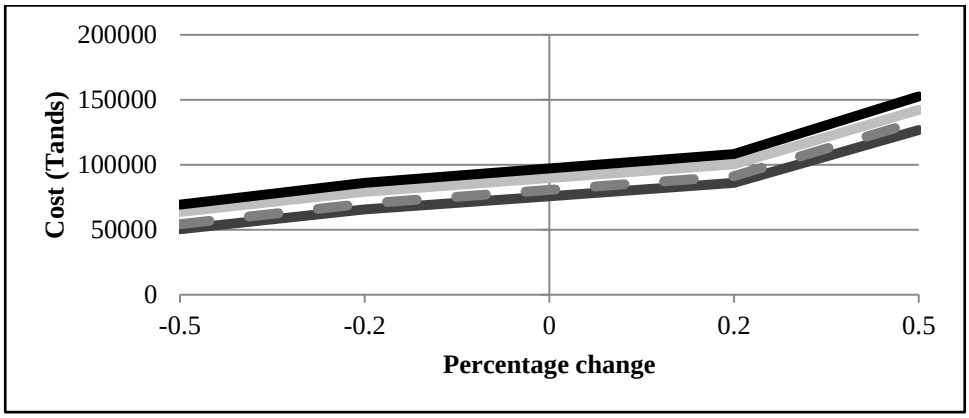


Figure 3.36 The impact the cost of chemotherapy has on the total cost of advanced CRC treatment for four treatment regimens (FOLFOX – light grey, FOLFIRI – black, CAPOX – dark grey and XELIRI – dotted grey) **used in the private healthcare sector**

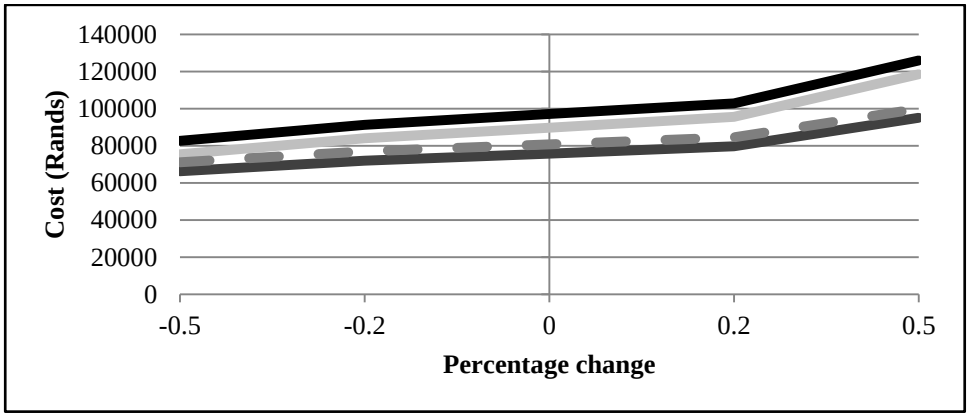


Figure 3.37 The impact the cost of administrative tasks has on the total cost of advanced CRC treatment for four treatment regimens (FOLFOX – light grey, FOLFIRI – black, CAPOX – dark grey and XELIRI – dotted grey) **used in the private healthcare sector**

4. CHAPTER FOUR – DISCUSSION

4.3 Treatment pathways

4.3.1 Developed treatment pathways

This research illustrates the limited chemotherapeutic options available to patients within South Africa's public healthcare sector patients while private healthcare sector patients have access to most therapies available globally, provided the local medicine regulatory authority, the South African Medicines Control Council (MCC) [93] has approved them. Certain unregistered medicines may be obtained following MCC approval under section 21 of Medicines and Related Substances Act 101 of 1965 (Figure 3.3, Figure 3.4, Figure 3.5, Figure 3.6). Various differences for each sector will be discussed under the relevant section headings.

4.3.2 Observed treatment pathways

4.3.2.1 The public healthcare sector

From Figure 3.3, early CRC disease treatment is dictated by the origin of the disease within the colorectal region. These patients are treated with either one of the regimens found in Figure 3.3 however they may be changed from one regimen to another at some point. Capecitabine can be used in place of 5-FU+LV as 1st line treatment due to proven non-inferiority to 5-FU+LV. Van Cutsem *et al*. (2001) showed that the overall response rate (18,9% vs. 15,0%), median time to disease progression (5.2 vs. 4.7 months), median time to treatment failure (4.2 vs. 4.0 months) as well as median overall survival (13.2 vs. 12.1 months) was non-inferior for patients treated with capecitabine compared to 5FU/LV [53]. Once metastasis occurs, choice of treatment is no longer based on the origin of CRC. This means that patients are able to start on a regimen containing oxaliplatin with either 5-FU+LV or capecitabine and then move onto a 2nd line therapy or Best Supportive Care as required.

Comparing the developed public sector pathways in this study to international guidelines, backbone therapies such as irinotecan were absent at the time. In addition, biological agents

such as bevacizumab and cetuximab are also unavailable in the public sector. While these agents have become standard therapy in many parts of the world, public sector patients are unlikely to receive any biological therapy however a small number were able to receive irinotecan (section 3.1.3.1 and 3.1.3.2) [25, 26, 128, 129, 158-162]. Although most of the guidelines used for comparison are international, South Africa's private sector guidelines do include medicines such as irinotecan, bevacizumab and cetuximab [126, 127]. This result, albeit, unexpected does indicate that patients do have limited access to such therapies however; is not standard therapy and majority of patients reliant on public healthcare will not receive this treatment should they require it. Irinotecan is however, under review for inclusion on the EML.

The use of mitomycin-C use was infrequent and unexpected. Although little research has been conducted, Dimou and colleagues (2010) [199] did show that there may be benefit to some patients even though it was the previous standard of care (prior to oxaliplatin and irinotecan) [199]. In this instance, it is assumed to be prescribed on a compassionate basis for patients who couldn't acquire irinotecan for that cycle. Similarly, capecitabine monotherapy was prescribed for maintenance therapy in a few instances, although not standard practice due to a lack of evidence for use in CRC, a fixed low-dose has previously been described for maintenance therapy [200]. This fixed low-dose appeared to be safe and well tolerated with only 13% of the study population discontinuing the regimen. This study, albeit limited, did show a median duration of 45 weeks of therapy [201]. From the current retrospective drug utilisation review, it cannot be concluded the benefit of maintenance therapy as only 5% of the total cohort were thought to receive maintenance therapy but could prove to be advantageous, as majority of these patients didn't require further treatment. These findings aren't conclusive but should be studied further.

The retrospective drug utilisation review did also indicate a preference for capecitabine over 5-FU + LV as 1st line therapy even though the two regimens have been proven to be equivalent [53]. It can't be concluded that this was due to patient's preferences, decided by the oncologist or decided by the patient's calculated ECOG score. This is an area of study that should be conducted particularly for decision makers and pathway developers. Previous studies on patient preference have been conducted elsewhere and are conflicting as a trial conducted by Borner and colleagues (2002) [202] concluded that patients preferred oral therapy provided efficacy isn't compromised [202]. A more recent trial, using the same cross over methodology, concluded that patients preferred a regimen with less toxicity as opposed

to ease of administration thus more patients preferred the I.V. Nordic 5-FU + LV regimen [203].

In addition to the frequently administered capecitabine, the treatment pathways clearly indicate CAPOX for early CRC high-risk patients however; the retrospective drug utilisation review revealed a high use of CAPOX as a 1st choice regimen for early CRC (Figure 3.7). Risk factors such as age and co-morbidities play an important role, not only in chemotherapy choice but also if chemotherapy should be administered [204, 205]. Upon analysis, 76% of elderly patients (>70yrs) diagnosed with advanced CRC disease received oxaliplatin in their treatment. Although not prescribed in accordance with the clinical pathways, treatment is patient dependent and could indicate healthy elderly patients; however in a recent study where more than half of patients over 75yrs received oxaliplatin, cost of treatment increased with no survival benefit [206]. Unfortunately the patient records at the oncology clinic do not include co-morbidities or factors that could indicate high-risk. Therefore it couldn't be determined if all patients that received CAPOX as a 1st choice regimen were high-risk. It is unclear from the patient records whether or not risk-assessments are performed but chemotherapy treatment is variable and this patient cohort might be at a higher-risk than another cohort. It could also be a more aggressive plan of treatment so as to ensure that disease progression is delayed for as long as possible but also to try achieve disease remission with the hope of reducing long term consumption of already limited resources. For this patient cohort, 25% of patients treated with CAPOX initially were changed to an alternative regimen nevertheless it can't be presumed that disease progression occurred as neuropathy development is common with oxaliplatin treatment [48].

The high number of patients initially treated with oxaliplatin could also indicate the substantial suspected incidence of peripheral neuropathy, which resulted in dose alterations. This is concerning as full dose intensity is favoured for a desired response [207]. It is recommended that in severe cases treatment may need to be stopped or delayed and dose reductions can also relieve symptoms. International recommendations indicate duloxetine as effective treatment for peripheral neuropathy [208, 209], gabapentin and pregabalin may also be favoured [210] however, these are unavailable in the public sector and therefore amitriptyline is most likely to be prescribed.

In comparison to the theoretical pathways, some patients do switch to an alternative regimen. 2 of the early staged CRC patients were observed to have a definite change in treatment

regimen, such as the addition of oxaliplatin (Figure 3.7). This is not standard practice when comparing to local and international guidelines [25, 26, 126, 127, 156-162], it could possibly be an indication of metastasis but oxaliplatin-intolerance cannot be ruled out (Figure 3.7, Figure 3.8).

4.3.2.2 The private healthcare sector

Although treatment for early CRC is site specific, the data received for the private sector didn't account for this thus it is unclear as to which of the early CRC patients were affected by colon cancer and which by rectal cancer. The early CRC per patient results (Appendix I) shows that while a few patients may receive 1st choice regimens with a limited number of cycles; it can't be assumed that these patients are rectal cancer patients. These patients may well decide to discontinue treatment or oncologists may decide to withdrawal treatment and from the data this is unknown. Many factors found in the literature are seen to play a role in the discontinuation or withdrawal of treatment [211]. Clarke and colleagues (2015) [211] conducted a systematic review on literature in the USA and found that decisions around withdrawal occur over a period of time and include clinical factors (disease progression) and non-clinical factors (oncologists views or feelings) [211]. A study conducted with leukaemia patients indicated older patients are more likely to discontinue chemotherapy for various reasons including increased disease-related symptom severity, lower tolerance of adverse effects and financial difficulties [212]. Apart from these studies, the literature appears to be limited and has a focus on older patients [213] however this issue of discontinuation should be followed up and factors affecting the South African population should be studied.

The observed treatment pathways in the private sector did also reveal the use of unproven/unconventional CRC chemotherapy (Figure 3.32; Figure 3.33). The reason for the use of unproven/unconventional chemotherapy cannot be ascertained from the database however it is suspected to be either an off-label use, where prescribers feel that it may be appropriate for the patient, or may indicate the presence of a secondary cancer that was not captured. Apart from the clinical inappropriateness of these medicines, the cost contributions to the patient's total cost of treatment are unnecessary. For example the use of carboplatin+paclitaxel in this patient cohort increased total cost by approximately R 23 000. This would be one area whereby cost could be reduced and improve resource utilisation. This

is not as much of an issue in the public sector as resources are constrained and access controlled by EMLs which indirectly prohibits off-label use (Figure 3.29; Figure 3.31).

Similarly the decision for no treatment or BSC only is unknown due to the nature of the data. The reasons for these treatment decisions would be beneficial to know particularly for the early CRC group of patients as early CRC disease has a better prognosis and treatment is favoured. A recent study by Sankaranarayanan and colleagues (2010) [173] clearly indicated that early detection is key to survival but so is the healthcare service resources and development [173]. Survival rates are high for colorectal cancer in comparison to other cancer and treatment should favour an increased survival however there is conflicting literature that this is the case [26]. Research has indicated that chemotherapy might only increase survival by 2% but this research is outdated [214]. Thus for the private sector patient cohort, this may indicate that the advanced CRC status of patients on the database may be incorrectly captured. The regimen change trend within a line of treatment seen in the public sector, particularly for the 1st line treatments, is similar for this sector however in the private sector, 2nd line treatments are easily attainable thus less change occurs between 1st line therapies. There are more 2nd line therapies present in the recorded pathways for the private sector indicating more regimen changes within the 2nd line of treatment. Likewise with this sector once metastasis occurs the treatment is not based on the origin. This is clear from the high number of cycles patients receive in 1st line treatments as well as the apparent quick change from 1st to 2nd treatment lines.

Comparing the developed treatment pathways to international guidelines indicates that many of the treatments available elsewhere globally are available to private sector patients in South Africa. Standard therapy including irinotecan, bevacizumab and cetuximab is thus available to these patients unlike patients reliant on public healthcare [25, 26, 126-129, 158-162]. This does give some indication that chemotherapy treatment for CRC in South Africa does follow international trends but there was an absence of medicines such as aflibercept and panitumumab as these are yet to be approved by the MCC and are not yet available on Section 21. Regorafenib was prescribed for a few patients as it is available on Section 21 and will most likely be prescribed more frequently once MCC approval is obtained although availability will also be dependent on funding for reimbursement. These newer therapies are costly and are more likely to be limited to the number of patients that will ultimately receive them. This is highlighted in section 4.4.3.5.

Maintenance therapy only became apparent following the retrospective drug utilisation review of the public sector as it isn't the standard of practice for a cancer such as colorectal. This trend of maintenance therapy is also seen in the private sector. Similarly to the public sector, capecitabine was used in maintenance therapy, as was 5-FU. Monotherapy with either one of these fluoropyrimidines has been found to be effective [201, 215, 216]. Although research is limited for colorectal cancer maintenance therapy recently more studies have been published. Many of these studies include biological agents for the use in maintenance therapy such as bevacizumab. The CONcePT trial indicates an increased time to treatment failure (4.2 months vs. 5.7 months) and the STOP and GO trial showed significant increases in progression free survival (8.3 months vs. 11 months) and overall survival (20.2 months vs 23.8 months) [217, 218]. The benefits of maintenance therapy, whether it is conventional treatment such as capecitabine or biological therapies such as bevacizumab, seem to be becoming more apparent in colorectal cancer and as such should be included into the developed treatment pathways. The use of mitomycin-C was infrequent in the private sector nevertheless was unexpected due to the greater number of medicines available to this sector of patients than in the public sector. Even though some patients may benefit from mitomycin-C it is the previous standard of care [199]. Most notably mitomycin-C was only prescribed as last line therapy for the respective patients. This may well be an indication that no other medicines were appropriate at the time and it was decided to try mitomycin-C. In addition to the use of mitomycin-C, tegafur was also used albeit very infrequent.

Recent literature has looked at the benefit of monotherapy with tegafur/uracil as well as in combination with irinotecan particularly for advanced colorectal cancer [202, 219, 220]. Tegafur/uracil or UFT is an oral prodrug of 5-flurouracil combined with a DPD inhibitor which has been found to benefit mCRC patients. There are studies that have looked at patient preference and pharmacoeconomic comparisons of oral UFT versus intravenous 5-flurouracil [202, 221]. However from the private sector drug utilisation, capecitabine is the medicine of choice when oral therapies are prescribed. Although UFT could be studied further in order determine its possible place in therapy as it is no longer available.

Comparing the first treatments received, capecitabine-containing regimens are favoured for early CRC patients whereas the advanced CRC treatment pathways indicate a higher use of 5-FU+LV-containing regimens even though the two regimens have proven non-inferiority for any stage of CRC [53]. Based on the high use of capecitabine in the public sector, it is not unexpected to see a high use of capecitabine in the private sector. It is unexpected to see a

greater use of 5-FU+LV for advanced CRC disease in the private sector but majority of regimens contain intravenous medicines other than 5-Fluorouracil thus it may be preference to receive treatment all at once. Many patients diagnosed with advanced CRC disease in this sector have access to newer biological agents that can only be administered intravenously and this may be a factor for the preference for 5-FU+LV over capecitabine when used in combination with conventional regimens. Studies have indicated patient preference for capecitabine as capecitabine is less toxic and administration is easier thus this does raise an important issue in the private sector as to what the drivers are for choice of treatment [202, 203]. In this study, the choice of chemotherapy regimen in the public sector appear to be driven by cost as 5-FU+LV regimens would cost more. The choice of chemotherapy regimen for advanced CRC disease in particular for this sector isn't as clear thus more studies are required with regard to this area of patients receiving chemotherapy.

In addition to the preference for capecitabine in early CRC disease for the private sector, the treatment pathways mapped for the patient cohort show an extensive use of regimens such as CAPOX (FOLFOX) and XELIRI (FOLFIRI). Regimens such as these are usually reserved for high-risk (e.g. 70 years) early CRC patients and there appears to be better adherence to this in the private sector as less than half the patients over 70 years received a chemotherapy regimen containing oxaliplatin or irinotecan first up. It is likely that patients that did receive one of these cytostatic agents most likely had disease progression following the initial 1st choice regimen. Interestingly all the patients that received these medicines were much younger in the over 70yr age group. This does indicate that age and co-morbidities play a role in chemotherapy choice and if chemotherapy should even be administered [204, 205].

The preferred use of oxaliplatin versus irinotecan is interesting, as regimens containing these medicines have been found to have no difference in time to progression (7mnths vs. 7mnths) and overall survival (14mnths vs. 15mnths) [183]. In addition for patients that have experienced 1st choice 5-FU treatment regimen failure, 2nd choice regimens contained either FOLFIRI or FOLFOX4. These regimens however have shown no significant difference in overall survival [189]. The costs did differ for the different stages of the disease as the cost data structure for this research didn't allow for the identification of 1st and 2nd line treatments for advanced CRC or 1st and 2nd choice regimens for early CRC. When comparing early CRC disease to advanced CRC disease however, oxaliplatin containing regimens are more costly. Early CRC disease shows that FOLFIRI is 13% cheaper (for the same number of cycles) and 22% cheaper for advanced CRC disease (1 cycle less). The cost saving is due to the irinotecan

cost despite the inclusion of atropine for administration purposes. In this patient cohort, both early and advanced CRC, oxaliplatin regimens appear to be more frequently prescribed in the 1st line treatments for advanced CRC or as a 1st choice in high-risk early CRC patients. This is seen in the high number of irinotecan-containing regimens in the 2nd line of treatment for advanced CRC. Furthermore to this oxaliplatin can cause peripheral neuropathy therefore the increased number of irinotecan regimens in the 2nd line may be due to intolerability of oxaliplatin and not necessarily be due to disease progression [48].

In comparison to the theoretical pathways, it isn't unexpected to see multiple treatment lines for advanced CRC disease however due to the observations made in the public sector; there is a likelihood of 2nd choice treatment regimens for early CRC disease. The patients that did receive more than just 1st choice treatment regimens were few and possibly were classified incorrectly on the database. The presence of adverse drug reactions can also not be ruled out. The advanced CRC disease group of patients had multiple treatment lines, more than was expected in the theoretical treatment pathways. This indicates the complexity of chemotherapy moreover the increased number of treatments available to these patients furthermore increases the level of complexity as oncologists and patients may well try as much as possible.

4.4 Retrospective Drug Utilisation Review - patient cohort demographics

4.4.1 Public healthcare sector

4.4.1.1 Patient cohort characteristics

The patient cohort for the oncology clinic is not necessarily reflective of all populations within South Africa as environmental and lifestyle factors play a major role in colorectal cancer development and is likely to differ with the country [24, 26]. This retrospective drug utilisation review does give insight into possible patient characteristics for a sub-population within South Africa.

4.4.1.2 Gender

Although CRC is not a gender-specific cancer such as breast or prostate cancer, the disease affected more males for this cohort. Interestingly the patient cohort studied revealed that this is only the case for early CRC diagnoses. Advanced CRC disease incidence is more similar with nearly 50% of the population diagnosed being female thereby could indicate the increase in older females having a greater risk. This result was expected as previous research, albeit with larger cohorts, does reveal more males are affected [222]. When compared to the NCR statistics for 2012, more males were diagnosed than females however the percentage difference between the genders was only 8% for colorectal cancer [32].

4.4.1.3 Age

Published research has indicated that risk of CRC development increases over the age of 40 with sharp increases over 50 years of age [24, 26, 223]. More recent research published by Siegel and colleagues (2014) [224] indicated that new CRC cases for 2014 peaked between the ages of 50 and 79 for both sexes. Other research indicated that patterns of incidence by age only displayed increases between 60 – 79 years for distal colon cancer and 60 - 69 years for rectal cancer [222, 224]. This pattern of incidence is similar to the data collected as the number of patients over 50 years show these increases where proximal cancer rates are much less and even show a decrease in males. Additional research has indicated that women over the age of 65 years have a greater risk of developing colorectal cancer however many more males were diagnosed than females in this patient cohort and although the risk is present it can't be deduced that cancer will develop [11]. The median age of the patient cohort at CMJAH is no different to literature and was expected to be over 50 years of age [27]. This finding isn't surprising and is most likely due to increased westernisation in South Africa and in particular the Johannesburg region. This might well differ in other LMICs within the Sub-Saharan region. More than 60% of females and 70% of males from the patient cohort were in this age group, which is similar to the 60% and 71% seen by Siegel and colleagues (2014) [224] in the United States [223, 224].

4.4.1.4 Tumour sub-sites – Left vs. Right-sided CRC

Little research has been published with regard to patient diagnosis based on tumour sub-sites within the colorectal region but according to the National Cancer Institute, most colon cancers are left sided [225]. This is the case for this patient cohort whereby 38% of patients have left-sided colon cancer however, Siegel and colleagues (2014) [224] as well as Murphy and colleagues [222] reported more proximal colon cases as with a mortality study conducted by Weiss and colleagues [222, 224, 226]. These studies also indicated that females were more likely to have right-sided cancers. Even if the 13% of unspecified colon cancer cases were to be confirmed as proximal cancers, this patient cohort would still indicate a greater incidence of distal colon cancer cases and males would still account for more of these cases. This finding should be investigated further as it is known that left and right-sided tumours have biological differences but there may be additional factors present in this population resulting in an increase of left-sided tumours. One such factor is a diet with increased red and processed meat consumption. Studies have indicated that distal colon cancers can be due to increased red meat consumption, bearing this is mind it could explain the increased number of distal colon and rectal cancer cases in this cohort [227-230]. South African's are known to have higher consumptions of red and processed meat regardless of socioeconomic status [231]. In addition to this finding, 31% of the patient cohort was diagnosed with rectal cancer and is much more similar to the findings of Siegel and colleagues (2014) [224] (28%) but differs once again according to gender. Although more males were recorded in the Siegel *et al*. (2014) [224] study, by far more males were diagnosed with rectal cancer [224]. This patient cohort indicated more females were diagnosed with rectal cancer. Smoking has been found to be an important risk factor for the development of rectal cancer likewise with alcohol consumption [232]. This could possibly play a role in the cohort.

Recent re-analysis of the FIRE-3 and CALGB/SWOG 80405 trials indicates the side the cancer originates may play a role in patient's responsiveness to treatment. Patients with left-sided cancer have an increased median overall survival regardless of the treatment regimen. Moreover right-sided cancer is more responsive to bevacizumab as opposed to cetuximab [97, 98]. This is discussed in more detail in section 1.4.8.3.4.3. Although this could not be seen in this patient cohort as regimens containing cetuximab and bevacizumab are unavailable, it should be studied in the private sector.

4.4.1.5 Ethnicity

Although ethnicity was not studied due to limitations in recording and multiple assumptions that would need to be made, studies such as those performed by Siegel *et al*. (2014) [224] have indicated that in the United States, the African American population has greater incidences of colorectal cancer while Asian/Pacific Islanders have the lowest for both genders. This difference was suggested to be due to the low socioeconomic status within the African American population thus should be studied further in South Africa as majority of the patients seen at clinics such as CMJAH are of low socioeconomic status [224].

4.4.2 Private healthcare sector

4.4.2.1 Patient cohort characteristics

The patient cohort used for the private sector is more representative than the public sector cohort as the medical scheme used has one of the largest memberships that covers patients countrywide and not only a region such as with the public sector cohort. Similarly to the public sector, this patient cohort can't be used to standardise the characteristics of CRC in South Africa as there is only a small percentage within the population which subscribe to private medical insurance furthermore most of these subscribers are middle- and high-income earners [4].

4.4.2.2 Gender

Similarly to the public sector, more males are affected than females albeit a non-gender specific disease. Interestingly both early CRC and advanced CRC subgroups displayed this occurrence and does follow the risk data as seen in the SEER statistics [27]. This observation is no different to the public sector however the percentages differ but due to the large number of patients in the cohort, it is probably more accurate. As previously discussed the mechanisms associated with these phenomena are unknown but possibly related to the risk factors and sex hormones [222]. Interestingly the percentage of women affected by the disease is less in the advanced CRC group unlike the public sector; it suggests that women within these socio-economic groups are more lifestyle conscious thereby lowering their lifestyle risk for developing CRC. This result is similar to a prospective study conducted in

Denmark that found patients who do adhere to health recommendations and guidelines can reduce their risk considerably [233].

4.4.2.3 Age

Similarly to the public sector data, patients aged between 50 and 79 years are the most likely to present with CRC in the private sector. Most of the cases are over the age of 60 and this is seen in the median age of the cohort and is similar to the literature for Sub-Saharan Africa [234]. In comparison to the public sector, the data indicates more than a 10% increase for the incidence of females in this age range and is similar to the males for the cohort but differs to the public sector. This result isn't unexpected as patients making use of private healthcare in South Africa are higher income earners that are able to lower their risk factors particularly those related to lifestyle and research indicates that diets high in fruits and vegetables and dietary fiber intake make a difference. Together with an increase of physical activity CRC risk can be decreased [223]. Although the difference isn't huge, it does illustrate the role lifestyle factors play in the development of CRC but also indicates that many factors that influence patients in the public sector also affect patients in the private sector. This is seen in the median age of the cohort, which is older for this sector when compared to the public sector, but is not as high as a developed country such as the USA [27].

4.4.2.4 Tumour sub-sites – Left vs. Right-sided CRC

Due to suboptimal data capture of the private sector data, no sub-site evaluation could take place. Data from the public sector and literature indicates there is a need to gather data based on the origin within the colorectal region [222, 226]. Including such data will enhance the quality of not only private sector data but data for South Africa for all cancers. The importance of left vs. right-sided origin is discussed under section 1.4.8.3.4.3.

4.4.2.5 Ethnicity

Ethnicity wasn't studied in this research thus no demographical data regarding race was received from the medical scheme. As previously discussed race does play a role in CRC incidence with certain ethnic groups having greater incidences [224]. Siegel and colleagues (2014) [224] noted an association between socio-economic status, race and the incidence of

the disease therefore it is an important aspect of demographical studies for a country such as South Africa and should be studied further [224]. Furthermore this data should be used to compare the two healthcare sectors and the population that makes use of each.

4.4.3 Treatment costs

4.4.3.1 Total cost for CRC treatment

4.4.3.1.1 Public healthcare sector

Costs associated with advanced CRC disease were expected to be more than for early CRC disease. This is because costs are influenced by disease state in that early CRC disease has better prognosis thus requiring fewer cycles of chemotherapy and possibly lower dosages. In addition, advanced CRC disease may be treated with newer therapies that tend to be costly for the public sector, treatment options are limited and therefore cost differences are generally due to cycle and dosage differences. Observed costs which are often lower than the theoretical costs, indicate the variability that occurs in a population and illustrates how difficult calculating costs for such a disease can be. The variability often results in lower doses and number of cycles than expected. The percentage changes for CAPOX range from 13% to 179% for 1st and 2nd line treatment lines respectively when early CRC and advanced CRC disease is compared. However, when early CRC costs are compared to theoretical costs the costs are similar but advanced CRC disease is less than 5% in comparison to the theoretical costs (Table 3.19 and Table 3.21). These changes aren't unforeseen however a regimen such as XELIRI indicates no percentage changes as irinotecan was not available at the time of the study to public sector patients nevertheless should irinotecan be included on the EML, the cost is expected to be less than the reported lowest SEP price for the private sector (Table 3.19 and Table 3.21). This is due to the tender procurement process in the public sector. Although the total cost per cycle will be lower than the lowest calculated SEP cost, the costs to the Provincial Department of Health will increase as access to irinotecan by all public sector patients will remove the self-paying portion most patients currently cover, in other words patients who are currently self-funding for irinotecan will expect it to be freely available in the public sector. This nonetheless will increase access to patients who cannot afford the medicine.

When comparing early staged colon to rectal disease, rectal cancer costs are lower by half except for 1st choice CAPOX. With regard to capecitabine costs, the theoretical costs have a range of costs due to the dosing range of the medicine. To simplify the comparison, the lowest theoretical cost i.e. the lowest dose was compared thus the percentage differences may be larger when comparing higher doses of capecitabine. Capecitabine was still on patent at the time of the study but is available in the public sector and is the most costly factor in the cost calculation for capecitabine-containing regimens. The change in cost is considerable when varying doses thus this research should be performed on various public sector cohorts in order to verify and understand the variations that will occur within a population. However, when the patent for capecitabine expires, the cost is likely to be reduced further and favour capecitabine-containing regimens even more.

This is particularly important when comparing equivalent regimens such as 5-FU+LV and capecitabine. These regimens have previously been shown to differ in cost and favour the use of capecitabine due to its oral administration [169, 235-238]. This study is in line with previous research and indicates that although the medicine price of capecitabine was calculated to be double the cost of 5-FU+LV, administration costs are lower as patients spend less time receiving chemotherapy and don't require the insertion of a port and pumps in addition to less administrative duties associated with capecitabine administration. This does indicate the complexity of economic-based decisions as medicine prices alone are not and should not be the only factors considered when determining the economic impact of treatment. In addition, there is a complexity to treatment and this can be seen in the variable adherence to these pathways.

When comparing the advanced CRC theoretical costs to the patient cohort costs for advanced CRC disease little change is seen. The total public healthcare sector patient cohort had more patients with advanced CRC disease so variables such as the number of cycles and dosages are more accurate and represent what has previously been recorded in literature and clinical trials for advanced CRC disease. A similar study conducted for advanced CRC in Brazil indicated the lack of biological agents available in their public healthcare system but more noticeably regimens containing 5-FU were over budget and surpassed the monthly reimbursement amounts. Likewise with our study, administration costs contributed the most to the treatment costs but in Brazil, medicine costs were lower than in our study [239].

4.4.3.1.2 Private healthcare sector

Although the expectation was that advanced CRC disease costs would be higher than early CRC disease costs as seen with the public sector, the average cost per cycle is similar for the same regimens. This is essentially due to similar dosages, which is a result of the assumption that the claimed vials are the prescribed doses. However in clinical practice these doses may well be lower as vial wastage does occur in order to accommodate dosing based on BMI or body weight. Wastage cost unfortunately can't be calculated from a claims database however these factors should be considered as a recent study published by Bach and colleagues (2016) [240] found that single-dose vials can lead to overspending as the vial sizes don't match the prescribed doses for many newer medicines [240]. In addition to vial wastage, vial sharing may also occur. Vial sharing limits the wastage of viable medicines however, patients are still be billed for the entire vial thus in clinical practice the dose and cost don't match. Bach and colleagues (2016) [240] do provide vial sharing as one method to curb costs however it is not recommended for all intravenous medicines [240]. Although vial sharing is likely to happen to limit chemotherapy wastage for a facility [241], due to the nature of the data collection and cost calculations, this practice won't have such an effect as each patient is billed per vial regardless. The savings are therefore achieved by the oncology facility. Consequently the difference rests in the average number of cycles calculated for the patient cohort, which influence the average total cost per regimen.

Additional costs are incurred in cases where patients received treatments that are neither conventional nor proven CRC treatments such as R 12 873,25 for 4 cycles of cisplatin (early CRC disease) or cisplatin with docetaxel at R 40 858,62 for 4 cycles (advanced CRC disease). Although these are regimens are not conventional nor proven for CRC, a secondary cancer cannot be ruled out.

In comparison to the theoretical costs in the private sector in which only conventional regimens could be compared, the theoretical costs were substantially more in many instances. Of all the regimens that were compared only 5-FU+LV showed an increase of less than 50% between theoretical costs and observed costs. This trend is similar to the percentage changes (Table 3.24, Table 3.25) seen in the public sector nevertheless the changes are greater for many regimens within the private sector. This could be due to the vast number of treatment options available to patients and oncologists in the private sector thus lowering the number of cycles a patient will receive per regimen and increasing the number of treatment regimens.

Due to the patient data not specifying if an early CRC patient was diagnosed with colon or rectal cancer, the costs are most likely an average for regimens such as 5-FU+LV and capecitabine. Rectal cancer patients are likely to receive less chemotherapy thereby lowering the cost.

The theoretical costs regarding capecitabine vary due to the dosing range however the lowest cost product was used for comparisons. Although 5-FU+LV and capecitabine are equivalent regimens and the costs should favour the use of capecitabine, [169, 235-238], it can be seen that many patients receive 5-FU in this sector. Although the chemotherapy costs are about double for capecitabine than 5-FU, the administrative costs are more than 70% for the I.V. regimen. This therefore may explain the increased use of 5-FU as facilities make more money when patients receive I.V. regimens as opposed to oral treatment although this only applies to monotherapy oral regimens. For multiple medicine regimens, the price of capecitabine is the largest contributor as all other medicines are averaged for all available products. Capecitabine regimens therefore are more expensive than 5-FU regimens but factors such as theatre time, ports and pumps were not included unlike in the public sector calculations. These costs should be included in order to allow for better comparisons especially once patents expire and generics become available to patients.

4.4.3.1.2.1 Out-Of-Pocket Costs

Out-of-Pocket costs are costs incurred by patients in the form of co-payments on medical scheme claims or expenses not covered for by the patient's medical scheme. These out-of-pocket expenses have rarely been studied in literature but it is well known that these costs vary based on the medical scheme coverage of the patient.

A recent study, looking at Medicare patients in the USA, found that without additional insurance supplementation significant OOP costs would be incurred [242]. The study determined these OOP costs using a prospective survey of a cohort of Medicare beneficiaries, of which 1409 beneficiaries were diagnosed with cancer during the study period [242].

While this body of research did not look at OOP costs, as OOP costs could not be determined using the claims database for the private sector as the data only reflects the actual costs paid for by the medical scheme, it would be beneficial to conduct a survey such as the previous

research mentioned above in order to quantify the OOP costs patients currently incur in the private sector.

4.4.3.2 Supportive care medicine costs

4.4.3.2.1 Public healthcare sector

Supportive care medicine costs, although a small portion of the cost per cycle, were found to vary from the theoretical cost calculations. This was expected as the theoretical costs were bundled together into "baskets" and the average calculated for a regimen. Upon investigation, it was found that all patients on I.V. regimens receive the same medication except if irinotecan is administered. Thus regimens such as 5-FU + LV and FOLFOX have the same supportive medicine costs at R44.48 per cycle. If FOLFIRI is administered, patients receive a vial of atropine in addition to the anti-emetics and corticosteroids. This increases cost marginally to R46.20. Oral regimens are cheaper as less supportive care medicines are required thus the cost savings are nearly R20.00 per cycle.

Other supportive care medicines that were unable to be included, due to a lack of clarity of cost, include Xeloda ® Cream (a lanolin-based cream), a donation from Roche, which is used for the hand-foot-skin (HFS) syndrome that may arise. Patients however do not always take a tub each month as not every patient uses it as much as the next. In addition to the cream, a mouthwash containing benzydamine hydrochloride such as Andolex® is usually prescribed. There is no EML price for 2014 but the cost, according to SEP, will range between R63.31 and R78.32 per bottle. Once again this cost is not enough to change the percentage differences between the theoretical and cohort costs but should not be ignored. A similar study conducted by Kruse and colleagues (2008) [243] indicated that 3% of the total cost per visit for metastatic breast cancer in a US population is due to antiemetic's and corticosteroids [243]. This is greater than for the South African public healthcare sector whereby the supportive care medicines contribute less than 1% for most regimens. This is also low as supportive care medicines are imitated in the public healthcare sector.

4.4.3.2.2 Private healthcare sector

The supportive care medicine costs are minimal when compared to the chemotherapy and administrative costs in the private sector. The supportive care medicines are the same classes of medicines as used in the public sector, namely a corticosteroid and antiemetic. The difference in cost between the two sectors is at least 600% more per cycle in the private sector for advanced CRC disease. This difference is due to the increased price in the private sector for the same classes of medicines e.g. palonosetron (Onicit®) versus generic ondansetron or granisetron, as well as the increasing number of products available particularly newer antiemetic's such as aprepitant, an NK-1 inhibitor. Most notably patients in the private sector would receive more than one class of antiemetic thus increasing the costs. Considering that CRC regimens have low to moderate emtogenicity, the recommended supportive care is a combination of a corticosteroid such as dexamethasone and one of the 5-HT3 receptor antagonists [244]. Thus the use of aprepitant for the (MEC) is not advised and should be reserved for highly emtogenic regimens (HEC) such as cisplatin or anthracycline + cyclophosphamide. In addition should oncologists prescribe generic ondansetron or granisetron in place of palonosetron, the cost savings of at least R 245,00 per cycle as only the originator of palonosetron (Onicit®) is available and the vial size is bigger. A recent review by Gyawali and colleagues (2016) [245] did indicate that there are many cheaper alternatives that could be prescribed for chemotherapy-induced nausea and vomiting (CINV) and it was stressed that this is of importance in low-resourced settings [245] however patients should be included in decisions such as this even in higher resourced settings. Another alternative is olanzapine. Olanzapine is an atypical antipsychotic which targets multiple receptors within the central nervous system and is advantageous as patients are only required to administer one medication as opposed to the current combinational therapy. The one disadvantage is the cost as many cheap generics are available for the medicines used in the combinational treatments [246]. Although this study clearly illustrates the contribution, albeit small, that these medicines have on total cost, it does also raise the question of ease of administration for the patient.

When irinotecan was prescribed, atropine was included in the supportive care costs however the cost is marginal as with the public sector and has no effect on the total cost contribution. Claims on secondary supportive care medicines, these are medicines used in support of the cancer patient other than a corticosteroid and 5-HT3 receptor antagonist, were included in the

dataset however they were excluded in the final costs as it was unclear whether or not these medicines were for chronic co-morbidities or for the treatment of an adverse drug reaction. A few of these medicines included loperamide (diarrhea), lidocaine (irregular heart rhythms), lansoprazole (intestinal ulcers or esophagitis) and iron (iron deficiency or anaemia). The average cost for all medicines classified as secondary supportive care amounted to R 265,75 for early CRC disease and R 306,69 for advanced CRC disease. Moreover this is an indication that advanced CRC patients have higher costs, which are not only due to chemotherapy.

Use of pain medication was also considered from the database. Although it was initially not calculated for the public sector cohort, it become apparent in the private sector patient cohort that many patients receive pain management care particularly for advanced CRC patients. Pain management included medicines such as acetylsalicylic acid, codeine, ibuprofen, morphine and paracetamol. The cost contribution was much greater than the supportive care, secondary supportive care or administration costs and was calculated to be an average of R 490,00 and R 692,56 per patient per cycle for early CRC and advanced CRC disease respectively. This should be studied further as it appears to contribute to the cost of chemotherapy but also to the best supportive care regimens many patients receive.

4.4.3.3 Administration costs

4.4.3.3.1 Public healthcare sector

Administration costs refer to the costs associated with receiving chemotherapy such as admixture bags, needles, drip sets etc. These costs were calculated based on a previous study carried out in South Africa in 2011 [169] and adjusted by inflation. The costs however may be lower for regimens containing 5-FU+LV than recorded in this study as clinical practice reveals that administration ports are not inserted each cycle but patients may use a port for several cycles and this would reduce the average cost for a patient cohort. It does however still indicate a large cost contribution (between 60% and 90%) to a regimen containing 5-FU+LV and impacts the cost when comparing equivalent regimens such as 5-FU+LV and capecitabine. This does play a role in treatment choice in a resource-constraint environment such as the public healthcare sector in South Africa. Recent research published by Kruse and colleagues (2014) [247] indicated that chemotherapy administration costs for treating peripheral T-cell lymphoma account for 2 – 32% of the total costs [247]. This indicates much

variability in relative cost however when looking at the patient cohort in CMJAH, the administration costs vary between 0 and 62%. This is more than previously published literature for other cancers [247] and is partly due to the inclusion of a new port for each cycle administration of 5-FU+LV although patients may not necessarily receive a new port each cycle. These results are however in line with a study that compared CAPOX to FOLFOX in which administration costs can account for more than 70% due to the central vein catheter insertion and hospital stay [237]. The literature is limited thus comparisons such as this, is not that accurate nonetheless does indicate the need for further studies.

4.4.3.3.2 Private healthcare sector

The administration costs were based on the same cost components as for the public sector, namely drip bags i.e. carbohydrates or sodium chloride, antiseptics and other costs directly related to the administration of the chemotherapy, however, costs associated with 5-FU administration were difficult to ascertain in the private sector. These costs included the theatre time required for port insertion as well as the cost of the ports and pumps for 5-FU administration. All other materials such as the infusion drip sets, needles and swabs etc. are all included in the administrative costs for this sector. Therefore the administration costs appear to be negligible and much lower for 5-FU regimens when compared to the public sector. Due to this the administration costs don't contribute more than 3% to the total cost per cycle and is on the lower side when compared to literature such as the Kruse study [247]. In addition the private sector costs were calculated for early CRC and advanced CRC patients unlike with the public sector due to the larger amount of data that was obtained. This can and has been shown to change the costs for components such as the administration and administrative costs depending on the disease state. A better understanding of the process by which patients receive chemotherapy in the private sector and insight into the coding for the claims and inclusions for each tariff is required in order to improve accuracy and enhance quality with both the administrative and administration costs in the private sector. Taking these factors into consideration, it is foreseen that capecitabine regimens will therefore also be lower in cost than the 5-FU regimens. This will most definitely be of benefit to both the patients and the medical scheme paying for the treatments.

4.4.3.4 Administrative costs

4.4.3.4.1 Public healthcare sector

Administrative costs for this sector had not previously been researched and the costs associated with delivering chemotherapy to a patient are unknown in the public healthcare sector of South Africa. Thus a time and motion study was performed at the oncology clinic. Previous research has indicated that administrative costs can account for over 70% of the total cost of a monotherapy regimen [237]. This unfortunately was not the case for most regimens in this sector as they are multiple medicine regimens. Administrative costs accounted for as much as 13% for early CRC disease and 15% for advanced CRC disease. Observed cost indicated a greater contribution for intravenous regimens per cycle. A study conducted in Canada found that administrative costs contributed less for chemotherapy regimens containing expensive medicines and is similar to these findings in the public healthcare sector of South Africa [248]. The time and motion study was however very simplistic and should be expanded with more people recording the times in order to refine the costs for I.V. and oral therapies as well as if more than one medicine is administered. In addition to this, per patient recording could be more valuable but this does provide logistical problems in this setting. Per patient recording would allow more accurate time capture per patient as the patient would be followed through the process from arrival at the clinic until the time of departure moreover the time the patient spends at the clinic could be calculated and equated to a cost.

Literature dose cite a lack of methodological standardisation for time and motion studies [249]. However, comparing the time and motion study conducted at CMJAH and other research, there is consistency within selecting steps based on a patient's entire visit to a facility for chemotherapy. There are differences within the process for the various facilities so direct comparison is difficult [170, 171]. The limitations for the studies found in literature and those experienced during this research also don't differ by much as timings and related costs were irrespective of chemotherapy regimens and dosing and may differ in the real-world between regimens and even cancers [170, 171]. The Schindler study also gathered timings in groups and not on a per patient basis however, the consistency of the timings is more important [170].

These costs can furthermore be used in pharmacoeconomic studies such as cost of illness studies in order to determine the burden of disease in monetary terms [152]. This would

present a comprehensive picture of the cost of colorectal cancer for all stakeholders. This would however cause a logistical issue as the clinic is busy most days and could cause more issues trying to follow patients through the process in addition ethical approval may be difficult to obtain. Therefore the costs reported here are most likely higher than what was recorded. Over and above the limitations mentioned earlier, this study had multiple recording days which doesn't ensure that the same staff employees are recorded but does indicate the inevitable variation. Also only one investigator was recording and monitoring the stopwatch therefore human error does play a role in readings.

4.4.3.4.2 Private healthcare sector

The administrative costs for this sector include the global fee and facility fees as set out by the medical scheme tariffs but excluded the claims related to consultations as not every patient was charged a consultation fee for every cycle and in certain instances the consultations charged didn't correspond to oncologists but a surgeon or radiologist. A consultation fee was included for some patients over and above the global and facility fee however was excluded from the administrative costs. The consultation cost is a substantial amount (R 747,10 per consult) and should be further investigated.

In comparison to the time and motion study conducted in the public sector, the administrative costs are much higher and do have a contributing effect on the total costs as seen in the sensitivity analysis (Appendix Q). On average the cost contribution is between 10% and 45% of the total cost depending on the chemotherapy regimen. This is in line with previous research but is below the 70% threshold as found by Aitini and colleagues (2012) [237] in their economic comparison of CAPOX and FOLFOX [237]. On average for an I.V. regimen patients in the private sector will be charged 500% more and an oral regimen will be 600% more for administrative costs compared to the public sector. The public sector costs also include the time spent in a consultation with the specialist which were not included in the private sector calculations. Even though the salaries are higher in the private sector, a time and motion study should be undertaken in a similar manner to the public sector to validate the tariffs charged and to allow for a more accurate comparison.

4.4.3.5 Costs for multiple lines of therapies

Colorectal cancer has fewer lines of therapy in comparison to other cancers i.e. breast cancer however many more treatments are becoming available to patients particularly in the private healthcare sector. These newer therapies are aimed at advanced stages of the disease and come at a substantial price for disease progression to be marginally prolonged nevertheless the emotional benefits i.e. the hope given to patients and their families is of value to the patients. As more lines of therapies are included in the treatment of colorectal cancer, the cost of treatment will increase further more. Research directly related to colorectal cancer cost for multiple lines of treatment is lacking but from breast cancer research it is known that advanced breast cancer chemotherapy treatment is complex and resource intensive thereby increasing the cost [250]. These will become concerns as colorectal cancer treatment develops more complexity and cost savings require greater considerations as this will limit the number of patients that will have access to all available treatment.

4.5 Limitations

4.5.1 The public healthcare sector

Most limitations occurred in the retrospective drug utilisation reviews for each sector. For the public sector, there was no electronic data capturing system at the CMJAH oncology clinic – unit 495 thus the patient cohort might well be larger as the "new case" books were used to identify patients. If any incorrect entry was made into the "new case" books it would be overlooked. Also not all the "new case" books were attainable for the time period and as such approximately 10 months of new patients information was unknown. This was encountered a few times where patients weren't CRC patients but initial records reflect this. Due to the alphabetical filing system used in the clinic, patient files that were mistakenly filed incorrectly weren't located and were thus excluded. In addition, patient files weren't accessible if the patient names were misspelt or the "new case" books were illegible or when the hospital number (GT number) and patient names didn't match. Patient's that are still receiving treatment at the clinic, which proved to be more often than not the more recently diagnosed, files were taken out in order for them to be seen thus had not been filed back in time for data collection.

For the data capture, files didn't always contain all the necessary information such as co-morbidities. This would be helpful for data analysis so as to examine the number of patients on certain regimens. Pathology results weren't always available thus some instances required assumption of whether or not metastasis occurred. Photocopies of medical history or reports weren't always clear or the doctors handwriting may have been illegible thus assumptions may have had to be made.

Costing data in certain instances proved difficult and was unavailable for 2014 thus 2015 costs were used. Non-EML medicine costs were determined from the lowest cost SEP however; these costs will be lower if the medicines were on the EML. The administrative costs were for 2015 for both sectors however; the time and motion study had several limitations in that times were recorded irrespective of cancer. The type of cancer may play a role in the administrative costs and should be considered. Also certain days appeared to be busier at the clinic and will impact the performance of tasks. The time and motion study was only conducted at the one clinic and would need to be performed at various public healthcare sectors in order to determine the true cost to the State. The cost of adverse drug reactions can't be ignored when calculating the cost associated with chemotherapy but proves difficult as recording keeping and cross-referencing the diagnosis of patients presenting to emergency departments or doctors don't always coincide with the chemotherapy.

4.5.2 Private healthcare sector

The use of claims data as opposed to patient records is limited in that the additional clinical information is not captured therefore information such as right vs. left sided colorectal cancer can't be determined. Due to the type of the claims captured on the claims database, the average cost per regimen doesn't account for the line of therapy but is the average for the either the advanced CRC or early CRC group within the cohort. A comprehensive breakdown of the cost and equipment inclusions for the administrative costs was unavailable thus clarity and accuracy is lacking with respect to these costs and the administration costs.

4.5.3 Comparative analysis between the healthcare sectors

The variation in the data collection and type of data from each sector limits the comparisons that can be made particularly with the administration and administrative costs.

4.6 Conclusion

This study clearly illustrates the variation within chemotherapy treatment between the two South African healthcare sectors. Clinical practice guidelines and essential medicine lists may guide treatment. Although treatment pathways have shown cost savings such as reported by Feinberg and colleagues (2013) [123] that showed more than $ 8 million of savings, there has been debate as to whether or not these are essential. From this study it clearly indicates the need for treatment pathways as many regimens (approximately 30% - Table 3.24; Table 3.25) were prescribed unnecessarily and it seemed as though treatments lacked a "direction" or plan. This is particularly seen in the variation in both the chemotherapy and the supportive care medicines within the private sector. Treatment pathways should provide oncologists with evidence-based protocols thereby standardising treatments and limiting wastage and unnecessary financial strain.

This study does provide insight into the cost components and the most costly components of cancer therapy for each sector but also highlights the fewer options available to patients and their oncologists in the South African public sector, based on the treatment regimens found to be used in this study. It highlights the vast differences in treatment access for the same disease within the South African healthcare sector as a whole (4 public sector regimens excluding irinotecan vs. 12 private sector regimens excluding aflibercept). This indicates a need for further resource utilisation studies in order to ensure effective use of the available resources and to limited resource wastage for the respective funders.

4.7 Recommendations

The public sector retrospective drug utilisation review and time and motion study should be replicated in several other oncology facilities within Gauteng. These results should be compared to other provinces in order to determine if treatment is equitable between all public sector patients. Non-medical costs should be incorporated into the costing model, as should surgery and radiation for a complete costing of colorectal cancer. Additional economic evaluations such as cost-effectiveness calculations should be performed to refine pathways but also increase resource utilization as this basic cost analysis is a primary step required prior to additional value-based economic analysis. In addition, a trial could be designed to compare a treatment pathway cohort to a current practice cohort in order to see if there is any cost savings. In order for better comparisons, the methodology employed in the public sector

should be repeated at a private oncology clinic in order to ascertain data that is more comparable. This would particularly be with regard to the administration and administrative costs associated with receiving chemotherapy.

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APPENDICES

<u>Appendix A</u> Data collection sheet for Time and motion study **Date: _____**

TASK	TIME 1			TIME 2			TIME 3		
	Start	End	Total	Start	End	Total	Start	End	Total
Check-in									
Pink File									
Phlebotomy									
Lab									
Physician visit									
Pharmacy									
Drip administration and file completion									
Administration and Monitoring									
NOTES									

Appendix B Data Collection Sheet for Drug Utilisation Study

Patient information	
Patient identification code:	Date of Birth/ Age:
Gender:	
Date of first diagnosis:	Primary tumour site:
Previous surgery: Y ☐ N ☐ Previous radiotherapy: Y ☐ N ☐ *for colorectal cancer	
ICD code:	ECOG status:
Disease stage:	Metastases: Y ☐ N ☐ If Yes where: and date of diagnosis:

Treatment History			
Date	Drug	Dosage and Form	Instructions

Treatment plan				
No of cycles:				
Chemotherapy/Biologics:				
Drug	Originator/Generic	Dosage and Form	Frequency	Comments
Supportive therapies:				
Drug	Originator/Generic	Dosage and Form	Frequency	Comments

Treatment received					
No of cycles:					
Date of Administration	**Chemotherapy/Biologics:**				
	Drug	Originator/Generic	Dosage and Form	Frequency	Comments

Date of Administration	**Supportive therapies:**				
	Drug	Originator/Generic	Dosage and Form	Frequency	Comments

Pathology etc.:

<u>Appendix C</u> Medicine list and classification for claimed medicines within private sector patient cohort grouped by class based on the ATC classification system

ATC Classification	ATC Description	STRENGTH	DOSAGE FORM
Admin meds	ANTISEPTICS AND DISINFECTANTS		SLN
Admin meds	Carbohydrates – Dextrose OR Glucose		INF/INJ
Admin meds	Cetrimide		SLN
Admin meds	Chlorhexidine		SLN/SPR
Admin meds	Povidone-iodine		SLN/TUL
Admin meds	Silver nitrate		STI
Admin meds	Sodium chloride		INF/INJ/SLN
Admin meds	Solvents and diluting agents, incl. irrigating solutions - Water		INJ/INF/SLN/ MLS
Admin meds	Chloroform water		MLS
Chemotherapy	Azacitidine	100	INJ
Chemotherapy	Bevacizumab	400/100	INF
Chemotherapy	Calcium folinate	300/200/100/175/50/25/15	INJ/TAB
Chemotherapy	Capecitabine	500/150	TAB
Chemotherapy	Carboplatin	450	INJ
Chemotherapy	Cetuximab	5/2	INF
Chemotherapy	Cisplatin	50/10/0,5	INJ
Chemotherapy	Docetaxel	80/20	INF
Chemotherapy	Fludarabine	50	INJ
Chemotherapy	Fluorouracil	5000/1000/500/50/5	INJ/OIN
Chemotherapy	Gemcitabine	200/10	INJ
Chemotherapy	Idarubicin	10/5	INJ
Chemotherapy	Irinotecan	100/40/20	INF
Chemotherapy	Mitomycin	10/2	INJ
Chemotherapy	Oxaliplatin	100/50	INF
Chemotherapy	Paclitaxel	300/30	INF
Chemotherapy	Regorafenib	40	TAB
Chemotherapy	Tegafur, combinations		CAP
Chemotherapy	Tretinoin	10	CAP
Pain management	Acetylsalicylic acid	81	ECT
Pain management	Alfentanil	0,5	INJ
Pain management	Buprenorphine	20/10/5/0,2	TAB/PTD
Pain management	Celecoxib	200/100	CAP
Pain management	Codeine	30	TAB
Pain management	Diclofenac	100/50	DSP/SUP
Pain management	Dihydrocodeine	30	TAB
Pain management	Etoricoxib	90/60	TAB
Pain management	Fentanyl	100/75/50/25/12	INJ/PTD
Pain management	Hydromorphone	8/4	TAB

Pain management	Ibuprofen, combinations		CAP/TAB
Pain management	Lornoxicam	8	TAB
Pain management	Meloxicam	15/7,5	TAB
Pain management	Morphine - MST	60/30/10	SRT
Pain management	Morphine	15/10	PDR/INJ
Pain management	Oxycodone	80/40/20/10/5	SRT/CAP
Pain management	Paracetamol	500/1	TAB/CAP/INF
Pain management	Paracetamol, combinations excl. psycholeptics		TAB/CAP
Pain management	Tramadol	200/150/100/50	SRT/CAP/INJ
Pain management	Tramadol, combinations		TAB
Pain management	Tramadol, combinations		TAB
Pain management	Tramadol, combinations		TAB
Supportive meds	Aprepitant		KIT-CAP
Supportive meds	Aprepitant	125/80	CAP
Supportive meds	Betamethasone	6/5/4/0,6/0,5	INJ/TAB/SYR
Supportive meds	Cyclizine	100/50	SUP/TAB
Supportive meds	Dexamethasone	4	INJ
Supportive meds	Diazepam	10	INJ
Supportive meds	Domperidone	10	TAB
Supportive meds	Granisetron	3/2/1	TAB/INJ
Supportive meds	Haloperidol	5	TAB
Supportive meds	Hydrocortisone	100	INJ
Supportive meds	Lorazepam	2,5/1	TAB/SLT
Supportive meds	Methylprednisolone	500/125/40/16/4	TAB/INJ/OIN
Supportive meds	Metoclopramide	10/5	TAB/INJ/SYR
Supportive meds	Ondansetron	8/4	INJ/TAB/DSP
Supportive meds	Palonosetron	50	INJ
Supportive meds	Prednisone	20/5	TAB
Supportive meds	Prochlorperazine	25/12,5/5	TAB/SUP/INJ
Supportive meds	Promethazine	25/10/2,5	INJ/CRE/TAB
Supportive meds (additional)	Atropine	1/0,6/0,5	INJ/OPD

Appendix D Pivot table builders

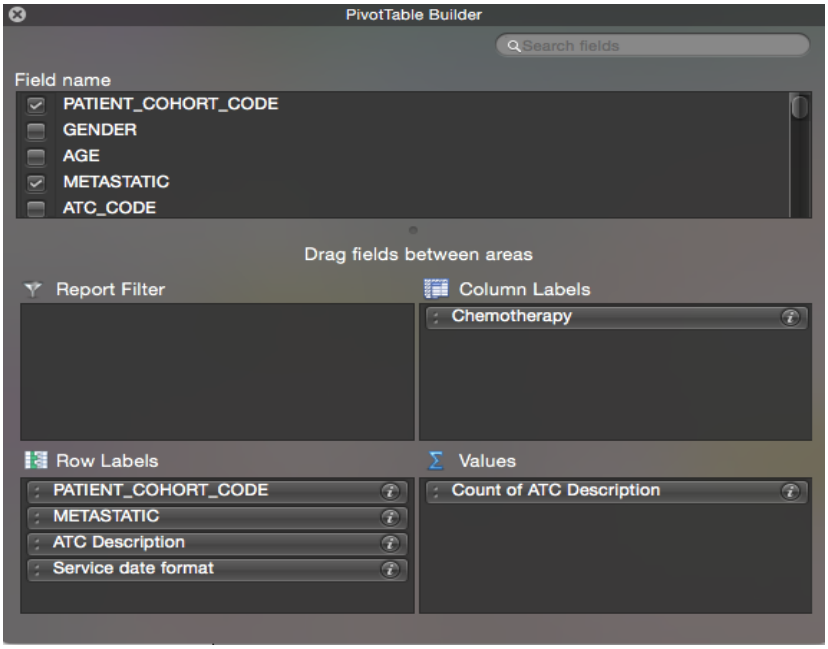

Figure 1 Pivot table builder for initial summary of data set A4 in order to determine treatment pathways - Based on the treatment pathways, patients were excluded if the treatment claimed/received was for other cancers such as breast, prostrate, lymphoma, ovary and myeloma to name a few.

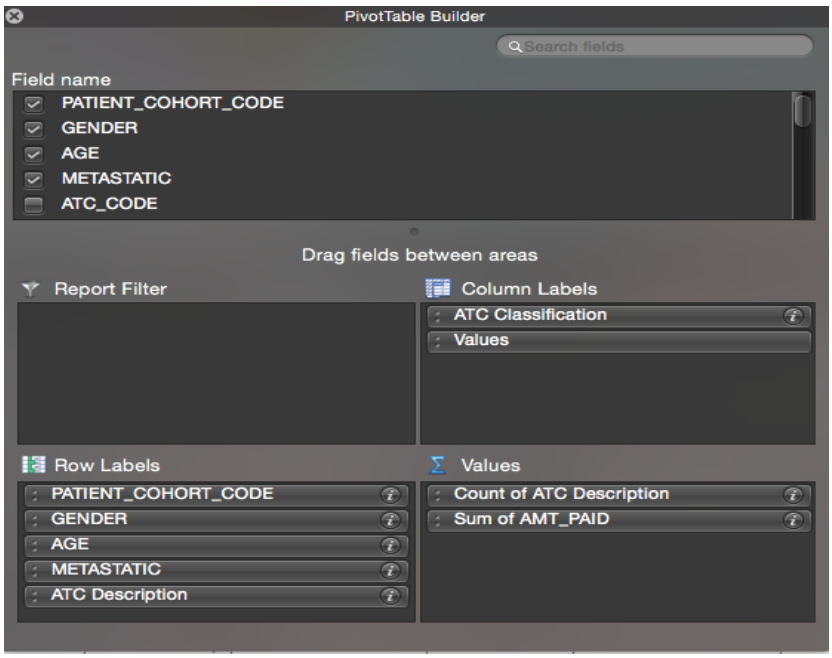

Figure 2 Pivot table builder for initial summary of data set A7 in order to determine claimed costs

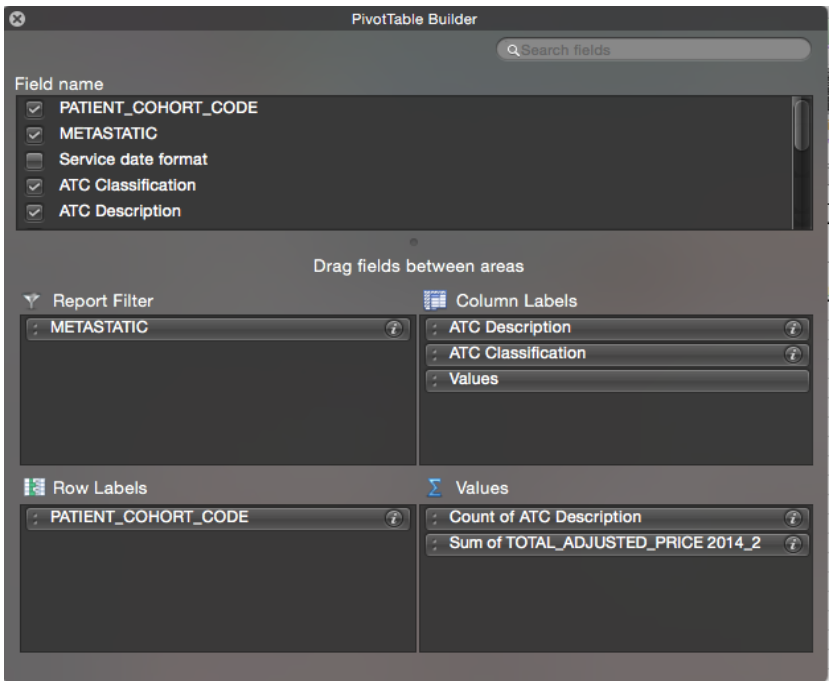

Figure 3 Pivot table builder for cost adjustment data in order to calculate the average costs and number of cycles – Filter will be either advanced CRC or early CRC

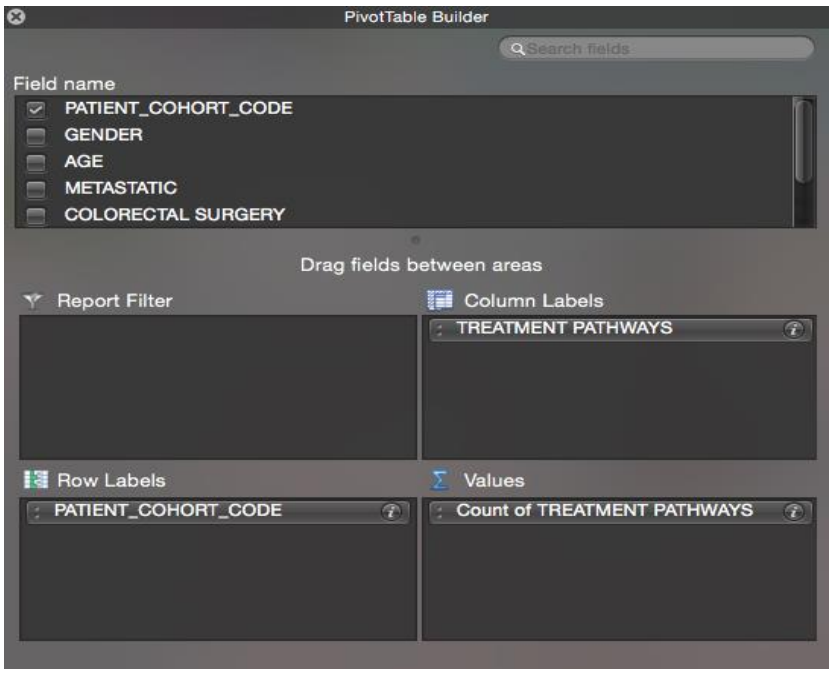

Figure 4 Pivot table generated in order to calculate the number of cycles per regimen and subsequently the average number of cycles per regimen – Each column used for the treatment pathways was denoted as 1, 2 etc.

Appendix E Medicine Lists

Table 1 Public healthcare sector - Chemotherapy (Essential Medicine List, 2014)

MEDICINE NAME	ATC	DOSAGE/S	PRODUCT NAME	CONTRACT NUMBER	PRICE (Rands)	LEVEL OF CARE
5-FLUOROURACIL	L01BC	50mg/ml	5-Fluorouracil 50 mg/mL 10 mL vial	HP04-2012Onc	**15,05**	TER
CAPECITABINE	L01BC	150mg	Capecitabine 150 mg 60 tablets	HP04-2012Onc	**413,54** [per tab = 6,89]	TER
		500mg	Capecitabine 500 mg 120 tablets	HP04-2012Onc	**2 782,42** [per tab = 23,19]	TER
FOLINIC ACID (Sodium or Calcium folinate/ Folinic acid)	V03AF	10mg/ml	Calcium folinate 10 mg/mL 20 mL vial	HP04-2012Onc	**120**	TER
		15mg	Calcium folinate 15 mg 10 tablets	HP04-2012Onc	**1 46,89**	TER
		300mg/30ml	Calcium folinate 300 mg/30mL 30 mL vial	HP04-2012Onc	**180**	TER
		50mg/vial	Calcium folinate 50 mg/vial 1 vial	HP04-2012Onc	**30**	TER
OXALIPLATIN	L01XA	50mg/ml	Oxaliplatin 50 mg/vial 1 vial	HP04-2012Onc	**702,68**	TER
		100mg/ml	Oxaliplatin 100 mg/vial 1 vial	HP04-2012Onc	**1 405,34**	TER

Table 2 Public healthcare sector – Supportive care medicines (Essential Medicine List, 2014)

MEDICINE NAME	ATC	DOSAGE/S	PRODUCT NAME	CONTRACT NUMBER	PRICE (Rands)	LEVEL OF CARE
5HT3 INHIBITORS	A004AA	4mg	Ondansetron 4 mg 10 tablets	HP04-2012ONC-01	**15,38** [per tab = 1,54]	HOSP
		4mg vial	Ondansetron 4 mg/2mL 2 mL ampoule	HP04-2012Onc	**4,45**	HOSP
		8mg	Ondansetron 8 mg 10 tablets	HP04-2012ONC-01	**16,90** [per tab = 1,69]	HOSP
		8mg vial	Ondansetron 8 mg/4mL 4 mL ampoule	HP04-2012Onc	**7,15**	HOSP
		1mg	Granisetron 1 mg 10 tablets	HP04-2012Onc	**201,78** [per tab = 20,18]	TER
		3mg vial	Granisetron 1 mg/mL 3 mL ampoule	HP04-2012Onc	**63,28**	TER
CORTICOSTEROIDS	H02AB	4mg vial	Dexamethasone 4 mg/mL 1 mL ampoule	HP06-2012SVP	**4,01**	HOSP
		5mg	Prednisone 5 mg 100 tablets	HP09-2012SD	**10,51** [per tab = 0,11]	HOSP
		5mg	Prednisone 5 mg 40 tablets	HP09-2012SD	**4,00** [per tab = 0,10]	HOSP
		5mg	Prednisone 5 mg 500 tablets	HP09-2012SD	**41,53** [per tab = 008]	HOSP
		5mg	Prednisone 5 mg 5000 tablets	HP09-2012-01	**410,11** [per tab = 0,08]	HOSP
DOPAMINE INHIBITORS		10mg	Metoclopramide 10 mg 100 tablets	HP09-2012SD	**6,63** [per tab = 0,07]	HOSP
		10mg	Metoclopramide 10 mg 500 tablets	HP09-2012SD	**19,45** [per tab = 0,04]	HOSP

Table 3 Public healthcare sector - Chemotherapy (Single exit price, 2014)

MEDICINE NAME	ATC	DOSAGE/S	PRODUCT NAME	NAPPI CODE	SEP (Rands)	LOWEST COST (Rands)	HIGHEST COST (Rands)	AVERAGE COST (Rands)
5-FLUOROURACIL	L01BC	50mg/ml	Floracor 50mg/ml Injection	711364001	**15,66**	**15,66**	**28,30**	**21,98**
			Floracor 50mg/ml Injection	711366001	**28,30**			
BEVACIZUMAB	L01XC	100mg/4ml	Avastin 100Mg 4Ml [251]	706042002	**3 682,56**	**3 682,56**	**3 682,56**	**3 682,56**
		400mg/16ml	Avastin 400Mg 16Ml [251]	706041002	**14 730,25**	**14 730,25**	**14 730,25**	**14 730,25**
CAPECITABINE	L01BC	150mg	Xeloda 150 [251]	870072005	**743,93**	**743,93**	**743,93**	**743,93**
		500mg	Xeloda 500 [251]	870080008	**5 005,51**	**5 005,51**	**5 005,51**	**5 005,51**
			Price per tab Xeloda 150:			**12,40**	**12,40**	**12,40**
			Price per tab Xeloda 500:			**41,71**	**41,71**	**41,71**
CETUXIMAB	L01XC	2mg/ml (not available)	Erbitux 2Mg/Ml (Merck)	710034001	**2 897,69**	**2 897,69**	**2 897,69**	**2 897,69**
		5mg/ml (20ml vial)	Erbitux 5Mg/Ml (Merck)	715052001	**2 897,69**	**2 897,69**	**2 897,69**	**2 897,69**
IRINOTECAN	L01XX	20mg/ml	Irinotas (Accord)	712643001	**370,50**	**370,50**	**370,50**	**370,50**
		40mg/2ml	Campto 40mg/2ml (Pfizer)	829560009	**1 025,44**	**374,40**	**1 025,44**	**494,94**
			Irinotecan Safeline 40 Mg/2 Ml	718488001	**375,00**			
			Sandoz Irinotecan 40	711903001	**380,00**			
			Mylan Irinotecan 40mg/2ml (Xixia)	717026001	**412,70**			
			Accord Irinotecan 40	712603001	**374,4**			
			Cipla Irinotecan 40 mg/2 ml	716182001	**402,12**			
		100mg/5ml	Campto 100mg/5ml (Pfizer)	829579001	**2 563,58**	**934,80**	**2 563,58**	**1 194,13**
			Irinotecan Safeline 100 Mg/5 Ml	718489001	**937,50**			
			Sandoz Irinotecan 100	711902001	**950,00**			
			Mylan Irinotecan 100mg/5ml (Xixia)	717027001	**1 031,75**			

			Accord Irinotecan 100	712872001	**936**			
			Irinotas 100 (Accord)	712873001	**934,80**			
			Cipla Irinotecan 100 mg/5 ml	716183001	**1 005,29**			
FOLINIC ACID (Sodium folinate)	V03AF	10mg/ml	Leucovorin Faulding 10mg/ml (Pharmaplan)	781525004	**76,18**	**76,18**	**76,18**	**76,18**
		15mg	Rescuvolin Tab (Pharmachemie) 10 TABS – NOT OFTEN USED	788503006	**198,70**	**198,70**	**198,70**	**198,70**
		15mg/vial	Rescuvolin Pfi 15(Pharmachemie)	827541018	**32,24**	**32,24**	**32,24**	**32,24**
		50mg/vial	Rescuvolin Vial (Pharmachemie)	788511017	**107,46**	**107,46**	**107,46**	**107,46**
		100mg/10ml	Abic Leucovorin 100mg/10ml (Teva)	704608001	**184,00**	**184,00**	**184,00**	**184,00**
		200mg/20ml	Abic Leucovorin 200mg/20ml (Teva)	704609001	**368,00**	**368,00**	**368,00**	**368,00**
		300mg/30ml	Abic Leucovorin 300mg/30ml (Teva)	704610001	**552,00**	**552,00**	**552,00**	**552,00**
OXALIPLATIN	L01XA	50mg/10ml (5mg/ml)	Oxaliplatin Pch 50	717567001	**1 061,34**	**974,13**	**1 794,62**	**1 418,11**
			Eloxatin 50mg/10ml RTU (Sanofi Aventis)	707494001	**1 300,44**			
			Oxaliwin 50mg/10ml RTU (Winthrop)	710319001	**980**			
			Intas Oxaliplatin 50 (Accord)	717829001	**974,13**			
			Accord Oxaliplatin 50	718138001	**980,00**			
			Exiplat 50 (Pharmaplan)	716224001	**1 794,62**			
		100mg/20ml (5mg/ml)	Oxaliplatin Pch 100	717569001	**2 122,60**	**1 948,26**	**3 589,22**	**3 228,19**
			Eloxatin 100mg/20ml RTU (Sanofi Aventis)	707495001	**2 600,89**			
			Oxaliwin 100mg/20ml RTU (Winthrop)	710317001	**1 960,00**			
			Intas Oxaliplatin 100 (Accord)	717830001	**1 948,26**			
			Accord Oxaliplatin 100	718139001	**1 960,00**			
			Exiplat 100 (Pharmaplan)	716225001	**3 589,22**			

PANITUMUMAB – Not registered – Section 21 Price (Registered in 2016)		100mg/5ml	Vectibix 5ml	714612001	**7 170,97**	**7 170,97**	**7 170,97**	**7 170,97**
REGORAFENIB - Registered Dec 2014		40mg	Stivarga 40 mg (28 tabs)	720787001	**52 782,91**	**52 782,91**	**52 782,91**	**52 782,91**
			Price per tab Regorafenib:			**1 885,10**	**1 885,10**	**1 885,10**
AFLIBERCEPT – International price March 2014		100mg/vial	Zaltrap 100mg	N/A	**5280,31**	**5280,31**	**5280,31**	**5280,31**
		200mg/vial	Zaltrap 200mg	N/A	**10560,62**	**10560,62**	**10560,62**	**10560,62**

Table 4 Public healthcare sector – Supportive care medicines (Single exit price, 2014)

MEDICINE NAME	DOSAGE/S	PRODUCT NAME	NAPPI CODE	SEP (Rands)	LOWEST COST (Rands)	HIGHEST COST (Rands)	AVERAGE COST (Rands)
ONDANSETRON	4mg/2ml	Alepet 4	717049001	**85,00**	**51,30**	**247,08**	**178,24**
		Sabax Ondansetron injection 4mg/2ml	711904001	**231,00**			
		Nausetron 4,0 Mg Injection	705078001	**168,08**			
		Ondansetron Fresenius 2mg/ml (4mg/2ml)	718557001	**51,3**			
		Zofran 4mg Injection	785806008	**240,53**			
		Mylan Ondansetron 4 Mg/2 Ml	705537001	**71,64**			
		Aspen Ondansetron 4Mg/2Ml	705458001	**247,08**			
		Zofer 4 Mg Injection	705941001	**102,11**			
		Dantron 4 Injection	708105001	**154,13**			
		Ondansetron - Hexal 4Mg Injection	710419001	**164,93**			
		Danset 4 Mg	710908001	**88,92**			
		Zydus-Ondansetron 4 mg Injection	711906001	**177,63**			
	8mg/4ml	Alepet 8	717050001	**170,00**	**102,60**	**494,16**	**321,97**
		Sabax Ondansetron injection 8mg/4ml	711905001	**462,01**			
		Nausetron 8,0 Mg Injection	705079001	**336,19**			
		Ondansetron Fresenius 2mg/ml (8mg/4ml)	718558001	**102,6**			
		Zofran 8mg Injection	785822003	**481,07**			
		Mylan Ondansetron 8 Mg /4 Ml	705538001	**143,2**			
		Aspen Ondansetron 8 Mg/4Ml	705460001	**494,16**			
		Zofer 8 Mg Injection	705943001	**204,21**			
		Dantron 8 Injection	708106001	**308,35**			
		Ondansetron - Hexal 8Mg Injection	710420001	**303,53**			
		Danset 8 Mg	710909001	**177,84**			
		Vomiz 8 mg Injection	711533001	**325,26**			
		Zydus-Ondansetron 8 mg Injection	711907001	**355,22**			
	4mg (pack-5)	Austell Ondansetron 4mg Tablets (pack-5)	716720001	**96,19**	**6,41 per tab**	**44,38 per tab**	**21,13 per tab**

		Dantron (pack-5)	704858002	**150,43**			
	4mg (pack-10)	Cipla-Ondansetron 4 (pack-10)	716801001	**153,16**			
		Zofer 4 Mg Tablets (pack-10)	705944001	**182,02**			
		Vomiz 4 mg Tablets (pack-10)	711531001	**144,72**			
	4mg (pack-15)	Zofran 4 (pack-15)	785814019	**665,66**			
		Dantron (pack-15)	704858001	**451,30**			
	4mg (pack-30)	Austell Ondansetron 4mg Tablets (30)	716720002	**192,39**			
	8mg (pack-5)	Austell Ondansetron 8mg Tablets (pack-5)	717154001	**192,33**	**12,82 per tab**	**70,04 per tab**	**35,60 per tab**
	8mg (pack-10)	Vomiz 8 mg Tablets (pack-10)	711532001	**289,47**			
		Cipla-Ondansetron 8 (pack-10)	716802001	**306,32**			
		Zofer 8 Mg Tablets (pack-10)	705945001	**364,03**			
	8mg (pack-15)	Zofran 8 (pack-15)	785830006	**1 050,65**			
		Dantron (pack-15)	706703001	**709,74**			
	8mg (pack-30)	Austell Ondansetron 8mg Tablets (30)	716154002	**384,66**			
GRANISETRON	1mg/ml	Granitril Injection	715706001	**168,86**	**151,62**	**425,53**	**225,26**
		Kytril Iv 1Ml	861863003	**425,53**			
		Sandoz Granisetron 1Mg/1Ml	714500001	**191,45**			
		Granisetron Teva 1	718524001	**151,62**			
		Adco Granisetron 1 Mg/1 Ml	712891001	**188,83**			
	3mg/3ml	Kytril Iv 3Ml	787019003	**854,78**	**545,63**	**854,78**	**635,31**
		Mylan Granisetron 3 Mg/3 Ml	714109001	**545,63**			
		Sandoz Granisetron 3Mg/3Ml	714501001	**574,34**			
		Adco Granisetron 3 Mg/3 Ml	712892001	**566,49**			
	1mg	Granitril 1Mg Tablet (pack-10)	715707001	**256,04**	**17,88 per tab**	**77,92 per tab**	**38,90 per tab**
		Kytril Oral (pack-10)	812374003	**779,24**			
		Granicip 1mg (pack-10)	716740001	**178,84**			
		Aspen Granisetron 1 Mg	713782001	**342**			

	2mg	Kytril Oral (pack-5)	701453001	**799,75**	**58,20 per tab**	**159,95 per tab**	**91,32 per tab**
		Granicip 2 mg (pack-5)	715305001	**291,01**			
		Aspen Granisetron 2 Mg	713784001	**279**			
DOLASETRON	100mg/20ml	Zamanon 100 mg IV	869961004	**1 232,01**	**1 232,01**	**1 232,01**	**1 232,01**
	200mg	Zamanon 200 mg Tablets (pack-3)	869988018	**379,57**	**126,52 per tab**	**126,52 per tab**	**126,52 per tab**
TROPISETRON	5mg/5ml	Navoban	806641010	**1 463,95**	**1 463,95**	**1 463,95**	**1 463,95**
	5mg	Navoban (pack-5)	806633018	**625,07**	**125,01 p/tab**	**125,01 p/tab**	**125,01 p/tab**
PALONOSETRON	50mcg/ml	Onicit	708388001	**465,14**	**465,14**	**465,14**	**465,14**
DEXAMETHASONE	4mg/ml	Decasone Injection 4Mg/Ml	818763019	**441,38**	**76,00**	**441,38**	**173,59**
		Pharma-Q Dexamethasone Phosphate Injection 4Mg/1Ml	701589001	**92,44**			
		Mylan Dexamethasone 4 Mg/Ml	718224001	**84,55**			
		Fresenius Dexamethasone 4 mg/1 ml	720206001	**76,00**			
PROCHLORPERAZINE	12,5mg/ml	Stemetil 1.25% M/V Inj 1 ml	766461009	**129,32**	**129,32**	**129,32**	**129,32**
	5mg (pack-25)	Stemetil (pack-25)	766542009	**70,68**	**0,16 per tab**	**2,83 per tab**	**1,52 per tab**
	5mg (pack-250)	Stemetil 5 mg Tablets (pack-250)	766542017	**617,88**			
		Mitil (pack-250)	744182026	**169,53**			
	5mg (pack-500)	Scripto-Metic 5Mg (pack-500)	762849126	**82,46**			
METOCLOPRAMIDE	10mg (pack-20)	Setin (pack-20)	783285019	**3,34**	**0,09 per tab**	**2,12 per tab**	**0,62 per tab**
		Maxolon t (pack-20)	740519018	**42,47**			
		Sandoz Metoclopramide (pack-20)	757845002	**4,58**			
	10mg (pack-100)	Setin (pack-100)	783285027	**16,71**			
		Maxolon t (pack-100)	740519026	**212,28**			
	10mg (pack-	Adco Contromet Tablet (pack-500)	715875124	**56,91**			

	500)	Betaclopramide (pack-500)	787817023	**62,49**			
		Bio Metoclopramide (pack-500)	717891001	**44,97**			
		Merck-Metoclopramide (pack-500)	701430001	**65,27**			
		Clopamon (pack-500)	714828017	**143,48**			
	10mg (pack-1000)	Setin (pack-1000)	783285035	**131,81**			
	10mg/2ml	Sabax Metoclopramide 10Mg/2Ml	856134007	**25,35**	**25,35**	**92,94**	**54,94**
		Pramalon	832839019	**29,64**			
		Clopamon Injection 10 mg/2 ml	714836001	**68,88**			
		Maxolon i 2ml (pack-10)	740535005	**92,94**			
		Pharma-Q Metoclopramide Injection 10Mg/2Ml	705973001	**32,58**			
APREPITANT	80mg	Emend (pack-5)	705301001	**1 191,18**	**238,24**	**238,24**	**238,24**
	125mg	Emend (pack-5)	705302001	**1 191,18**			
	COMBO PACK	Emend Combi Pack (1x125 + 2x80)	716467001	**714,71**			
ATROPINE	0,5mg/ml	Sabax Atropine 0.5mg/ml (1ml)	798428007	**22,11**	**22,11**	**43,23**	**29,91**
		Atropine Sulphate Fresenius 0.5Mg/1Ml	705551008	**43,23**			
		Pharma-Q Atropine Injection 0,5Mg/1Ml	700218001	**24,38**			
	1mg/ml	Sabax Atropine 1 Mg/Ml	798436018	**29,64**	**29,64**	**43,43**	**32,14**
		Atropine Sulphate Fresenius 1Mg/1Ml	705578003	**43,43**			
		Mylan Atropine	832758019	**24,84**			
		Pharma-Q Atropine Injection 1 Mg/1 Ml	700226001	**30,63**			

Appendix F Review articles used to identify the relevant clinical trials

Author/s	Title	Journal and Publication date	doi	PubMed or SCOPUS
Tol and Punt (2010) [175]	*Monoclonal antibodies in the treatment of metastatic colorectal cancer: a review*	Clin Ther. 2010 Mar;32(3):437-53	10.1016/j.clinthera.2010.03.012.	PubMed and SCOPUS
Edwards *et al.* (2012) *[176]*	*A systematic review of treatment guidelines for metastatic colorectal cancer*	Colorectal Dis. 2012 Feb;14(2):e31-47	10.1111/j.1463-1318.2011.02765.x.	PubMed and SCOPUS
Bekaii-Saab and Wu (2014) [179]	*Seeing the forest through the trees: a systematic review of the safety and efficacy of combination chemotherapies used in the treatment of metastatic colorectal cancer*	Crit Rev Oncol Hematol. 2014 Jul;91(1):9-34	10.1016/j.critrevonc.2014.01.001. Epub 2014 Jan 15.	PubMed
Kordatou, Kountourakis and Papamichael (2014) [178]	*Treatment of older patients with colorectal cancer: a perspective review*	Ther Adv Med Oncol. 2014 May;6(3):128-40	10.1177/1758834014523328.	PubMed and SCOPUS
Heinemann *et al.* (2013) *[177]*	*Targeted therapy in advanced CRC colorectal cancer-an example of personalised medicine in action*	Cancer Treat Rev. 2013 Oct;39(6):592-601	10.1016/j.ctrv.2012.12.011. Epub 2013 Jan 31.	PubMed
Fakih (2015) [180]	*Metastatic colorectal cancer: current state and future directions*	J Clin Oncol. 2015 Apr;33 [online]	10.1200/JCO.2014.59.7633	PubMed
Golfinopoulos, Pentheroudakis and Pavlidis (2006) [174]	*Treatment of colorectal cancer in the elderly: A review of the literature*	Cancer Treat Rev. 2006 32:1-8	10.1016/j.ctrv.2005.10.002.	SCOPUS

<u>Appendix G</u> Sample of early CRC group of patients stratified by site of origin of the colorectal cancer – The site of origin starts with general diagnosis of colon [252], followed by all right sided colon cancer diagnosis (purple), left sided colon cancer diagnosis including rectal cancer (pink/red) and lastly if more than one site was diagnosed (green). Treatment regimens are colour coded based on the treatment line, 1st line: Blue, 2nd line: Green, Maintenance: Orange, BSC: Yellow and if no therapy was administered: White. ***These tables are not the full data set but give an indication as to what data was recorded and analysed for the 2012 year at the CMJAH Oncology Clinic.***

Patient ID Code	G	Age	Treatment lines				
2012_001	M	63	**5FU + LV**				
2012_042	F	52	**NONE**				
2012_093	F	73	**CAPOX**	**CAPECITABINE**			
2012_069	F	56	**CAPOX**				
2012_046	F	72	**5FU + LV**				
2012_055	M	40	**CAPOX**				
2012_066	M	78	**NONE**				
2012_079	M	70	**CAPOX**				
2012_080	F	46	**NONE**				
2012_082	M	38	**CAPECITABINE**				
2012_107	M	60	**CAPOX**				
2012_108	M	63	**CAPOX**	**CAPECITABINE**			
2012_117	F	34	**CAPOX**	**CAPECITABINE**			
2012_119	F	U	**CAPOX**				
2012_137	F	44	**CAPOX**	**CAPECITABINE**			
2012_148	M	80	**NONE**				
2012_024	F	69	**NONE**				
2012_026	M	64	**CAPOX**				
2012_048	F	55	**NONE**				
2012_064	F	60	**CAPOX**	**CAPECITABINE**			

<u>Appendix H</u> Sample of advanced CRC group of patients stratified by site of origin of the colorectal cancer – The site of origin starts with general diagnosis of colon [252], followed by all right sided colon cancer diagnosis (purple), left sided colon cancer diagnosis including rectal cancer (pink/red) and lastly if more than one site was diagnosed (green). Treatment regimens are colour coded based on the treatment line, 1st line: Blue, 2nd line: Green, Maintenance: Orange, BSC: Yellow and if no therapy was administered: White. ***These tables are not the full data set but give an indication as to what data was recorded and analysed for the 2012 year at the CMJAH Oncology Clinic.***

Patient ID Code	G	Age	Treatment Pathways						
2012_030	F	67	CAPOX	BSC					
2012_040	F	43	BSC						
2012_070	F	60	NONE						
2012_099	M	59	CAPOX	XELIRI	CAPECITABINE + MITOMYCIN				
2012_127	F	74	CAPECITABINE	CAPOX	CAPECITABINE	XELIRI	CAPECITABINE + MITOMYCIN		CAPECITABINE
2012_136	M	46	CAPOX						
2012_023	F	50	CAPOX	CAPECITABINE					
2012_114	M	53	CAPOX	CAPECITABINE	XELIRI				
2012_129	M	58	CAPOX	XELIRI	CAPECITABINE				
2012_143	F	26	NONE						
2012_149	M	52	CAPOX						
2012_004	M	51	CAPOX	CAPECITABINE	CAPOX				
2012_131	M	U	BSC						
2012_009	F	56	CAPOX	CAPECITABINE	FOLFIRI	CAPECITABINE + MITOMYCIN		BSC	
2012_016	M	62	CAPOX	CAPECITABINE					
2012_144	M	62	CAPOX	CAPECITABINE	CAPECITABINE + MITOMYCIN				
2012_150	F	59	CAPOX	BSC					
2012_151	M	38	CAPECITABINE	CAPOX					
2012_025	F	65	CAPOX	CAPECITABINE					
2012_106	F	47	CAPOX	XELIRI	CAPECITABINE + MITOMYCIN		CAPECITABINE	BSC	

<u>Appendix I</u> Sample of treatment pathways and total claimed medical cost per early CRC patient – G: Gender, A: Age, METS: Advanced CRC status, CRC SURG: Colorectal surgery. Treatment pathway colour coding relates to the treatment line, Blue: 1st line, Green: 2nd line, Red: 3rd line, Turquoise: 4th line, Purple: 5th Line, White: NONE (no treatment but claims include diagnostic/radiation medicines etc.), Yellow: Best Supportive Care (BSC) and Orange: Maintenance therapy. Any non-conventional treatment line is indicated in one shade lighter for respective line. ***These tables are not the full data set but give an indication as to what data was recorded and analysed for the medical scheme claims database.***

PATIENT COHORT CODE	G	Age	CRC SURG.	TOTAL MEDICAL COST	TREATMENT PATHWAYS				
B0001	M	68	Y	R99 291,48	FOLFOX (6 CYCLES)				
B0002	M	73	Y	R769,61	BSC				
B0004	M	69	Y	R2 300,04	NONE				
B0011	F	55	Y	R116 987,64	5FU (9 CYCLES)	FOLFOX (7 CYCLES)	FOLFIRI (12 CYCLES)		
B0027	M	47	Y	R107 995,20	5FU (2 CYCLES)	FOLFOX (8 CYCLES)	CAPECITABINE (2 CYCLES)	IRINOTECAN (6 CYCLES)	
B0046	M	52	Y	R100 950,28	CAPOX (6 CYCLES)	CAPECITABINE (1 CYCLE)	XELIRI (1 CYCLE)	5FU (1 CYCLE)	FOLFIRI (1 CYCLE)
B0094	M	74	Y	R157 510,04	IRINOTECAN (1 CYCLE)	FOLFIRI (1 CYCLE)	CAPECITABINE (7 CYCLES)	FOLFOX (6 CYCLES)	5FU (2 CYCLES)
					FOLFIRI (8 CYCLES)				
B0173	M	56	Y	R45 015,29	CAPOX (1 CYCLE)	5FU (15 CYCLES)			
B0400	M	64	Y	R138 931,86	CAPOX (4 CYCLES)	IRINOTECAN (1 CYCLE)	FOLFIRI (2 CYCLES)	IRINOTECAN (1 CYCLE)	FOLFIRI (7 CYCLES)
B0401	F	68	Y	R4 495,04	BSC				
B0402	M	56	Y	R16 261,34	CAPOX (1 CYCLE)				
B0403	M	58	Y	R42 074,14	FOLFOX (4 CYCLES)	CAPOX (1 CYCLE)			
B0407	F	57	Y	R3 300,78	NONE				
B0408	M	58	Y	R76 366,38	CAPOX (7 CYCLES)	CAPECITABINE (1 CYCLE)			
B0409	M	56	Y	R83 849,07	CAPOX (8 CYCLES)				
B0517	M	75	Y	R344 114,95	FOLFOX (11 CYCLES)	FOLFIRI (17 CYCLES)	CAPOX (1 CYCLE)	FOLFOX (11 CYCLES)	
B0569	F	66	Y	R3 667,34	BSC				
B0690	F	36	Y	R74 994,89	FOLFOX (3 CYCLES)	FOLFOX + FLUDARABINE (1 CYCLE)	5FU (8 CYCLES)		

B0692	M	52	Y	R58 291,89	CAPECITABINE (7 CYCLES)				
B0696	F	65	Y	R53 087,95	CAPOX (4 CYCLES)	5FU (12 CYCLES)			
B0795	F	72	Y	R105 239,27	FOLFIRI (12 CYCLES)	5FU (1 CYCLE)	FOLFIRI (1 CYCLE)	5FU (1 CYCLE)	FOLFIRI (2 CYCLES)
					CAPOX (1 CYCLE)				
B0818	F	91	Y	R1 131,35	NONE				
B0821	F	70	Y	R3 337,46	BSC				
B0862	F	53	Y	R101 149,08	5FU (1 CYCLE)	CAPECITABINE (7 CYCLES)	CISPLATIN (4 CYCLES)	CAPOX (1 CYCLE)	
B0961	F	76	Y	R98 612,61	FOLFOX (6 CYCLES)	OXALIPATIN (1 CYCLE)	FOLFOX (3 CYCLES)		
B0991	M	40	N	R925,23	NONE				
B1162	F	68	Y	R101 229,28	OXALIPLATIN + TEGAFUR INCL. CA FOLINATE (7 CYCLES)				
B1267	M	73	Y	R231 350,50	CAPECITABINE (20 CYCLES)	IRINOTECAN (4 CYCLES)	CAPOX (8 CYCLES)	CAPECITABINE (7 CYCLES)	
B1283	M	63	Y	R38 011,75	CAPOX (2 CYCLES)	IRINOTECAN (5 CYCLES)			
B1285	M	71	Y	R4 142,28	5FU (1 CYCLE)				
B1326	M	60	N	R318 213,95	CAPOX (6 CYCLES)	5FU (1 CYCLE)	FOLFIRI (19 CYCLES)	OXALIPLATIN (1 CYCLE)	FOLFIRI (5 CYCLES)
B1327	F	68	Y	R91 823,88	CAPOX (2 CYCLES)	FOLFOX (5 CYCLES)			
B1350	F	54	Y	R107 220,21	FOLFOX (11 CYCLES)				
B1351	M	67	Y	R122 886,73	CAPOX (6 CYCLES)	CAPECITABINE (11 CYCLES)			
B1393	M	68	Y	R14 392,47	CAPECITABINE (1 CYCLE)	CAPECITABINE + MITOMYCIN (1 CYCLE)	CAPECITABINE (2 CYCLES)	CAPECITABINE + MITOMYCIN (1 CYCLE)	

<u>Appendix J</u> Treatment pathways and total claimed medical cost per advanced CRC patient – G: Gender, A: Age, METS: Advanced CRC status, CRC SURG: Colorectal surgery. Treatment pathway colour coding relates to the treatment line, Blue: 1st line, Green: 2nd line, Red: 3rd line, Turquoise: 4th line, Purple: 5th Line, Teal: 6th line, White: NONE (no treatment), Yellow: Best Supportive Care (BSC) and Orange: Maintenance therapy. Any non-conventional treatment line is indicated in one shade lighter for respective line. ***These tables are not the full data set but give an indication as to what data was recorded and analysed for the medical scheme claims database.***

PATIENT COHORT CODE	G	Age	CR SURG.	TOTAL MEDICAL COST	TREATMENT PATHWAYS				
B0003	F	59	Y	R373 466,69	FOLFOX (3 CYCLES)	FOLFIRI (10 CYCLES)	FOLFOX + BEV (9 CYCLES)	FOLFOX (1 CYCLE)	
B0008	M	69	Y	R214 314,01	FOLFOX + BEV (4 CYCLES)	FOLFOXIRI + BEV (1 CYCLE)	IRINOTECAN (1 CYCLE)	FOLFIRI (29 CYCLES)	IRINOTECAN (1 CYCLE)
B0010	M	69	N	R94 789,42	FOLFIRI (3 CYCLES)	IRINOTECAN (1 CYCLE)	FOLFIRI (7 CYCLES)	CAPOX (2 CYCLES)	
B0014	M	66	Y	R747 629,05	CAPOX (8 CYCLES)	XELIRI + BEV (16 CYCLES)			
B0015	M	70	Y	R293 055,60	FOLFOX (1 CYCLE)	FOLFOX + BEV (11 CYCLES)	CAPECITABINE (1 CYCLE)		
B0018	M	57	Y	R225 066,20	CAPOX (8 CYCLES)	CAPECITABINE (15 CYCLES)	XELIRI (2 CYCLES)		
B0019	M	68	Y	R125 658,72	CAPOX (1 CYCLE)	CAPOX + BEV (3 CYCLES)	XELIRI (1 CYCLE)		
B0022	M	68	Y	R381 349,71	FOLFOX + BEV (6 CYCLES)	FOLFOX (1 CYCLE)	FOLFOX + BEV (1 CYCLE)	FOLFOX (1 CYCLE)	FOLFOX + BEV (4 CYCLES)
					FOLFIRI (12 CYCLES)				
B0118	F	80	N	R200 724,72	FOLFIRI (15 CYCLES)	FOLFOX (12 CYCLES)	XELIRI (8 CYCLES)	5FU (10 CYCLES)	
B0121	M	60	Y	R399 114,72	CAPOX + BEV (7 CYCLES)	CAPOX (1 CYCLE)	IRINOTECAN (2 CYCLES)	FOLFIRI (1 CYCLE)	IRINOTECAN (3 CYCLES)
					FOLFIRI (1 CYCLE)				
B0123	F	49	N	R939 820,04	CAPOX + BEV (6 CYCLES)	FOLFIRI + BEV (1 CYCLE)	FOLFIRI (1 CYCLE)	FOLFIRI + BEV (11 CYCLES)	
B0124	F	64	Y	R81 955,97	FOLFOX (11 CYCLES)				
B0155	M	58	Y	R230 315,57	CAPECITABINE (4 CYCLES)	CAPOX (4 CYCLES)	FOLFIRI (1 CYCLE)	FOLFIRI + BEV (5 CYCLES)	CAPECITABINE (1 CYCLE)
					FOLFIRI (2 CYCLES)	FOLFIRI + BEV (1 CYCLE)			

B0170	M	58	Y	R475 803,94	CAPOX + BEV (4 CYCLES)	OXALIPLATIN (1 CYCLE)	FOLFIRI (15 CYCLES)	FOLFOXIRI (6 CYCLES)	CAPECITABINE + BEV (3 CYCLES)
					BEV (1 CYCLE)	CAPECITABINE + BEV (1 CYCLE)	BEV (1 CYCLE)	REGORAFENIB (1 CYCLE)	
B0174	M	57	Y	R107 222,09	FOLFOX (9 CYCLES)	5FU (3 CYCLES)			
B0205	F	55	Y	R166 197,93	FOLFOX (6 CYCLES)	FOLFIRI (3 CYCLES)	CARBOPLATIN + PACLITAXEL (3 CYCLES)	CISPLATIN + GEMCITABINE (1 CYCLE)	CARBOPLATIN + PACLITAXEL (1 CYCLE)
B0332	F	58	Y	R95 340,09	CAPOX (3 CYCLES)	OXALIPLATIN (1 CYCLE)	TEGAFUR, COMBO + IRINOTECAN (2 CYCLES)		
B0346	F	72	Y	R264 471,93	TEGAFUR, COMBO (1 CYCLE)	XELIRI (7 CYCLES)	OXALIPLATIN (6 CYCLES)	OXALIPLATIN + BEV (6 CYCLES)	
B0351	F	59	Y	R768 518,83	FOLFOX + CET (5 CYCLES)	FOLFIRI (1 CYCLE)	FOLFIRI + BEV (4 CYCLES)	5FU + BEV (5 CYCLES)	BEV (1 CYCLE)
					FOLFOX + CET (1 CYCLE)				
B0382	F	46	Y	R497 547,15	FOLFOX (4 CYCLES)	BEV (5 CYCLES)	XELIRI (5 CYCLES)	IRINOTECAN + BEV (7 CYCLES)	CAPOX + CET (1 CYCLE)
					CAPOX (1 CYCLE)	CAPOX + CET (1 CYCLE)			
B0383	F	59	N	R608 323,18	CAPOX + BEV (4 CYCLES)	OXALIPLATIN + BEV (3 CYCLES)	CAPECITABINE + BEV (10 CYCLES)	CAPECITABINE (5 CYCLES)	
B0388	M	40	Y	R248 240,05	FOLFOX (10 CYCLES)	IRINOTECAN + CET (3 CYCLES)			
B0390	M	38	Y	R756 363,48	CAPOX (6 CYCLES)	OXALIPLATIN (1 CYCLE)	FOLFIRI (9 CYCLES)	IRINOTECAN + CET (2 CYCLES)	FOLFIRI + CET (3 CYCLES)
					CAPECITABINE + CET (1 CYCLE)	IRINOTECAN + BEV (3 CYCLES)	FOLFOX + CET (1 CYCLE)		
B0392	F	61	Y	R144 328,15	FOLFOX (6 CYCLES)				
B0395	M	55	Y	R132 083,10	OXALIPLATIN (1 CYCLE)	FOLFOX + BEV (5 CYCLES)			
B0404	M	70	Y	R253 027,45	FOLFOX (10 CYCLES)	FOLFIRI + BEV (7 CYCLES)			

Appendix K Theoretical costs calculated from costing model for public healthcare sector

Table 5 Theoretical chemotherapy costs for early CRC colon cancer in the public healthcare sector

Chemotherapy costs for early CRC colon costs							
Chemotherapy cost per cycle is based on cost per vial, not on cost per mg.							
	5-FU	**LV**	**Capecitabine**	**Capecitabine**	**Capecitabine**	**Oxaliplatin**	**Rationale / Reference**
No. of cycles	6	6	8	8	8	6	*see pvt sector SAOC primary LOC
No. of administration per cycle	1	1	28	28	28	1	
Average BSA (m2)	**1,73**	**1,73**	**1,73**	**1,73**	**1,73**	**1,73**	Av BSA for cancer patient (Heaf, 2007; McIntosh et al., 1928)
Dose (mg/m2)	2800	400	850	1050	1250	85	Clinical trial data and treatment guidelines (NCCN)
Dose per administration (mg)	4844	692	1470,5	1816,5	2162,5	147,05	
Dose per cycle (mg)	4844	692	41174	50862	60550	147,05	
No. of vials (tabs) per cycle	10	4	84	102	122	2	
	(500mg x 10)	(300mg x 2), (50mg x 2)	(500mg x 82), (150mg x 2)	(500mg x 102)	(500mg x 121), (150mg x 1)	(100mg x 1), (50mg x 1)	
Medicine price / vial (tab)	R 15,05	R 180,00	R6,89	R23,19	R6,89	R 702,68	EML Feb 2014
(medicine 1, medicine 2 ect)		R 30,00	R23,19		R23,19	R 1 405,34	
Medicine costs per cycle	**R150,50**	**R420,00**	**R1 915,36**	**R2 365,38**	**R2 812,88**	**R2 108,02**	
Total medicine costs (x cycles)	**R903,00**	**R2 520,00**	**R15 322,88**	**R18 923,04**	**R22 503,04**	**R12 648,12**	

Table 6 Theoretical chemotherapy costs for early CRC rectal cancer in the public healthcare sector

Chemotherapy costs for early CRC rectal cancer			
Chemotherapy cost per cycle is based on cost per vial, not on cost per mg.			
	5-FU	**LV**	**Rationale / Reference**
No. of cycles	4	4	*see pvt sector SAOC primary LOC (2+2)
No. of administration per cycle	1	1	
Average BSA (m2)	**1,73**	**1,73**	Av BSA for cancer patient (Heaf, 2007; McIntosh et al., 1928)
Dose (mg/m2)	2800	400	Clinical trial data and treatment guidelines (NCCN)
Dose per administration (mg)	4844	692	
Dose per cycle (mg)	4844	692	
No. of vials per cycle	10	4	
	(500mg x 10)	(300mg x 2), (50mg x 2)	
Medicine price / vial	R 15,05	R 180,00	EML Feb 2014
(medicine 1, medicine 2 ect)		R 30,00	
Medicine costs per cycle	**R150,50**	**R420,00**	
Total medicine costs (x cycles)	**R602,00**	**R1 680,00**	

Table 7 Theoretical chemotherapy costs for advanced CRC in the public healthcare sector

Chemotherapy costs for advanced CRC							
Chemotherapy cost per cycle is based on cost per vial, not on cost per mg.							
	5-FU	**LV**	**Capecitabine**	**Capecitabine**	**Capecitabine**	**Oxaliplatin**	**Rationale / Reference**
No. of cycles	6	6	8	8	8	6	*see pvt sector SAOC primary LOC
No. of administration per cycle	1	1	28	28	28	1	
Average BSA (m2)	**1,73**	**1,73**	**1,73**	**1,73**	**1,73**	**1,73**	Av BSA for cancer patient (Heaf, 2007; McIntosh et al., 1928)
Dose (mg/m2)	2800	400	850	1050	1250	85	Clinical trial data and treatment guidelines (NCCN)
Dose per administration (mg)	4844	692	1470,5	1816,5	2162,5	147,05	
Dose per cycle (mg)	4844	692	41174	50862	60550	147,05	
No. of vials (tabs) per cycle	10	4	84	102	122	2	
	(500mg x 10)	(300mg x 2), (50mg x 2)	(500mg x 82), (150mg x 2)	(500mg x 102)	(500mg x 121), (150mg x 1)	(100mg x 1), (50mg x 1)	
Medicine price / vial (tab)	R15,05	R180,00	R6,89	R23,19	R6,89	R702,68	EML Feb 2014
(medicine 1, medicine 2 ect)		R30,00	R23,19		R23,19	R1 405,34	
Medicine costs per cycle	**R150,50**	**R420,00**	**R1 915,36**	**R2 365,38**	**R2 812,88**	**R2 108,02**	
Total medicine costs (x cycles)	**R903,00**	**R2 520,00**	**R15 322,88**	**R18 923,04**	**R22 503,04**	**R12 648,12**	

Appendix L Theoretical costs calculated from costing model for private healthcare sector

Table 8 Theoretical chemotherapy costs for early CRC (colon) in the private healthcare sector

Chemotherapy costs for early CRC colon (lowest SEP)								
Chemotherapy cost per cycle is based on cost per vial, not on cost per mg.								
	5-FU	**LV**	**Capecitabine**	**Capecitabine**	**Capecitabine**	**Oxaliplatin**	**Irinotecan**	**Rationale / Reference**
No. of cycles	6	6	8	8	8	6	6	SAOC Aug 2014 Guidelines (Std LOC)
No. of administration per cycle	1	1	28	28	28	1	1	
Average BSA (m2)	**1,73**	**1,73**	**1,73**	**1,73**	**1,73**	**1,73**	**1,73**	Av BSA for cancer patient (Heaf, 2007; McIntosh et al., 1928)
Dose (mg/m2)	2800	400	850	1050	1250	85	180	Clinical trial data and treatment guidelines (NCCN)
Dose per administration (mg)	4844	692	1470,5	1816,5	2162,5	147,05	311,4	
Dose per cycle (mg)	4844	692	41174	50862	60550	147,05	311,4	
No. of vials per cycle	10	3	84	102	122	2	4	
	(500mg x 10)	(100mg x 1), (300mg x 2)	(500mg x 82), (150mg x 2)	(500mg x 102)	(500mg x 121), (150mg x 1)	(100mg x 1), (50mg x 1)	(20mg X 1) (100mg X 3)	
Medicine price / vial	R 15,66	R 184,00	R 12,40	R 12,40	R 12,40	R 974,13	R370,50	SEP Aug 2014
(medicine 1, medicine 2 etc.)		R 552,00	R 41,71	R 41,71	R 41,71	R 1 948,26	R934,80	
Medicine costs per cycle	**R 156,61**	**R 1 288,00**	**R3 445,02**	**R4 254,42**	**R5 059,31**	**R 2 922,39**	**R3 174,90**	
Total medicine costs (x cycles)	**R 939,68**	**R 7 728,00**	**R27 560,16**	**R34 035,36**	**R40 474,48**	**R 17 534,34**	**R19 049,40**	

Table 9 Theoretical chemotherapy costs for early CRC (rectal) in the private healthcare sector

Chemotherapy costs for early CRC (lowest SEP)			
Chemotherapy cost per cycle is based on cost per vial, not on cost per mg.			
	5-FU	**LV**	**Rationale / Reference**
No. of cycles	4	4	SAOC Aug 2014 Guidelines (Std LOC) - (2+2)
No. of administration per cycle	1	1	
Average BSA (m2)	**1,73**	**1,73**	Av BSA for cancer patient (Heaf, 2007; McIntosh et al., 1928)
Dose (mg/m2)	2800	400	Clinical trial data and treatment guidelines (NCCN)
Dose per administration (mg)	4844	692	
Dose per cycle (mg)	4844	692	
No. of vials per cycle	10	3	
	(500mg x 10)	(100mg x 1), (300mg x 2)	
Medicine price / vial	R 15,66	R 184,00	SEP Aug 2014
(medicine 1, medicine 2 ect)		R 552,00	
Medicine costs per cycle	**R 156,61**	**R 1 288,00**	
Total medicine costs (x cycles)	**R 626,45**	**R 5 152,00**	

Table 10 Theoretical chemotherapy costs for advanced CRC in the private healthcare sector

Chemotherapy costs for advanced CRC (lowest SEP)								
Medicine cost per cycle is based on cost per vial (tab), not on cost per mg.								
	5-FU	**LV**	**Capecitabine**	**Capecitabine**	**Capecitabine**	**Oxaliplatin**	**Irinotecan**	**Rationale / Reference**
No. of cycles	6	6	8	8	8	6	12	(SAOC Aug 2014 Guidelines)
No. of administration per cycle	1	1	28	28	28	1	1	
Average BSA (m2)	**1,73**	**1,73**	**1,73**	**1,73**	**1,73**	**1,73**	**1,73**	Av BSA for cancer patient (Heaf, 2007; McIntosh et al., 1928)
Dose (mg/m2)	2800	400	850	1050	1250	85	180	Clinical trial data and treatment guidelines (NCCN)
Dose per administration (mg)	4844	692	1470,5	1816,5	2162,5	147,05	311,4	
Dose per cycle (mg)	4844	692	41174	50862	60550	147,05	311,4	
No. of vials (tabs) per cycle	10	3	84	102	122	2	4	
	(500mg x 10)	(100mg x 1), (300mg x 2)	(500mg x 82), (150mg x 2)	(500mg x 102)	(500mg x 121), (150mg x 1)	(100mg x 1), (50mg x 1)	(100mg x 3), (20mg x 1)	
Medicine price / vial	R15,66	R184,00	R12,40	R12,40	R12,40	R974,13	R370,50	SEP Aug 2014
(medicine 1, medicine 2 ect)		R552,00	R41,71	R41,71	R41,71	R1 948,26	R934,80	
Medicine costs per cycle	**R156,61**	**R1 288,00**	**R3 445,02**	**R4 254,42**	**R5 059,31**	**R2 922,39**	**R3 174,90**	
Total medicine costs (x cycles)	**R939,68**	**R7 728,00**	**R27 560,16**	**R34 035,36**	**R40 474,48**	**R17 534,34**	**R38 098,80**	

Table 11 Theoretical biological medicine costs for advanced CRC in the private healthcare sector

Chemotherapy costs for advanced CRC (biologics) NB! Only originators available								
Medicine cost per cycle is based on cost per vial (tab), not on cost per mg.								
	Bevacizumab (1st line)	**Bevacizumab (2nd line)**	**Cetuximab (loading dose)**	**Cetuximab**	**Panitumumab**	**Aflibercept**	**Regorafenib**	**Rationale/Reference**
No. of cycles	10	10	1	8	8	9	3	(SAOC Aug 2014 Guidelines)/ Literature for unreg/newly reg
No. of administration per cycle	1	1	1	2	1	1	21	Av BSA for cancer patient (Heaf, 2007; McIntosh et al., 1928),
Average BSA (m2) or BW (kg)	70	70	1,73	1,73	70	70		Conventional ideal BW [164]
Dose (mg/m2)	5	10	400	250	6	4	Flat dose	Clinical trial data and treatment guidelines (NCCN)
Dose per administration (mg)	350	700	692	432,5	420	280	160	
Dose per cycle (mg)	350	700	692	865	420	280	3360	
No. of vials (tabs) per cycle	1	4	7	9	5	3	84	
	(4oomg x 1)	(400mg x 1), (100mg x 3)	(100mg x 7)	(100mg x 9)	(100mg x 5)	(100mg x 1), (200mg x 1)	(40mg)	
Medicine price / vial (medicine 1, medicine 2 ect)	R3 682,56	R3 682,56	R2 897,69	R2 897,69	R7 170,97	R5 280,31	R628,37	SEP Aug 2014/ SEP Mar 2015/ Section 21 2014 (Amgen)
	R14 730,25	R14 730,25				R10 560,62		
Medicine costs per cycle	**R14 730,25**	**R25 777,94**	**R20 283,83**	**R26 079,21**	**R35 854,85**	**R15 840,93**	**R52 782,80**	
Total medicine costs (x cycles)	**R147 302,49**	**R257 779,40**	**R20 283,83**	**R208 633,68**	**R286 838,80**	**R142 568,37**	**R158 348,40**	
			Therefore for CET: Loading dose +					
			Cycle doses =					
			R228 917,51					

<u>Appendix M</u> Total theoretical treatment pathways costs for advanced CRC in the private healthcare sector for RAS mutant type patients– Due to all the possible dose combinations for regimens comprised of Capecitabine (Cape), CAPOX and XELIRI doses are seen at the top of the columns for the costs and CAPOX/Bev doses are in brackets behind regimen.

Total Pathway costs RAS mutant type (average for two type of facilities):	CAPOX + XELIRI dose combinations	**(850 +850)**	**(1050+850)**	**(1250+850)**	**(850 +1050)**	**(1050+1050)**	**(1250+1050)**	**(850 +1250)**	**(1050+1250)**	**(1250+1250)**
	CAPOX, XELIRI, FOLFOX/BEV, FOLFIRI/AFLIBERCEPT, REGORAFENIB	R755 958,54	R762 433,74	R768 872,86	R762 433,74	R768 908,94	R775 348,06	R768 872,86	R775 348,06	R781 787,18
	CAPOX, XELIRI, CAPOX/BEV (850), FOLFIRI/AFLIBERCEPT, REGORAFENIB	R775 962,60	R782 437,80	R788 876,92	R782 437,80	R788 913,00	R795 352,12	R788 876,92	R795 352,12	R801 791,24
	CAPOX, XELIRI, CAPOX/BEV (1050), FOLFIRI/AFLIBERCEPT, REGORAFENIB	R784 056,60	R790 531,80	R796 970,92	R790 531,80	R797 007,00	R803 446,12	R796 970,92	R803 446,12	R809 885,24
	CAPOX, XELIRI, CAPOX/BEV (1250), FOLFIRI/AFLIBERCEPT, REGORAFENIB	R792 105,50	R798 580,70	R805 019,82	R798 580,70	R805 055,90	R811 495,02	R805 019,82	R811 495,02	R817 934,14
	CAPOX, XELIRI, FOLFIRI/BEV, FOLFIRI/AFLIBERCEPT, REGORAFENIB	R737 020,29	R743 495,49	R749 934,61	R743 495,49	R749 970,69	R756 409,81	R749 934,61	R756 409,81	R762 848,93
	CAPOX dose	**850**	**1050**	**1250**						
	CAPOX, FOLFIRI, FOLFOX/BEV, FOLFIRI/AFLIBERCEPT, REGORAFENIB	R772 376,98	R778 852,18	R785 291,30						
	CAPOX, FOLFIRI, CAPOX/BEV (850), FOLFIRI/AFLIBERCEPT, REGORAFENIB	R792 381,05	R798 856,25	R805 295,37						
	CAPOX, FOLFIRI, CAPOX/BEV (1050), FOLFIRI/AFLIBERCEPT, REGORAFENIB	R800 475,05	R806 950,25	R813 389,37						

	CAPOX, FOLFIRI, CAPOX/BEV (1250), FOLFIRI/AFLIBERCEPT, REGORAFENIB	R808 523,95	R814 999,15	R821 438,27						
	CAPOX, FOLFIRI, FOLFIRI/BEV, FOLFIRI/AFLIBERCEPT, REGORAFENIB	R753 438,73	R759 913,93	R766 353,05						
	FOLFOX, FOLFIRI, FOLFOX/BEV, FOLFIRI/AFLIBERCEPT, REGORAFENIB	R786 348,11								
	FOLFOX, FOLFIRI, CAPOX/BEV (850), FOLFIRI/AFLIBERCEPT, REGORAFENIB	R806 352,17								
	FOLFOX, FOLFIRI, CAPOX/BEV (1050), FOLFIRI/AFLIBERCEPT, REGORAFENIB	R814 446,17								
	FOLFOX, FOLFIRI, CAPOX/BEV (1250), FOLFIRI/AFLIBERCEPT, REGORAFENIB	R822 495,07								
	FOLFOX, FOLFIRI, FOLFIRI/BEV, FOLFIRI/AFLIBERCEPT, REGORAFENIB	R767 409,86								
	XELIRI dose	**850**	**1050**	**1250**						
	FOLFOX, XELIRI, FOLFOX/BEV, FOLFIRI/AFLIBERCEPT, REGORAFENIB	R769 929,66	R776 404,86	R782 843,98						
	FOLFOX, XELIRI, CAPOX/BEV (850), FOLFIRI/AFLIBERCEPT, REGORAFENIB	R789 933,73	R796 408,93	R802 848,05						
	FOLFOX, XELIRI, CAPOX/BEV (1050), FOLFIRI/AFLIBERCEPT, REGORAFENIB	R798 027,73	R804 502,93	R810 942,05						

	FOLFOX, XELIRI, CAPOX/BEV (1250), FOLFIRI/AFLIBERCEPT, REGORAFENIB	R806 076,63	R812 551,83	R818 990,95						
	FOLFOX, XELIRI, FOLFIRI/BEV, FOLFIRI/AFLIBERCEPT, REGORAFENIB	R750 991,41	R757 466,61	R763 905,73						

<u>Appendix N</u> Total theoretical treatment pathways costs for advanced CRC in the private healthcare sector for RAS wildtype patients – Due to all the possible dose combinations for regimens comprised of Capecitabine (Cape), CAPOX and XELIRI doses are seen at the top of the columns for the costs and CAPOX/Bev doses are in brackets behind regimen.

Total Pathway costs RAS wildtype (average for two type of facilities):	CAPOX dose	**850**	**1050**	**1250**							
	CAPOX, FOLFIRI, FOLFIRI/CET, FOLFOX/BEV, FOLFIRI/AFLIBERCEPT, REGORAFENIB	R1 403 389,32	R1 409 864,52	R1 416 303,64							
	CAPOX, FOLFIRI, FOLFOX/PAN, FOLFIRI/BEV, FOLFIRI/AFLIBERCEPT, REGORAFENIB	R1 100 226,28	R1 106 701,48	R1 113 140,60							
	CAPOX + XELIRI dose combination	**(850 +850)**	**(1050+850)**	**(1250+850)**	**(850 +1050)**	**(1050+1050)**	**(1250+1050)**	**(850 +1250)**	**(1050+1250)**	**(1250+1250)**	
	CAPOX, XELIRI, FOLFIRI/CET, FOLFOX/BEV, FOLFIRI/AFLIBERCEPT, REGORAFENIB	R1 386 970,87	R1 393 446,07	R1 399 885,19	R1 393 446,07	R1 399 921,27	R1 406 360,39	R1 399 885,19	R1 406 360,39	R1 412 799,51	
	CAPOX, XELIRI, FOLFOX/PAN, FOLFIRI/BEV, FOLFIRI/AFLIBERCEPT, REGORAFENIB	R1 083 807,84	R1 090 283,04	R1 096 722,16	R1 090 283,04	R1 096 758,24	R1 103 197,36	R1 096 722,16	R1 103 197,36	R1 109 636,48	
	FOLFOX, FOLFIRI, FOLFIRI/CET, FOLFOX/BEV, FOLFIRI/AFLIBERCEPT, REGORAFENIB	R1 417 360,44									

	FOLFOX, FOLFIRI, FOLFOX/PAN, FOLFIRI/BEV, FOLFIRI/AFLIBERCEPT, REGORAFENIB	R1 114 197,41								
	XELIRI dose	**850**	**1050**	**1250**						
	FOLFOX, XELIRI, FOLFIRI/CET, FOLFOX/BEV, FOLFIRI/AFLIBERCEPT, REGORAFENIB	R1 400 942,00	R1 407 417,20	R1 413 856,32						
	FOLFOX, XELIRI, FOLFOX/PAN, FOLFIRI/BEV, FOLFIRI/AFLIBERCEPT, REGORAFENIB	R1 097 778,96	R1 104 254,16	R1 110 693,28						

<u>Appendix O</u> Theoretical chemotherapy costs per healthcare sector - Ramucirumab and TAS-102 are unavailable in South Africa, 5FU/LV is 5-fluorouracil and folinic acid, Cape – capecitabine, CAPOX – capecitabine and oxaliplatin, FOLFOX - 5-fluorouracil, folinic acid and oxaliplatin. XELIRI – capecitabine and irinotecan, FOLFIRI – 5-fluorouracil, folinic acid and irinotecan, Bev – bevacizumab, Pani – panitumumab, CET – cetuximab.

Public sector chemotherapy costs*								
	5-FU + LV	**FOLFOX**	**Cape (850)**	**Cape (1050)**	**Cape (1250)**	**CAPOX (850)**	**CAPOX (1050)**	**CAPOX (1250)**
Cost per cycle	R570,50	R2 678,52	R1 915,36	R2 365,38	R2 812,88	R4 023,38	R4 473,40	R4 920,90
Private sector chemotherapy costs – early CRC								
	5-FU + LV	**FOLFOX**	**Cape (850)**	**Cape (1050)**	**Cape (1250)**	**CAPOX (850)**	**CAPOX (1050)**	**CAPOX (1250)**
Cost per cycle	R1 444,61	R4 367,00	R3 445,02	R4 254,42	R5 059,31	R6 367,41	R7 176,81	R7 981,70
Private sector chemotherapy costs – advanced CRC[♯]								
	CAPOX (850) + Bev	**CAPOX (1050) + Bev**	**CAPOX (1250) + Bev**	**FOLFOX + Bev**	**FOLFOX + Bev (2nd line)**	**FOLFIRI + Aflibercept**	**FOLFOX + Pani**	**Regorafenib**
Cost per cycle	R21 097,66	R21 907,06	R22 711,95	R19 097,25	R30 144,94	R20 460,44	R40 221,85	R158 348,40
	FOLFIRI + Cet	**FOLFIRI + Bev (2nd line)**	**XELIRI (850)**	**XELIRI (1050)**	**XELIRI (1250)**	**FOLFIRI**		
Cost per cycle	R50 982,55	R30 397,45	R6 619,92	R7 429,32	R8 234,21	R4 619,51		

* Costs are the same for both early and advanced CRC as the regimens are the same

[♯] Costs for regimens that differ from early

Appendix P Time and Motion Study Results

Time and Motion Study - Data Points										
Day 1: 28/9/2015										
Task	**Time 1**	**Time 2**	**Time 3**	**Time 4**	**Time 5**	**Time 6**	**Time 7**	**Time 8**	**Time 9**	**Average**
Check-in	00:01:06	00:01:35	00:02:00	00:02:02	00:01:54	00:02:05	00:02:44	00:01:11	00:01:51	00:01:50
Pink file	00:00:45	00:01:20	00:00:40	00:00:52	00:01:01	00:00:58	00:01:08	00:00:47	00:01:07	00:00:58
Phlebotomy	00:04:28	00:05:00	00:03:50	00:02:31	00:04:31	00:04:34	00:04:10	00:03:35	00:04:36	00:04:08
Lab	2 - 2,5 hrs. = 120 - 150 min									02:15:00 (MIDPOINT)
Physician visit	00:05:39	00:08:36	00:06:29	00:13:37	00:08:47	00:05:11	00:04:38	00:09:33	00:09:03	00:07:57
Pharmacy - oral	00:02:10	00:03:05	00:01:18	00:02:39	00:02:54	00:06:28	00:01:39	00:03:48	00:04:04	00:03:07
Pharmacy - mixing	00:09:40	00:10:35	00:08:48	00:10:09	00:10:24	00:13:58	00:09:09	00:11:18	00:11:34	00:10:37 (ORAL SCRIPT PREP + MIDPOINT MIXING TIME 00:07:30)
Drip admin + file update	00:02:17	00:03:25	00:02:37	00:03:25	00:03:11	00:02:59	00:03:39	00:03:32	00:04:14	00:03:15
Administration + Monitoring	2 - 2,5 hrs. = 120 - 150 min									02:15:00 (MIDPOINT)

Time and Motion Study - Data Points										
Day 2: 6/10/2015										
Task	**Time 1**	**Time 2**	**Time 3**	**Time 4**	**Time 5**	**Time 6**	**Time 7**	**Time 8**	**Time 9**	**Average**
Check-in	00:01:17	00:01:52	00:01:44	00:01:39	00:02:32	00:01:04	00:01:02	00:00:58	00:01:51	00:01:33
Pink file	00:01:02	00:01:22	00:00:58	00:01:31	00:01:11	00:01:17	00:01:11	00:01:17	00:01:08	00:01:13
Phlebotomy	00:02:40	00:02:27	00:02:31	00:03:23	00:02:04	00:03:59	00:02:48	00:03:07	00:06:38	00:03:17
Lab	2 - 2,5 hrs. = 120 - 150 min									02:15:00 (MIDPOINT)

Physician visit	00:34:42	00:06:59	00:07:18	00:03:38	00:06:25	00:08:39	00:05:48	00:18:21	00:16:57	00:12:05
Pharmacy - oral	00:02:28	00:02:59	00:03:15	00:05:48	00:02:08	00:01:50	00:04:25	00:04:05	00:02:20	00:03:15
Pharmacy - mixing	00:09:58	00:10:29	00:10:45	00:13:18	00:09:38	00:09:20	00:11:55	00:11:35	00:09:50	00:10:45 (ORAL SCRIPT PREP + MIDPOINT MIXING TIME 00:07:30)
Drip admin + file update	00:05:05	00:04:06	00:03:05	00:03:05	00:03:40	00:03:02	00:03:23	00:03:07	00:03:12	00:03:32
Administration + Monitoring	2 - 2,5 hrs. = 120 - 150 min									02:15:00 (MIDPOINT)

Time and Motion Study - Data Points										
Day 3: 7/10/2015										
Task	**Time 1**	**Time 2**	**Time 3**	**Time 4**	**Time 5**	**Time 6**	**Time 7**	**Time 8**	**Time 9**	**Average**
Check-in	00:01:54	00:02:43	00:01:11	00:02:35	00:02:13	00:01:09	00:01:00	00:00:27	00:00:30	00:01:31
Pink file	00:01:15	00:01:40	00:01:23	00:00:46	00:01:07	00:01:05	00:01:10	00:01:15	00:01:19	00:01:13
Phlebotomy	00:04:39	00:04:56	00:05:01	00:05:44	00:05:07	00:04:12	00:04:40	00:02:51	00:04:17	00:04:36
Lab	2 - 2,5 hrs. = 120 - 150 min									02:15:00 (MIDPOINT)
Physician visit	00:05:36	00:06:48	00:08:45	00:03:56	00:05:52	00:15:44	00:03:12	00:20:57	00:11:13	00:09:07
Pharmacy - oral	00:02:04	00:03:34	00:04:40	00:02:00	00:02:03	00:02:32	00:01:49	00:00:58	00:01:25	00:02:21
Pharmacy - mixing	00:09:34	00:11:04	00:12:10	00:09:30	00:09:33	00:10:02	00:09:19	00:08:28	00:08:55	00:09:51 (ORAL SCRIPT PREP + MIDPOINT MIXING TIME 00:07:30)
Drip admin + file update	00:04:59	00:03:06	00:02:32	00:05:48	00:01:23	00:03:30	00:03:08	00:03:30	00:03:29	00:03:29
Administration + Monitoring	2 - 2,5 hrs. = 120 - 150 min									02:15:00 (MIDPOINT)

Salaries for professionals (www.govpage.co.za)					
Profession	**Lowest pa**	**Highest pa**	**Average pa**	***Average ph**	**Average pm**
Medical Specialist	R859 086,00	R1 139 958,00	R999 522,00	R480,54	**R8,01**
Pharmacist	R533 496,00	R679 986,00	R606 741,00	R291,70	**R4,86**
Nurse	R294 861,00	R362 655,00	R328 758,00	R158,06	**R2,63**
Admin Clerk	R132 399,00	R155 961,00	R144 180,00	R69,32	**R1,16**

***For an average 40 hour work week, the total number of hours worked is 40 X 52 = 2080 hours**

Appendix Q Sensitivity analysis tables

Table 12 Sensitivity analysis for the public healthcare sector - Each variable was varied by -50%, -20%, 20% and 50%. The number of cycles was rounded up to the nearest whole number if a decimal number was calculated for the variation. The table indicates the lowest and highest total costs when the respective variable was changed.

Variable	Theoretical CRC Regimens							
	5FU+LV		FOLFOX		Capecitabine		CAPOX	
Chemotherapy costs	**R42 743,58**	**R47 878,09**	**R98 598,33**	**R146 811,69**	**R8 756,26**	**R31 740,58**	**R20 727,18**	**R69 007,74**
Supportive care medicine costs	**R44 379,46**	**R44 606,37**	**R114 305,92**	**R115 396,49**	**R16 316,85**	**R16 619,40**	**R36 578,35**	**R37 305,40**
Administrative costs (TM study)	**R42 927,49**	**R47 510,29**	**R111 614,25**	**R120 779,85**	**R15 971,14**	**R17 310,82**	**R34 783,90**	**R40 894,30**
Administration costs	**R25 542,28**	**R82 280,71**	**R76 824,57**	**R190 359,21**	**R16 417,70**	**R16 417,70**	**R36 783,02**	**R36 896,06**
Number of cycles	**R22 227,55**	**R88 910,19**	**R57 334,72**	**R229 338,89**	**R8 208,85**	**R32 835,40**	**R18 410,35**	**R73 641,40**

Table 13 Sensitivity analysis for early CRC disease in the private healthcare sector - Each variable was varied by -50%, -20%, 20% and 50%. The number of cycles was rounded up to the nearest whole number if a decimal number was calculated for the variation. The table indicates the lowest and highest total costs when the respective variable was changed.

Variable	Theoretical CRC Regimens							
	5FU+LV		FOLFOX		Capecitabine		CAPOX	
Chemotherapy costs	R20 164,99	R33 166,52	R62 233,70	R140 839,77	R21 659,48	R62 999,72	R49 490,76	R125 899,68
Supportive care medicine costs	R24 456,52	R26 636,55	R86 166,40	R97 080,52	R34 470,66	R37 377,37	R73 447,52	R80 723,60
Administrative costs (av. of two facilities)	R17 994,29	R39 560,99	R75 426,64	R118 560,04	R32 468,76	R41 381,16	R66 287,68	R95 043,28
Administration costs	R24 841,01	R25 867,55	R89 120,08	R91 173,16	R35 439,56	R35 439,56	R75 416,64	R76 785,36
Number of cycles	R12 591,60	R50 366,39	R44 902,22	R179 608,89	R17 719,78	R70 879,13	R37 936,44	R151 745,76
Variable	**Theoretical CRC Regimens**							
	FOLFIRI		**XELIRI**					
Chemotherapy costs	R66 960,56	R150 111,81	R52 642,00	R132 081,04				
Supportive care medicine costs	R90 861,76	R102 309,40	R76 459,20	R83 735,28				
Administrative costs (av. of two facilities)	R79 556,14	R124 920,64	R69 040,68	R99 283,68				
Administration costs	R93 993,28	R96 046,36	R78 665,44	R80 034,16				
Number of cycles	R47 338,82	R189 355,29	R79 121,68	R79 121,68				

Table 14 Sensitivity analysis for advanced CRC disease in the private healthcare sector - Each variable was varied by -50%, -20%, 20% and 50%. The number of cycles was rounded up to the nearest whole number if a decimal number was calculated for the variation. The table indicates the lowest and highest total costs when the respective variable was changed.

Variable	Theoretical CRC Regimens							
	Capecitabine		CAPOX + Bevacizumab		FOLFOX + Bevacizumab		FOLFIRI + Aflibercept	
Chemotherapy costs	R21 659,48	R62 999,72	R136 595,00	R453 059,88	R126 592,96	R413 051,75	R123 301,91	R399 517,89
Supportive care medicine costs	R34 470,66	R37 377,37	R239 051,59	R248 146,69	R219 047,53	R228 142,63	R211 028,43	R224 064,84
Administrative costs (av. of two facilities)	R32 468,76	R41 381,16	R230 101,79	R266 046,29	R210 097,73	R246 042,23	R204 590,55	R236 940,60
Administration costs	R35 439,56	R35 439,56	R241 543,14	R243 163,59	R221 539,08	R223 159,53	R214 887,77	R216 346,17
Number of cycles	R17 719,78	R70 879,13	R121 041,65	R484 166,58	R111 039,61	R444 158,45	R119 652,17	R430 747,80
Variable	**Theoretical CRC Regimens**							
	FOLFOX + Panitumumab		Regorafenib		FOLFIRI + Cetuximab		FOLFIRI + Bevacizumab	
Chemotherapy costs	R187 755,97	R670 418,22	R240 477,39	R953 045,19	R695 070,40	R2 530 442,33	R112 012,30	R385 589,38
Supportive care medicine costs	R346 218,03	R353 494,11	R477 636,65	R478 726,68	R1 295 273,13	R1 330 036,88	R200 307,68	R208 998,62
Administrative costs (av. of two facilities)	R338 066,59	R369 796,99	R476 885,94	R480 228,09	R1 278 105,44	R1 364 372,24	R196 015,76	R217 582,46
Administration costs	R348 211,27	R349 507,63	R477 999,99	R477 999,99	R1 305 564,68	R1 309 453,76	R202 880,57	R203 852,84
Number of cycles	R174 321,69	R697 286,78	R318 666,66	R955 999,98	R653 430,52	R2 613 722,09	R101 602,33	R406 409,32
Variable	**Theoretical CRC Regimens**							
	XELIRI		CAPOX		FOLFIRI		FOLFOX	
Chemotherapy costs	R54 239,60	R133 678,64	R50 355,00	R126 763,92	R69 356,96	R152 508,21	R63 530,06	R142 136,13
Supportive care medicine costs	R76 856,64	R88 444,56	R73 399,28	R80 675,36	R91 280,08	R108 661,96	R86 094,04	R97 008,16
Administrative costs (av. of two facilities)	R71 134,08	R99 889,68	R66 239,44	R94 995,04	R82 696,24	R125 829,64	R75 354,28	R118 487,68
Administration costs	R80 287,16	R81 583,52	R75 392,52	R76 688,88	R96 425,86	R98 370,40	R89 083,90	R91 028,44
Number of cycles	R40 359,64	R161 438,56	R37 912,32	R151 649,28	R48 537,02	R194 148,09	R44 866,04	R179 464,17

Appendix R Ethical Clearance for study

R14/49 Ms Candice-Lee Herbst

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M140809

NAME: (Principal Investigator)	Ms Candice-Lee Herbst
DEPARTMENT:	Pharmacy and Pharmacology Charlotte Maxeke Johannesburg Academic Hospital Chris Hani Baragwanath Academic Hospital
PROJECT TITLE:	Cost Comparison of Chemotherapeutic Medicines used in the Treatment of Breast and Colon Cancers between the Public and Private Health Sectors in South Africa
DATE CONSIDERED:	29/08/2014
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Shirra Moch and Jacqui Miot
APPROVED BY:	Professor P Cleaton-Jones, Chairperson, HREC (Medical)
DATE OF APPROVAL:	06/02/2015

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Secretary in Room 10004, 10th floor, Senate House, University.

I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report**.

Principal Investigator Signature Date

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES