DEVELOPMENT OF A MODEL TO PREDICT THE COST OF TREATMENT OF BREAST CANCER WITH CHEMOTHERAPY AT GROOTE SCHUUR HOSPITAL

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A thesis submitted in partial fulfilment of the requirements for the degree of *Magister Pharmaceuticae,* to the University of the Western Cape.

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November 2017

KEYWORDS

Cost

Costing model

Breast cancer

Chemotherapy

Adverse events

Tertiary hospital

GLOSSARY OF ABBREVIATIONS

BC	Breast Cancer
BSA	Body Surface Area
CT	Computed Tomography
D	Docetaxel
DF	Degrees of freedom
DCIS	Ductal Carcinoma in Situ
ECOG	Eastern Cooperative Oncology Group
EC	Epirubicin and Cyclophosphamide
EPR	Electronic Patient Record
ER	Estrogen Receptor
ERNA	Equilibrium Radio-Nucleotide Angiocardiography
FEC	5-Fluorouracil, Epirubicin and Cyclophosphamide
FBC	Full Blood Count
GSH	Groote Schuur hospital
HER2	Human Epidermal Growth Factor Receptor 2
IDC	Invasive Ductal Carcinoma
IV	Intravenous
LCIS	Lobular Carcinoma in Situ
MI	Medical Informatics
MRI	Magnetic Resonance Infrared
NCI	National Cancer Institute
NCR	National Cancer Registry
NHLS	National Health Laboratory Services
NOS	No Other Symptoms/ Not Otherwise Stated

P	Paclitaxel
PR	Progesterone receptor
PS	Performance status
ROD	Radiation Oncology department
TM	Time and motion
TPL	Tender Price List
UCT	University of Cape Town
UPFS	Uniform Patient Fee Schedule
UWC	University of the Western Cape

ABSTRACT

In South Africa, breast cancer dominates other forms of cancer affecting women in both prevalence and mortality rates according to the National Cancer Registry. The incidence and cost of breast cancer have been on the rise particularly in developing countries. To date, there has been no study on the financial burden of breast cancer in the South African public sector. The aim of this study was to develop a method of costing breast cancer treatment with chemotherapy at Groote Schuur hospital (GSH), a government hospital. The objective was to determine the direct medical costs associated with breast cancer treatment and management of chemotherapy adverse events.

Retrospective patient level data were collected from electronic databases and patient folders between 2013 and 2015. Electronic data were obtained for all patients treated with chemotherapy. Two hundred (200) patients' folders were randomly selected to supplement data from the electronic databases. The main sources of cost were the Uniform Patient Fee Schedule (UPFS) and time and motion studies. Cost analyses were conducted at patient level from the health funder's perspective. Multiple regression analysis was used to investigate the relationship between the dependent variable (cost of treatment) and a set of independent variables (clinical stage, age at diagnosis, status of treatment, protocol and treatment approach) of the study sample.

The total direct medical cost for treatment of breast cancer at GSH for 200 patients was R3 154 877.90 and the average episode of care cost was R15 774.39 per patient.

The cost of management of adverse events arising from the various treatment modalities was on average R13 133 per patient. It was found that the cost of treating a patient with adverse events is 1.8 times more than the cost of treating a patient without adverse events. Of the patients, 86.5% managed to complete their prescribed chemotherapy and the average cost of treatment of these patients was 1.3 times more than the average for patients who could not complete their treatment. The cost of compounding of chemotherapy by the pharmacist, determined by time and motion studies, increased the total cost of chemotherapy medicines by 5.3%. It was found in this study that the cost of compounding of chemotherapy medicines was not accounted for by the UPFS.

A decision tree was developed to estimate the cost of treatment of breast cancer based on the probabilities of the stage of breast cancer and whether the treatment was completed or not. The model utilised a formula of calculating the total episode of care costs using costs obtained from the study and respective probabilities.

In conclusion, the method of costing of breast cancer was developed with 2 scenarios of costing, i.e. scenario 1 (costs derived from UPFS) and scenario 2 (costs derived from the UPFS and the time and motion studies). The cost of treatment and its adverse events was determined at patient level according to the GSH treatment protocol. The method, scenarios and predictive model developed in this study are crucial for calculating episode of care costs and can be used by the funder of care (government) for improved budget development.

DECLARATION

I, **NYASHA GUZHA** declare that the entirety of the work contained in this thesis, *Development of a model to predict the cost of treatment of breast cancer with chemotherapy at Groote Schuur hospital*, is my own original work, that it has not been submitted before for any degree or examination in any other university, and that all the sources I have used or quoted have been indicated and acknowledged as complete references

November 2017

Signed: 

ACKNOWLEDGEMENTS

Prima facea, I am grateful to **God Almighty** for His grace, wisdom and good health that were necessary to complete this venture.

I place on record, **Professor Praneet Valodia**, my supervisor, School of Pharmacy, UWC. I am extremely thankful and indebted to him for sharing his expertise, valuable guidance, encouragement and unparalleled patience to me during the course of this project. Thank you for challenging me to be a better person.

I am also grateful to my co-supervisor, **Professor Nadine Butler**, School of Pharmacy, UWC, for her continuous encouragement and support throughout the duration of my studies. I am gratefully indebted to her for her very valuable comments on the thesis.

I wish to express my sincere thanks to the following for their contributions during the course of the study:

Professor Raymond Abratt, former Director of the Radiation Oncology department, GSH, for granting approval to use the department as my research site.

Doctor Leon van Wijk, my liaison person at GSH, for his wealth of advice and enormous heart that is willing to help in every way he can and to the rest of the team of doctors, nurses and clerical staff at Radiation Oncology department, GSH who made sure the process of data collection flowed effortlessly.

Ms Wendy Bryant and **Ms Salwa Kriel**, Medical Informatics department, GSH, for their assistance with extracting data from the hospital database.

Mr Kobus Botha, developer of the EPR database, for his input during data collection.

Ms Vanishree Naicker, Pharmacy manager and **Theresa Blockman**, Director of Information Management, Tygerberg Hospital, for their assistance and insight towards chemotherapy medicine prices and fees.

Ms Karin Maritz, UPFS Patient Fees: Compliance Auditing, Training & Support, for her assistance with UPFS pricing.

Ms Suzette Munroe, GSH case manager, for her valued input towards hospital billing system and fees.

Mr Lourens Wepener, for his time and assistance with the cost template.

Mr Daniel Adeniyi, School of Postgraduate Studies, UWC, for his input with regards to data analysis and statistics.

To my family, I must express my profound gratitude to my parents for planting within me a seed of passion for greater things. Thank you for supporting me and giving me a vision in life. I am forever indebted to my husband **Doctor Makomborero Nyoni** for providing me with unfailing emotional support and continuous encouragement throughout the process of researching and writing of this thesis.

Finally to my son, **Prince Grey Nyoni**, your arrival during the course of this study was my motivation to continue working hard and see this project complete. Thank you for being a good boy during the study period.

This accomplishment would not have been possible without the aforementioned. Thank you.

Galatians 6:9,

And let us not grow weary in doing well,

for in due season we shall reap, if we do not give up!

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CHAPTER 1

INTRODUCTION

Cancer has proved to be one of the major health care challenges that funders of care should vigorously assess to reduce the economic burden imposed. Breast cancer in particular has more than 1.7 million women worldwide diagnosed every year (Ginsburg *et al.*, 2017). The National Cancer Registry data, published in 2012, reported that breast cancer cases comprise of 21.79% of all cancers affecting women in South Africa, thus making breast cancer the most prevalent cancer affecting women in South Africa (Davari *et al*., 2013).

The majority of the burden is dominant in developing countries where there are great economic crises and health problems, i.e. delayed diagnosis and lack of funds that allow for appropriate treatment (Boutayeb *et al.*, 2010). Breast cancer in South Africa is the leading cause of cancer related deaths in women. Projections for future mortality rates highlight that the burden of cancer will increase year by year (WHO, 2010). Apart from the burden on mortality, breast cancer poses a great economic burden worldwide. Breast cancer expenditure in South African public sector has not been researched and presents a huge gap for budget development and resource allocation. Non-peer reviewed literature by Laganparsad (2016), described cancer cost as a debt sentence due to the high treatment cost of the disease in the private sector. As more than 86% of the population is serviced at public sector hospitals in South Africa, it is important to understand the cost of treatment from that perspective.

The economic evaluation is central to health care decision makers as this will allow the proper allocation of budgets for the treatment of breast cancer.

The South African health care system is preparing for the introduction of the National Health Insurance (NHI). Therefore, it is important that costs of common diseases affecting women, such as breast cancer, are known. The knowledge of these costs will help the funder of care, i.e. the government in financial planning and allocation of already scarce resources.

It is acknowledged that the costs of management of breast cancer and associated adverse events are important. Of equal importance is the actual method used to calculate the costs, as this can be used on another data set of another hospital. It is crucial to develop a method of costing because such a method of costing, according to our knowledge, is not available in the public sector in South Africa.

This study was conducted at Groote Schuur hospital (GSH), a tertiary public sector hospital. The study was conducted from the perspective of the funder of care. The aim of the study was to develop a method and model to predict the cost of breast cancer treatment with chemotherapy.

The study objectives were to:

i. develop a method to determine the episode of care cost for breast cancer patients treated with chemotherapy at GSH by quantifying the direct medical costs and resource use relating to chemotherapy in the management of breast cancer;

ii. determine all the cost components involved in treatment of breast cancer and identify the cost drivers;

iii. develop and compare various scenarios of costing derived from the method of costing;

iv. quantify the cost components crucial for the management of adverse events due to chemotherapy;

v. explore the relationship of the costs between the various types of chemotherapy treatment, and to categorise the costs according to stage of cancer, age at diagnosis, treatment approach, primary and salvage treatment;

vi. ascertain the time spent by medical personnel such as nurses and doctors in relation to contact with the patient, chemotherapy administration and time spent by the pharmacist in preparing or compounding chemotherapy medicines through time and motion studies and how these contribute to the total cost of treatment; and

vii. develop a model which could predict the cost of breast cancer care at GSH.

CHAPTER 2

LITERATURE REVIEW

This literature review will focus on the methods used to determine the cost of treatment of breast cancer. Where literature is available, the costs associated with chemotherapy and its adverse events will also be reviewed. The few available studies conducted in this field will be described and evaluated for their relevance to the South African public sector.

This literature review was conducted through journal database searches of Pubmed, Medline, EbscoHost, Google Scholar and Science Direct, in combination with published text-books on the topic. The search strategy employed key words such as 'cost of chemotherapy', 'treatment of breast cancer', 'costing models' and 'costing methodology'.

The first part of the review highlights the aetiology of breast cancer and an overview of prevalence of breast cancer globally and locally. This section is followed by an overview of background information on breast cancer more importantly in relation to its treatment with chemotherapy and cost of treatment. Finally, an evaluation of the different methodologies of costing studies is drawn with the intention of developing an appropriate method.

2.1 Global incidence and prevalence of breast cancer

Every year, more than 1.7 million women worldwide are diagnosed with breast cancer (Ginsburg *et al.,* 2017). Breast cancer is the most prevalent cancer in women globally and accounts for approximately 400 000 deaths for each year in the past few years (Hoang Lan *et al*., 2013). An estimated 231 840 new cases of invasive breast cancer and 40 290 deaths were expected to occur in the United States of America (USA) alone in 2015 (Blumen *et al.,* 2016; De Santis *et al.,* 2015). In the year 2008, an estimate of 23% (1.38 million) total global cancer cases and 14% (458,400) of the total cancer deaths were due to breast cancer (Davari *et al.,* 2013). The average lifetime risk for developing breast cancer was estimated to be 1 in 8 in the USA, citing the burden of the disease in a developed country (Langhorne *et al.,* 2007). The mortality of breast cancer has been found to be dominant in low and middle-income countries (Ginsburg *et al.,* 2017). The reason for the aforementioned is due to limited availability of health care resources and good quality facilities for diagnosis and treatment services. The study published by Ginsburg and colleagues in 2017, collected data from population-based cancer registries obtained from countries of varied socioeconomic environments. The study predicted that the number of women with breast cancer globally will increase to almost 3.2 million per year by the year 2030 (Ginsburg *et al.,* 2017).

Another cancer parameter depicting the threat of breast cancer globally is the burden of mortality due to breast cancer which varies between developing and developed nations. The larger proportion of deaths were recorded in the developing nations

(Davari *et al.,* 2013; Kruger and Apffelstaedt 2007). However, a steady decline in burden of mortality is evident in developed nations, and this has been as a result of early detection programmes (Ferlay *et al.,* 2010). The incidence and mortality rates in the developing countries such as South Africa are still on the rise by approximately 5% per year (Groot *et al.,* 2006).

2.2 Incidence and prevalence of breast cancer in South Africa

The lifetime risk for developing breast cancer is approximately 1 in 26 for South African women. According to the data published by CANSA (2012) for the National Cancer Registry (NCR), breast cancer cases account for 21.79% of all cancers affecting women in South Africa. It is also reported that breast cancer is causing the highest mortality among the female cancer patients in South Africa (Dickens *et al.,* 2014).

The reported statistics of breast cancer in South Africa show that by province Gauteng has the highest prevalence of 40%, followed by the Western Cape with a prevalence of 25%, KwaZulu-Natal and the Free State together totaling a prevalence of 30%. The remaining prevalence of 5% occurred in the rest of the provinces in South Africa (Bateman. 2008). In future, the cancer incidence is projected to increase by 78% by 2030 in South Africa (Stefan *et al.,* 2013).

The rise is attributable to multiple factors such as fast paced lifestyles, increasing levels of pollution, ageing, obesity and viral infections endemic in the population such as HBV/HIV/HPV (Gopal *et al.,* 2014; Stewart. 2014).

A study by Ginsburg *et al.* (2017) suggested development of high quality cancer registries to capture the trends in incidence, mortality and survival of patients, especially in South Africa.

2.3 Breast cancer

Breast cancer presents as different types and in different stages depending on the extent of its spread. A malignancy confined to the ducts or lobules is classified as noninvasive and once the cancer cells penetrate the tissue outside the ducts it is classified as invasive (Sharma *et al*., 2010). Invasive ductal carcinoma is the most common type of breast cancer, accounting for 80% of breast cancer diagnoses whilst more than 15% of the carcinoma diagnosed in the USA is carcinoma in situ (Siegel *et al.,* 2015)

The concerns of the patient with breast cancer range from the timely diagnosis procedures, the treatment options, prognosis, costs of medical treatment and emotional support. In addition, the overall costs of breast cancer may overwhelm both the funder of care and the patient (Hoang Lan *et al.,* 2013).

2.4 Treatment of breast cancer

Breast cancer treatment options vary depending on disease characteristics (i.e. clinical stage, histologic grade, HER2 status, number of positive lymph nodes, hormone receptor status of the tumour) and on patient characteristics (i.e. age and menopausal status) (Pallis *et al.,* 2010). The types differ in their response to systemic treatment (Weigelt *et al.,* 2010).

The management of breast cancer is broadly categorised into surgery, radiotherapy, hormonal therapy and chemotherapy.

2.4.1 Chemotherapy in breast cancer treatment

Research has shown that breast cancer is a systemic disease (Redig and McAllister. 2013). This supports the use of chemotherapy and hormonal manipulation together with surgery and radiotherapy to improve patient survival. Breast cancer chemotherapy treatment is classified as adjuvant, neo-adjuvant and palliative. The goal of adjuvant and neo-adjuvant chemotherapy is generally curative, whereas the goal of chemotherapy in the metastatic stage is more palliative (Van Kleffens *et al.,* 2004). Adjuvant chemotherapy (post-operative) treatment has markedly reduced rates of death due to breast cancer (Parkin *et al.,* 2005). There are several chemotherapy combinations used in the treatment of cancer, e.g. the National Comprehensive Cancer Network (NCCN) guidelines outline the chemotherapy regimens for different types of breast cancer.

The choice of chemotherapy remains individualised yet patients receive optimal drug combinations suitable for better performance (Hultman *et al.,* 2012). The process of inhibiting cell proliferation affects all rapidly dividing cells, including some normal cells such as hair follicles, thereby causing adverse events. Despite the adverse events, use of chemotherapy is supported as the destruction of neoplastic cells occurs to a greater extent than the destruction of normal cells.

The use of chemotherapy is characterised by therapy efficacy and cost expenditure particularly cost associated with adverse events and cost of administration (Allies. 2008).

2.5 Cost of breast cancer treatment

The treatment of breast cancer has been shown to be costly and a large proportion of health care budgets are channelled towards these treatments. The WHO estimated the global total cancer expenditure to be US$1.16 trillion in 2014 (Stewart, World Cancer Report). Although no comparable cost data are yet available in the South African public sector, in their study Dickens and fellow researchers, (2014) mentioned that treatment of breast cancer is available at a 'small' (no figures were indicated) cost within the South Africa's public health sector (Dickens *et al.,* 2014). The research was a case study of over 1 000 women with breast cancer being treated at a public hospital in South Africa. There was no insight into the costs of treatment as the study only looked at the relationship between stage of breast cancer at diagnosis and the distance travelled by the patient to the diagnostic hospital.

In an article written by Rachelle Blidner (2013), for the Independent online news, she mentioned that in South Africa breast cancer treatment could cost between R700 000 and R1.5 million per patient in the private sector depending on the treatment protocol and on what is required for treatment (Blidner. 2013). She argued that with only 8 public hospitals equipped with oncology services, access to diagnosis and breast cancer care was difficult in South Africa.

Although important, the estimated cost of breast cancer in the private sector does not provide any indication of costs in the public sector, as the costs cannot be extrapolated due to the different operation, treatment protocols and pricing mechanisms viz. SEP versus tender prices.

According to the Council of Medical Schemes report, (2017), only 17.6% of the population had medical scheme coverage in 2016 leaving most of South African patients relying on public sector clinics and hospitals.

The majority of the cancer cost-based studies have been conducted in developed countries. One such cost-based study was conducted by Groot and co-workers in 2006. In this study health effects of breast cancer interventions and costs were compared for three epidemiologically different regions, i.e. Asia, Africa and North America. The data was compiled from electronic databases in the three regions. Their findings revealed a broad statistical variation and different costing methods among regions. The costs per patient per episode of care for stage I chemotherapy treatment was US$1 829 in Africa, $24 008 in North America, and $1 188 in Asia (Groot *et al.,* 2006). The specific African region studied was not mentioned and it was also noted that the costs were based on estimates and not actual treatment costs. This highlights the need for a local study, to investigate trends and costs that are specific to our region. As such, the true detailed perspective of cost of breast cancer in South Africa has not been researched. The author argued that the African resources (healthcare budgets) are better directed towards treatment of early stage disease and developing means for less expensive early diagnosis.

An Iranian study conducted at a public hospital, measured the direct medical costs of breast cancer with chemotherapy. The data were extracted from patients' profiles and analysed at patient level. The results indicated that the average direct costs per patient per month were US$222.17, $224.61, $316.51 and $828.52 for patient in stages I to IV respectively (Davari *et al.,* 2013). The results also showed that the cost per month of patients in stage IV was much more than the cost of other stages. It was concluded that the direct economic cost of breast cancer in Iran is very high.

A study in the USA conducted a retrospective analysis of claims data for breast cancer patients aged between 18 and 64 years (Blumen *et al.,* 2016). The average cost allowed for treatment was US$71 909, $97 066, $159 442 and $182 655 for patients in Stage I, II, III and IV respectively (Blumen *et al.,* 2016). The results of the study concurred with other published literature, that cost was high for patients whose cancer was more advanced at diagnosis (Hoang Lan *et al.,* 2013). Treating advanced cancer as compared to early stage cancer is associated with significant incremental costs particularly when adverse events occur.

A 2013 cancer population-based descriptive costing study conducted in Canada, estimated health care use and costs in the first year of diagnosis for patients with 7 common cancers. Patients' data were collected from an electronic database. For the cohort, chemotherapy cost increased 5-fold from CAD$2 286 to $11 834 for all patients. The author assumed the drastic changes were as a result of the rise in use of adjuvant chemotherapy following studies which demonstrated that such treatment improved patient survival (de Oliveira *et al.,* 2013).

Overall, De Oliveira *et al.* (2013) suggested that the increased incidence of breast cancer and the use of latest medicines, such as personalised biological treatment and technologies, have led to the growth of cancer expenditure. The increase in incidence has been affecting both developed and developing countries largely due to changes in lifestyle, diet, increase in age and survival (Ferlay *et al.,* 2010). It was found that the primary cause for the increase in the cost of cancer was due to an increase in the incidence of cancer (Ferlay *et al.,* 2010). Another study predicted a gradual increase in the cost of treatment as a result of the increase in the burden of cancer (Blumen *et al.,* 2016).

The cost of cancer treatment can be reduced in several ways. Some authors, (de Oliveira *et al.,* 2013) in Canada, found that costs could be minimised by use of gene expression profiling and personalised medicines aimed at specific growth factor receptors for women with breast cancer. The advancement of this hypothesis in developing countries, i.e. South Africa at present, could be a challenge because of lack of resources and funds.

Some studies suggest that raising awareness and employing effective screening methods for some cancers including breast cancer could reduce mortality and treatment costs for the funder of care (Lansdorp-vogelaar *et al.,* 2009).

The screening programme aims to identify cases of cancer in the early stage of the disease when appropriate treatment is far less costly and can prevent the fatal consequence. A study conducted at the University of Cape Town found that a greater proportion of women who were admitted with early stage breast cancer reported to

have done self-examination (Hoffman *et al.,* 2001). For colorectal cancer a model was developed to test the hypothesis that screening would become cost saving despite use of latest chemotherapeutic agents for treatment (Lansdorp-vogelaar *et al.,* 2009). This same approach could be translated to breast cancer.

In summary, a review of the various literature indicated that the cost of cancer treatment, in particular breast cancer, differs greatly depending on various factors such as economic perspective of study and private or public hospital. The cost studies recommended measures to reduce or minimise cost of treatment of cancer.

2.5.1 Cost drivers and factors affecting cost of breast cancer

The most common cost driver for cancer treatment is hospitalisation costs (de Oliveira *et al.,* 2013; Pagano *et al.,* 2012; Pompen *et al.,* 2009). According to Pagano *et al*., (2012), it was reported that hospitalisation constitutes 50-70% of direct medical costs of treatment of cancer. The majority of the costs of treatment are incurred during the initial phase of care, i.e. diagnosis and staging (Pagano *et al.,* 2012).

In Iran, research found that surgery cost was the main cost driver for stages I and II, whilst medication cost was the mainstay cost of treatment of stages III and IV breast cancer (Davari *et al.,* 2013)

In 2013, de Oliveira *et al*, concurred with Pagano *et al.* (2012) that most of the costs are incurred during the year of diagnosis. However, they argued that no resource or service was singled out as the cost driver as this is not yet fully understood.

In general, the care of cancer patients differed with age. It was reported that elderly patients were less likely to receive the same kind of care as the younger patients (Evans *et al.,* 1995; Sillman *et al.,* 1989; Chu *et al.,* 1987; Samet *et al.,* 1986). This ultimately influenced the cost of treatment based on the age of patient. According to a survey done by Hultman *et al*. (2012), in Canada, most patients (70%) diagnosed with breast cancer were younger than 65 years. A few years later in the same country, population statistics reported the patients younger than 65 years to be 58.8% of the population (Housser *et al.,* 2013). This means that the proportion of breast cancer patients is likely to increase when the population below 65 years increases. The costs of treatment are dependent on the age of patient (Yabroff *et al.,* 2008). The direct costs are also dependent on stage of disease (Korpela *et al.,* 2011) and the occurrence of adverse events (Hassett *et al.,* 2006).

2.5.2 Adverse events of chemotherapy use

Chemotherapy medicines were reported to be the highest cause of serious adverse events in women undergoing treatment of breast cancer (Hassett *et al.,* 2006). The cost of serious adverse events experienced by women receiving chemotherapy for breast cancer is unknown (Paessens *et al.,* 2011). A comparison of occurrence of adverse events in women who received chemotherapy and women who did not was conducted in the USA (Hassett *et al.,* 2006). It was found that women who received chemotherapy were more likely to be hospitalised, i.e. 61% versus 42% of women who did not receive chemotherapy.

There was a statistical difference indicating that chemotherapy recipients incurred substantial incremental costs related to adverse events due to additional therapeutic interventions, hospitalisation, ambulatory or emergency encounters. A population based study suggests that drug related adverse events contribute immensely towards costs of hospitalisation, emergency treatment and mortality (Hassett *et al.,* 2006). The table below (Table 1) shows the prevalence of adverse events as they occurred in 2 studies conducted in 2006 (Hassett *et al*., 2006; Russo *et al.,* 2006). In both studies, fever, infection and neutropenia were most prevalent. Although the studies were conducted in different countries, it was evident that the prevalence of adverse events generally increased as the study sample increased.

Table 1: Percentage of patients treated with chemotherapy experiencing adverse events

Author, year	Type of cancer	Number of patients included in the study	Country	Adverse events	Prevalence (%)
Hassett *et al*., 2006	Breast	4097	USA	Fever/ infection Neutropenia Anaemia Constitutional symptoms Electrolyte disorders Nausea, diarrhoea DVT Malnutrition	8.4 5.5 2.2 2.0 2.5 2.4 1.2 0.9
Russo *et al*., 2006	Breast	847	Italy	Fever/ infection Neutropenia Anaemia Constitutional symptoms Electrolyte disorders Nausea, diarrhoea DVT Malnutrition	5.1 6.5 5.6 0.4 0.8 0.6 0.2 1.1

2.5.3 Selection of cost components

The literature review indicates that the cost categories for breast cancer treatment were selected based on the nature and objective of the study. The major cost components used in other studies included medicines, hospital stay, outpatient (ambulatory procedure) visits, consultations, laboratory tests and scans (Pettersson *et al.,* 2012; Braud *et al.,* 2003). Other components were categorised as a combination of individual components, e.g. cost of management of adverse events.

Depending on the nature and objectives of the study, cost components can be excluded or included. Here are some examples from the literature. A study conducted by Demeter *et al*., (2007), excluded community health care events, i.e. visits to primary health care clinics, private consultations and home-based palliative care. The reason for exclusion was that the study measured cost from the economic perspective of the health care institution. The visits to other clinics or home-based palliative care did not have an effect on the expenditure of resources of the hospital and therefore were excluded. There are other components that were not taken into account by the authors Boutayeb *et al*. (2010), these included the cost of genetic counselling for high risk patients, e.g. BRCA gene testing and fertility counselling if the patient was premenopausal.

In another study that measured frequency and cost of chemotherapy related adverse events, the cost of outpatients visits was not taken into account (Hassett *et al.,* 2006). The study excluded outpatient visits to avoid over sampling bias given that chemotherapy patients normally have frequent outpatient visits. Scheduled outpatient

visits do not represent cost of adverse events although it is crucial to note that emergency outpatient visits for patients on chemotherapy were related to the cost of adverse events. A patient undergoes numerous tests and procedures for diagnosis, some of the tests were repeated whilst some were not performed on the patient at all.

When determining the cost of diagnostic tests, Evans *et al.* (1995), excluded this excessive testing in their model as it was difficult to incorporate this variability. To deal with excessive testing, specific information from patient folders can be used.

2.5.4 Methods used in cancer costing

According to Chien and Shih (2012), the cost of cancer care can be measured in two ways; these are the 'attributable cost approach' and the 'net cost approach'. The attributable cost approach measures the cost of cancer related medical services whilst the net cost approach compares cost between cancer and non-cancer populations. Whilst the former is more favourable, it has associated challenges, i.e. defining cancer related medical services. However, it allows flexibility whereby one can choose to eliminate certain cost categories, for example surgery or radiotherapy, and focus on chemotherapy (Chien and Shih 2012).

In the study conducted by Haywood *et al*. in 2012, tasks associated with administration of intravenous chemotherapy were identified and cost thereof determined from a health care system perspective. A model was developed which incorporated the tasks associated with chemotherapy administration, as well as the costs of resource use. The nurses' and pharmacists' time taken to perform their

specific roles related to chemotherapy administration were measured and cost derived.

The study conducted by de Oliveira *et al*. (2013), measured trends in resource use and cost for all health care services utilised in the treatment of several cancers. The researcher used administrative electronic data captured in various databases for a 12 month period after diagnosis. They examined the trends of use and mean costs for cancer related surgery, chemotherapy, radiotherapy and other cancer related admissions to hospital, as well as home care, for a cohort of about 200 000 patients.

In Paessens *et al*. (2011), a combination of patient interviews and pre-planned chart review was employed for data collection. The study enrolled 373 patients for the period of their treatment with chemotherapy. The costs were determined from a provider perspective.

Evans *et al*. (1995), explained another method of estimating the resource utilisation 'hotel' costs such as heating, security, housekeeping and lighting called the hotel approximation method. This method assumes a per diem cost of hospitalisation that is equal over all inpatient days regardless of the reason of admission. The Uniform Patient Fee Schedule (UPFS) in South Africa employs the same assumption equivalent to the hotel approximation method. The UPFS provides a guide for pricing of public hospital services and resources given to private fee-paying patients. Developing cost models provides a timely consistent and transparent approach to estimating treatment costs of standard or alternative therapy (Haywood *et al.,* 2012). This information is crucial for local policy makers in estimating cost of treatment.

2.5.5 Data sources used

Several studies on the costing of cancer therapy have relied on administration data mainly from patient folders as the source of data (Iezzoni., 1997). Data from patient folders is reliable and could provide accurate results if doctors or nurses wrote out detailed notes. Information written in the folder is patient specific rather than protocol-based (Pagano *et al.,* 2012) and therefore resource use can be measured at patient level. Studies that utilised folder data in their methodology were Davari *et al.* (2013); Hultman *et al*., (2012); and Demeter *et al*., (2007).

Another commonly utilised source of data for costing is the use of hospital computer databases or medical scheme registries. The electronic data source was utilised by de Oliveira *et al.* (2013); Haywood *et al*. (2012); and Petterson *et al.* (2012). The study conducted by Nomane *et al.* (2012) highlighted the benefits of combining both data sources for a study costing the management of diabetes mellitus at Groote Schuur hospital (GSH). Developing countries, for example, South Africa are relying on rarely updated statistics published by the NCR in 2006, 2010 and latest in 2012. This being greatly attributed to data unavailability and lack of current local cancer registries (Kruger and Apffelstaedt. 2007). This further emphasises the necessity of the development of a national registry.

The literature sources utilised focused on determining various cancer costs from the perspective of the health care funder which is the government. The perspective of the funder relies on costs incurred by the hospital and does not include indirect or patient extra costs due to cancer such as transportation, home-based care, food or accommodation.

2.6 Time and motion in costing studies

Observational time and motion studies provide an accurate measure of the time spent by health personnel performing individual tasks (Calhoun *et al*., 2005).

The time spent by the pharmacist compounding chemotherapy infusions was analysed by capturing tasks performed by the pharmacist in a time and motion study (Patton. 2011). The tool was used to evaluate the drug-related cost of compounding chemotherapy. The tasks involved in the time recording were identified through consultation with the specialist and the pharmacist. Thereafter, a flow chart of events was developed with the intention of maximising accuracy.

The National Patient Advocate Foundation (2005), in their study introduced another methodology of time and motion study motivated by the beta test which determined a potential miss of information if time and motion is based only on top identified drugs (Brixner *et al*., 2005). The survey assessed all tasks conducted by the pharmacist in a specified period of time (in one shift). A list of duties a pharmacist is responsible for on a typical day of work was developed and if a task not listed was performed, it was noted separately. The methodology improved their quality of results. A broader analysis is crucial when resources are sufficient.

Time and motion studies do not only include cost of resource use but an aspect of time spent on the task such as nurses' time administering IV infusion or pharmacists' time on compounding and preparing the medicines (Haywood *et al.,* 2012).

2.7 Overall comment on literature review

Escalating cancer treatment costs has made it crucial to evaluate the resources utilised in managing the treatment of cancer, not only in South Africa, but globally. A review of literature revealed that no studies have been published in South Africa on the total cost or the episode of care of breast cancer treatment including the adverse events of treatment. There was not a single study that portrayed a methodology similar to all the objectives set out for our study. The studies analysed helped in shaping the design of the current study. These differences in cost studies show that there is no standard method for estimating the costs of breast cancer treatment. An important consideration when assessing the cost studies is the perspective of the study as this can affect the way in which the cost results are interpreted. There are 3 main perspectives from which these studies were conducted, i.e. (i) the patient, (ii) the provider of health care and (iii) the funder of the treatment (Akobundu *et al.,* 2006). The focus on this literature review was from the perspective of the funder.

CHAPTER 3

MAP OF WORK

This section of the thesis is aimed at providing a brief theoretical framework of why and how the study was conducted. This study was conducted following a gap that was identified in the public sector on the treatment of breast cancer. It was also found that there is currently no data that quantified the costs of treatment of breast cancer in South Africa in the public hospitals. This study was developed to determine the cost of breast cancer treatment, particularly chemotherapy treatment. The full details of the method are described in the next chapter.

3.1 Study aim and objectives

3.1.1 Aim

The aim of the study was to develop a method and a model to predict the cost of breast cancer treatment with chemotherapy.

3.1.2 Objectives

The study objectives were to:

i. develop a method to determine the episode of care cost for breast cancer patients treated with chemotherapy at GSH by quantifying the direct medical costs and resource use relating to chemotherapy in the management of breast cancer;
ii. determine all the cost components involved in treatment of breast cancer and identify the cost drivers;

iii. develop and compare various scenarios of costing derived from the method of costing;

iv. quantify the cost components crucial for the management of adverse events due to chemotherapy;

v. explore the relationship of the costs between the various types of chemotherapy treatment, and to categorise the costs according to stage of cancer, age at diagnosis, treatment approach, primary and salvage treatment;

vi. ascertain the time spent by medical personnel such as nurses and doctors in relation to contact with the patient, chemotherapy administration and time spent by the pharmacist in preparing or compounding chemotherapy medicines through time and motion studies and how these contribute to the total cost of treatment; and

vii. develop a model which could predict the cost of breast cancer care at GSH.

3.2 Study flow summary

A flow diagram of how the study was conducted is illustrated in Figure 1. The breast cancer patients who received chemotherapy from the Radiation Oncology department (ROD) at Groote Schuur hospital (GSH) were selected from the electronic databases (Medical Informatics and Electronic Patient Records) for possible inclusion. The validation of a breast cancer diagnosis was conducted and applied. A random selection process was employed to obtain a sample size of 200 patients. The detailed methodology is available in Chapter 4.

The patient folders of the selected patients were searched from the hospital's medical records to supplement information recorded on the electronic database.

Therefore, the two main sources of data utilised at GSH were (1) electronic patient records and (2) patient folders. The patient extraction was conducted in line with the study's inclusion and exclusion criteria.

The collected information was classified and categorised into the following cost components: chemotherapy medicines, support medicines, administration of chemotherapy, laboratory tests, radiology scans and imaging, doctor visits and adverse events. The cost components were then used in the development of a cost template.

Time and motion studies were conducted on a set of new patients and data obtained were used on the study sample of 200 patients. Where possible some aspects of the total costs were substituted with the costs obtained from the time and motion studies. The motivation for conducting time and motion studies was reached when one of the cost components was deemed to be not fully accounted for by the Uniform Patient Fee Schedule (UPFS), e.g. compounding fee for chemotherapy medicines. We ensured that substitution of UPFS costs with time and motion costs did not result in double counting. The time and motion study presented an alternative cost for the following components:

i. compounding of chemotherapy cost;
ii. administration of chemotherapy cost; and
iii. outpatient doctor consultation cost.

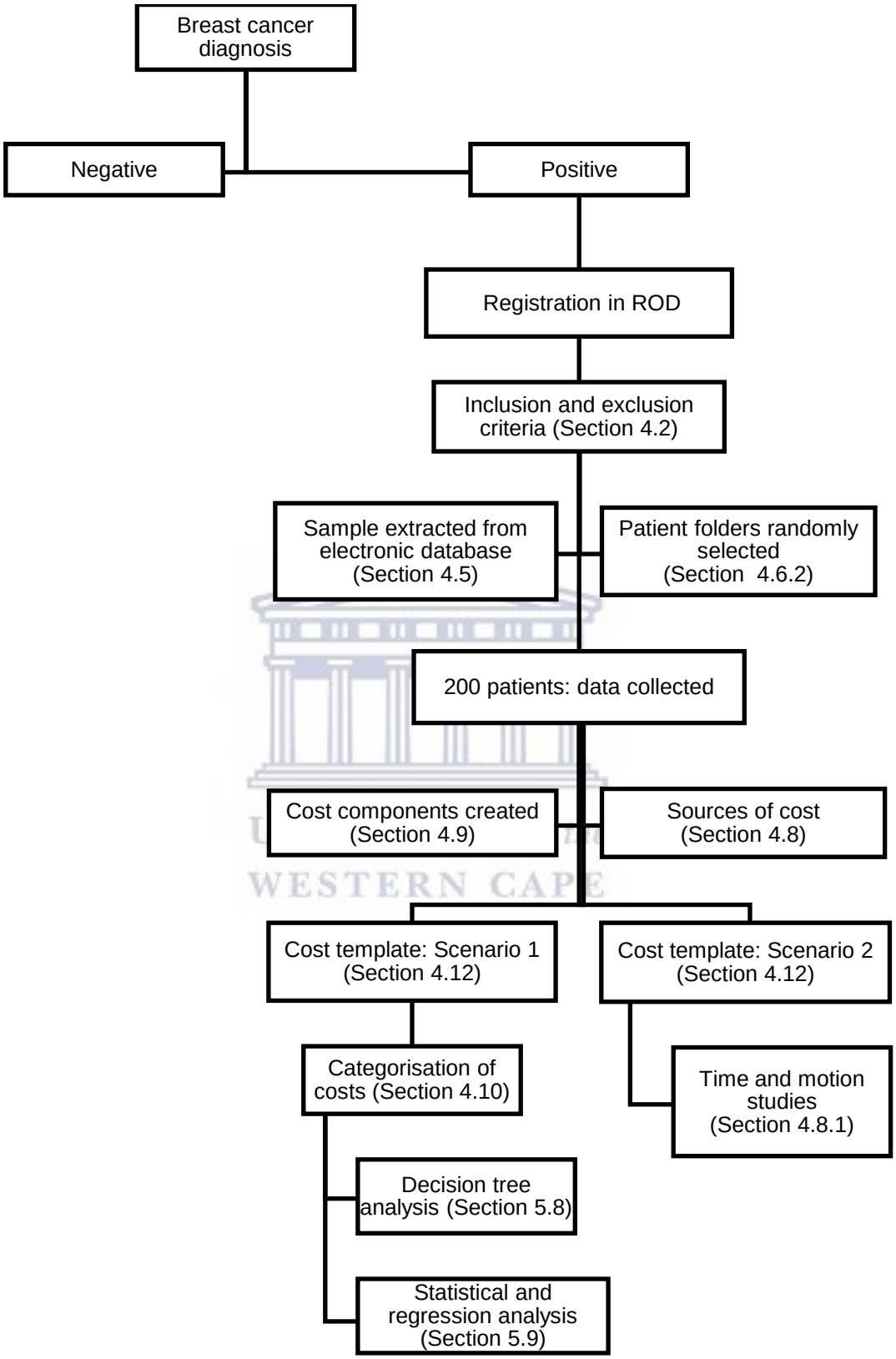


Figure 1: Summary flow diagram of study

3.3 Predictive model development

A predictive model for the management of breast cancer patients at GSH was developed. The model was based on the decision tree algorithm and according to the current treatment procedures. The data obtained from the 200 patients was used in the model development. Probabilities of a breast cancer patient completing treatment and the likelihood of presenting with either stage I, II, III or IV cancer at diagnosis were taken into account. Cost estimates for an episode of care period were obtained for each stage of breast cancer. The model assumed that resource use for all components was incurred at GSH. Hence, the full episode of care was considered.

CHAPTER 4

METHODS

The purpose of this chapter is to provide a detailed description of methods used in the study. The research methodology consists of the development of a costing method and the development of costing scenarios for the management of breast cancer at Groote Schuur hospital (GSH).

4.1 Selection of study site

Oncology services for breast cancer in the South African public health sector are offered at general or tertiary level hospitals (Vorobiof *et al*., 2001). GSH is a leading tertiary referral hospital located in the Cape Metropole, Western Cape. It is a public hospital under the management of the Department of Health in South Africa. GSH is a teaching hospital equipped with specialist doctors and nurses as well as equipment for diagnosis and treatment of patients with cancer. GSH is a government funded hospital which supports the study objective of costing treatment from the perspective of the funder of care.

4.2 Patient selection

4.2.1 Inclusion criteria

Patients were included in the study based on the following criteria:

i. a diagnosis of breast cancer as confirmed in the patients' folders;
ii. registration date at the Radiation Oncology department (ROD) within the period 1 April 2013 until 31 March 2015;
iii. evidence of receipt of chemotherapy with two or more health encounters related to breast cancer at the ROD. These could be a doctor consultation in Ward LE33 or mammogram scan (Vera-Llonch *et al.*, 2011); and
iv. 18 years and older.

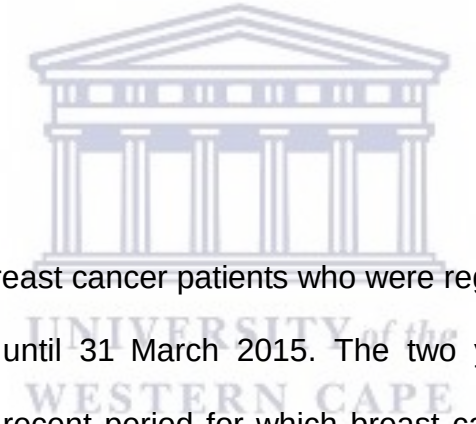
4.2.2 Exclusion criteria

Patients were excluded from the study based on the following criteria:

i. male;
ii. initiated on hormone therapy but not chemotherapy;
iii. enrolled in a clinical trial; and
iv. a primary diagnosis of cancer that is not breast cancer.

4.3 Study design

The study was a retrospective cohort analysis. The study reviewed a full episode of care for treatment with chemotherapy. The episode of care was defined as the care provided from 2 months prior to the date of commencing chemotherapy, during chemotherapy and 6 months after the date when the last cycle of chemotherapy was administered. This period included a diagnosis phase (period of 2 months prior to start of chemotherapy), treatment phase and follow-up phase (period of 6 months after completion of chemotherapy). The episode of care was on average a period of 10-12 months per patient.



4.4 Extraction timeline

Data were extracted for breast cancer patients who were registered at the ROD during the period 1 April 2013 until 31 March 2015. The two year period was selected because it was the most recent period for which breast cancer incidence data were available at the time of extraction.

The financial year of 1 April to 31 March was selected, because the financial calendar year of the main source of cost, the Uniform Patient Fee Schedule (UPFS) gazette, was updated according to that cycle.

4.5 Patient extraction

4.5.1 Electronic database extraction

Patients satisfying the selection criteria were screened from the hospital electronic database. The hospital had two electronic databases, viz. the Electronic Patient Records (EPR) system and the Medical Informatics (MI) database. The former is a unique independent database created for diagnosed cancer patients who attend the ROD and the latter is a universal database for all patients who attend the hospital. All patients at GSH have a hospital number and patients registered on the EPR database were assigned an RT number (hospital number for cancer patients). These two electronic records were screened for patients meeting the following criteria: registration date at the ROD between 1 April 2013 and 31 March 2015, a diagnosis of breast cancer and evidence of treatment with chemotherapy. Patients were extracted from the electronic database using key words such as ‘breast cancer’ and ‘chemotherapy’.

The method of extracting patients from the database was developed in consultation with Dr Leon van Wijk (Oncology specialist), Ms. Wendy Bryant (Director of the MI Department, GSH) and Mr Kobus Botha (Developer of the EPR database).

The patients diagnosed with breast cancer who attended the ROD at GSH were identified and selected for possible inclusion in the study. A list of breast cancer patients was extracted from the EPR database and collated with a list of patients extracted from the MI database. The extraction of patients from the EPR system was conducted in order to validate the MI patients’ list.

4.5.2 Sampling

A total of 1 024 patients were extracted from the electronic database. A random selection process was applied where 200 patients were selected. A random number generator was employed on excel spreadsheet. Patient folders were requested from the Radiation Oncology medical records at GSH.

Missing folders were followed up once every month during the data collection period. If the folder was not found at all, another patient was selected from the random sample to replace the patient with a missing folder.

4.6 Data collection

Data on every patient were collected from the electronic patient records and the patient folders. The data collection approach is discussed in detail hereunder.

4.6.1 Electronic database

Breast cancer patients were identified from the electronic database. Patients treated with chemotherapy were filtered from the EPR database. A patient list was retrieved with the following information for each patient:

- RT number;
- registration date;
- date of birth;
- diagnosis;
- stage of disease; and
- treatment intent.

The list retrieved from the EPR was then used to extract full patient treatment history from the MI database. The following information was obtained for each patient from the MI database:

- hospital identification number;
- RT number;
- medication history ;
- outpatient visits;
- inpatient hospitalisation data;
- scans and imaging; and
- laboratory tests history.

4.6.1.1 Data extracted from electronic database of patient records

The two electronic databases, i.e. the EPR and the MI databases were the primary sources of the following combined information:

i. patient demographics, i.e. name, surname, hospital number, RT number;
ii. medication profile which included the name of chemotherapy, date of issue, quantity issued, cost of each medicine;
iii. support medicines which included the name of medicine, dose of medicine, cost of each medicine, date of issue;
iv. laboratory tests which included the name of test, number of tests performed, date when test was performed;
v. scans and imaging data which included the name of procedure, number of procedures performed, date when scan was performed;

vi. consultation visits which included scheduled and emergency visits, date of consultation, department where patient attended; and

vii. inpatient hospitalisation data which included the date of admission, date of discharge, duration of stay, ward type and reason of admission.

The information available in the electronic database was obtained from the relevant departments within the hospital. The laboratory tests were obtained directly from the National Health Laboratory Services (NHLS) database.

The accuracy of the information in the database was reliant on the personnel who captured the data from the primary source. The data in the pharmacy system were captured by the pharmacy personnel (pharmacist, pharmacist intern, pharmacy assistant) and the consultation visits together with chemotherapy administration sessions were entered by the nurse personnel or receptionists at the ROD. There were some inconsistencies with the information in the pharmacy database e.g. cost of ondansetron 8mg tablets (6 tablets per pack) was recorded as R120.37 instead of R10.13. The price difference could be attributed to capture error or bulk pricing. This cost of R120.37 was identified out of 20 prices of ondansetron on the cost template and it was considered to be an outlier. Therefore, the price difference was attributed to be a capture error.

4.6.2 Folder data collection

The researcher was trained by Dr L. van Wijk on how to extract and interpret information from patient folders. A list of RT numbers was compiled and presented to the Radiation Oncology medical records department for extraction of patient folders.

A data collection form (Annexure 1) was used to obtain additional information from patient folders. The form was designed specifically for the study by the researchers and validated by the doctors at the ROD.

The information necessary for the cost analysis was extracted from the patient folders and recorded. Folder data collection process began in March 2015 and ended in December 2015. An average of 45-60 minutes was required to collect the required information for each patient using the data collection form.

4.6.2.1 Data extracted from the patient folders

Patient medical folders were used as the secondary data source of patient information. The following were obtained from this data source:

i. detailed patient demographics which included the date of birth, age at diagnosis, date of registration, stage of disease, weight, height, body surface area;
ii. detailed clinical information which included the histological type of disease, comorbidity, intention of treatment, hormone receptor status;
iii. medicines which included the name and dose of chemotherapy medicines, date of administration, dose and quantity of support medicines issued;
iv. laboratory tests which included the name of test, number of tests performed,

date when test was performed, results of test;

v. scans and imaging data which included the name of procedure, number of procedures performed, date when scan was performed, result of scan or radiological procedure;

vi. consultation visits which included scheduled and emergency visits, date of consultation, doctor notes on the visit; and

vii. adverse events data which included the date when event occurred associated emergency consultation, inpatient hospitalisation*, medication issued for the event, laboratory tests, scans and imaging.

*Inpatient hospitalisation data which included date of admission, date of discharge, ward type and reason of admission. Not all admissions were recorded in the patient folder

The accuracy of information recorded in the patient folders was subject to the attending doctor or nurse who recorded the above listed information and interpreted the results of tests or radiological scans. In some instances the histology and pathology test results of patients were not recorded. The results were obtained from the NHLS database to complete the data collection form.

The data on the electronic database and the patient folders were found to overlap on several occasions. Data were collected from patient folders mainly to supplement missing and incomplete patient information on the electronic database and to verify the information retrieved from the electronic databases for the each patient.

4.7 Validation

4.7.1 Diagnosis validation

In order to validate the diagnosis of breast cancer for each patient, criteria were developed for this purpose. If the patient met any one of the following criteria, the diagnosis of breast cancer was confirmed:

- diagnosis of breast cancer recorded in the patient folder;
- medication history consisting of chemotherapy for breast cancer or evidence of chemotherapy administration of breast cancer chemotherapy; and
- a record of radiology and laboratory tests specific to breast cancer diagnosis such as mammogram and breast biopsy.

4.7.2 Chemotherapy dose calculation

The dosage of chemotherapy medicines was calculated based on the patient's body surface area (BSA) (Boutayeb *et al.,* 2010; Ferro *et al.*, 2008). At GSH the consulting doctor calculated the relevant dosages. The pharmacist was responsible for checking the dosage as calculated by the doctor.

The method for validating the dosage in patients' folders was developed and applied with respect to GSH treatment protocols. The patients recorded on the cost template had their BSA recalculated by using the patients' weight and height as recorded in the patients' folders and on the data collection form. The process was randomly done

during the folder data collection to recheck the BSA figures recorded by the doctors in the patients' folders. The recorded BSA was found to be consistent with the patient's weight and height.

4.8 Sources of cost

The costs used for the study reflected the cost to GSH. The main sources of cost were the Uniform Patient Fee Schedule (UPFS), MI database and time and motion studies**.**

The sources of costs used in this study are further outlined below:

i. the cost for medicines (chemotherapy and support medicines) was obtained from the JAC system through the MI database. This cost reflected the acquisition cost to GSH;
ii. the cost data for laboratory tests was obtained from NHLS through the MI database. This reflected the cost to GSH for the laboratory tests; and
iii. the cost for the following list of components was obtained from the UPFS Provincial Gazette for Western Cape, No. 7245, 27 March 2014;
    - medicine dispensing fee;
    - administration of chemotherapy, ambulatory procedure facility fee and professional fee;
    - scheduled outpatient consultation facility fee and professional fee;
    - emergency outpatient consultation specialist or nurse fee and facility fee;
    - inpatient hospitalisation cost, specialist professional fee and facility fee;
    - scans and imaging cost of test and facility fee; and
    - drawing of blood cost for laboratory test.

Time and motion studies were also used as a source of cost for the following:

i. compounding cost for chemotherapy IV medicines;
ii. administration of chemotherapy medicines, specialist and nurse cost; and
iii. outpatient doctor consultation cost.

4.8.1 Time and motion studies

A standardised task list was developed with expert help from the oncology pharmacist. The task list was used to develop the timing process as well as assist in the designing of the form for recording captured times. An interim one week observation period was set aside before the actual data collection commenced. The observer utilised this time to familiarise herself with the routine and duties of the personnel under study. The observer used a digital stopwatch that displayed time in the units of hour, minute and second, for accurate capture of the time taken to complete a task.

The time for each activity was multiplied by the per-minute salary (Oglesby *et al*., 2009). The salaries of the pharmacists, doctors and nurses were derived from the annual estimates published by the Department of Public Service and Administration of South Africa (salary scales 2014).

4.8.1.1 Chemotherapy compounding time

A form (Annexure 2) designed for the pharmacist tasks was used to record the captured times taken to perform the tasks. The tasks were grouped into three stages according to the order of handling of a prescription by the pharmacist from the point a prescription is brought into the pharmacy to the point when it is signed off by the pharmacist as complete. The three stages were:

Stage 1 – checking the validity of the prescription and capturing of prescription onto the JAC system;

Stage 2 – assembling of chemotherapy products and consumables from the time it is picked from the shelf or fridge and taken to the aseptic unit; and

Stage 3 – actual compounding or mixing of intravenous (IV) chemotherapy, labelling, final checking and signing off as complete.

In some instances the pharmacist performed the stages of compounding process in batches i.e. subsequently checked several prescriptions, entered on the JAC system, and assembled products. In stage 3 each chemotherapy medicine type e.g. epirubicin was prepared in batches depending on the number of prescriptions available at that moment. For those tasks the time taken for all prescriptions was recorded and then divided by the number of prescriptions to obtain the time of processing one prescription. According to the method of costing, a pharmacist salary for level 3 pharmacist was used because a pharmacist at this level was compounding at the time of data collection.

4.8.1.2 Chemotherapy administration time

The process of chemotherapy administration was conducted by the nurses as an outpatient consultation. The time and motion study measured the time taken for the process of chemotherapy administration.

A data collection form (Annexure 3) was designed to capture the time taken to perform the relevant tasks undertaken by the health care professionals during the process of administering chemotherapy.

4.8.1.3 Doctor consultation time

A data collection form (Annexure 4) was used to record the time for the consultation. The process of observing and recording the time taken by the doctor during consultation with the patient was developed and approved by the doctors in the ROD. In order to maintain patient confidentiality the observer was not present in the consulting room during the consultation. The doctor informed the researcher of the reason for consult. The time taken by the doctor for the consultation with the breast cancer patient was measured.

4.9 Cost components studied

The cost components studied in this project represent the direct medical costs of managing breast cancer with chemotherapy as the mainstay of treatment. This section also details how the cost components were calculated.

The cost components studied are listed below and further explained in detail:

- chemotherapy medicines
- support medicines;
- chemotherapy administration;
- consultation visits;
- laboratory tests;
- imaging and scans;
- inpatient hospitalisation; and
- adverse events

4.9.1 Chemotherapy medicines

The oncology pharmacy under the pharmacy department at GSH provided all the medication to the patients. All intravenous chemotherapy infusion medicine bags were prepared at the oncology pharmacy.

The cost of these medicines was derived from the cost on the TPL or the cost charged by an external supplier (HP04 2014 ONC, Department of Health website).

Medicines were sourced from an external supplier when out-of-stock from the registered provider for tender medicines. The cost of infusions bags, syringes, needles, normal saline and other pharmacy materials were charged as part of medicines cost. The cost was calculated automatically on the JAC system through the stored formulas when the dosage of medicine was entered. The commonly used treatment regimens for primary breast cancer chemotherapy are listed in Table 2 below. Patient folders were assessed for any protocol adjustment or substitutions. No drug wastage was assumed (Maslove *et al.,* 2014). At the end of each day, the pharmacist tallies the number of all the breast cancer patients who received the same regimen and divides the cost according to the proportion of resources utilised.

The process of mixing chemotherapy medicines and preparing infusion bags for administration is conducted by a pharmacist. The pharmacist's professional time during this process of compounding does not seem to be accounted for in the cost presented in the UPFS. A component of cost called the compounding fee was developed in the study and determined by time and motion studies (refer section 4.8.1). The compounding fee was added to the medicine cost and dispensing fee in two different scenarios, i.e. scenario 1 included the medicine cost plus dispensing fee and scenario 2 included the medicine cost plus dispensing fee plus compounding fee.

Table 2: Breast cancer chemotherapy regimens at GSH

Chemotherapy regimen	Dosage instruction per cycle (IV bolus)	Duration of therapy
FEC	➢ 5FU 500mg/m^2 Epirubicin 75-100mg/m^2 Cyclophosphamide 500mg/m^2	Cycle repeated at 21 day intervals for 6 cycles
AC or EC	➢ Adriamycin 60 mg/m^2 Cyclophosphamide 600 mg/m^2 OR ➢ Epirubicin 100mg/m^2 Cyclophosphamide 600 mg/m^2	Cycle repeated at 21 day intervals for 4 cycles Same as for AC
FEC-P or FEC-D	➢ 5FU 500mg/m^2 Epirubicin 75-100mg/m^2 Cyclophosphamide 500mg/m^2 ➢ Paclitaxel 175mg/m^2 OR ➢ Docetaxel 75mg/m^2	Cycle repeated at 21 day intervals for 3 cycles Cycle repeated at 21 day intervals for 4 cycles
EC-P or EC-D	➢ Epirubicin 100mg/m^2 ➢ Cyclophosphamide 600 mg/m^2 ➢ Paclitaxel 175mg/m^2 ➢ OR ➢ Docetaxel 75mg/m^2	Cycle repeated at 21 day intervals for 3 cycles Cycle repeated at 21 day intervals for 4 cycles
DC	➢ Docetaxel 75mg/m^2 Cyclophosphamide 600mg/m^2	Cycle repeated at 21 day intervals for 4 cycles
Taxanes	➢ Paclitaxel 175mg/m^2 (cap dose at 330mg) ➢ Paclitaxel 60mg/m^2 ➢ Docetaxel 75mg/m^2	Cycle repeated at 21 day intervals Cycle repeated at 7 day intervals Cycle repeated at 21 day intervals for 6 cycles

A- Adriamycin, C-Cyclophosphamide, D-Docetaxel, E-Epirubicin, 5FU- 5-fluorouracil, P-Paclitaxel, m^2 – per metre squared

4.9.2 Support medicines

These were sourced on tender and therefore the TPL applied (HP09 2014 SD, Department of Health website). Medicine classes used as support medicines for chemotherapy treatment are listed in Table 3 below.

Table 3: Support medicines classes for patients with breast cancer

Medication category	Example of medicines
Analgesics	Paracetamol, tramadol, morphine
Anti-emetics	Ondansetron, metoclopramide, granisetron
Anti-inflammatories	Ibuprofen, corticosteroids e.g. prednisone
Anaemia prophylaxis	Ferrous sulphate, folic acid
Antibiotics	Varies e.g. Co-amoxyclav, flucloxacillin, piperacillin tazobactam, amikacin
Anti-fungals	Nystatin
Laxatives	Liquid paraffin, sorbitol 70% solution, Senna

Support medicines relating to breast cancer treatment with chemotherapy were included. Chronic medicines were excluded from the analysis. Only medicines issued during the episode of care period were included.

A dispensing fee of all medicines was charged per day regardless of the number of prescriptions presented to the pharmacy. The dispensing fee was charged to the chemotherapy cost. In instances where support medicines were issued on a particular day without chemotherapy, the dispensing fee was charged as a cost of support medicines. A dispensing fee was billed per patient per day for all the prescriptions presented to the pharmacy at GSH.

4.9.3 Chemotherapy administration

The cost due to the process of administering chemotherapy to the patient was accounted for. According to the UPFS the cost was classified under ambulatory procedures comprising of a professional fee and a facility fee component.

The professional fee accounted for the time of specialists, nurses and other health care professionals involved in the treatment of the patient. The facility fee covered the cost of the environment for providing the service and materials used. A professional fee and facility fee were charged for every cycle that chemotherapy was administered to the patient.

To determine the cost allocated for professional fee for scenario 2, a time and motion study was conducted during chemotherapy administration as described in section 4.8.1.

The time for nurses and doctors observed taking part during the process of chemotherapy administration was included in the cost. To avoid double counting on the final cost, only the professional fee (fee levied for doctors and nurses) was substituted with cost derived from the time and motion study.

4.9.4 Outpatient consultation visits

Routine outpatient consultations during diagnosis, treatment with chemotherapy and follow-up were recorded with an ICD-10 and/or a description on the MI database. Only consultations conducted by a specialist in the ROD were considered. The consultation fee costs were derived from the UPFS.

The cost of each visit was made up of the professional fee (specialist, doctors and other health care professionals) and facility fee. Total cost of consultation per patient was obtained from the sum cost of all visits during the episode of care.

4.9.4.1 Scheduled visits

Doctor consultations conducted in the ROD and Breast clinic at GSH were selected. The date of consultation was required to be within the study period and confirmed with the doctor's notes available in the folders. The reasons for consultation ranged from clinical examination, diagnosis, treatment planning, treatment assessment, adverse events management and follow-up care.

4.9.4.2 Emergency visits

These were outpatient visits that were not scheduled visits. Patients presented at the casualty ward with an emergency situation requiring urgent attention. With respect to breast cancer treatment, these could have been due to adverse events or complications of chemotherapy. Costing was conducted for the particular event thereof. Tasks undertaken during this visit were, but not limited to, nurses' time providing care, doctor consultation, medicines provided and laboratory tests

conducted. The information was obtained from the hospital database and patient folders.

4.9.5 Laboratory tests

The cost for laboratory tests consisted of cost of test (as listed on the MI database) and cost of drawing of blood by the nurse. The drawing of blood cost (obtained from the UPFS) was charged for each day laboratory tests were conducted. The drawing of blood cost consisted of nurses' time and materials used during the preparation of blood samples which were sent for testing.

Routine full blood count (FBC) and platelet tests were conducted at each cycle before chemotherapy administration. Additional tests done to rule out other possible diagnoses and co-morbidities such as tuberculosis or Human Immunodeficiency Virus tests were not factored into the final cost (Evans *et al*., 1995).

4.9.6 Scans and imaging

Routine diagnostic tests included, but were not limited to, mammograms, chest X-rays, ultrasounds, magnetic resonance infrared (MRI) and bone scans. Equilibrium Radio-Nucleotide Angiocardiography (ERNA) was exclusively for monitoring the cardiac toxicity which could potentially have been caused by anthracycline therapy (Shan *et al.*, 1996). Total cost of scans was a sum of procedure cost and facility fee for all scans conducted. Unit cost of a scan procedure was available in the radiology code book (Annexure J of the UPFS Government Gazzette). The procedures were grouped into 5 price categories, i.e. Category A–E. The facility fee was also listed in

the UPFS. With the expert assistance of Dr L. van Wijk, the correct price was allocated to each procedure.

Other procedures that are not directly related to treatment of breast cancer with chemotherapy, such as electrocardiogram (ECG) or colonoscopy, were excluded.

4.9.7 Inpatient hospitalisation

In this study the inpatient hospitalisation episodes were mainly for the management of adverse events or for chemotherapy administration for patients boarding in the day ward for convenience purposes when they are receiving chemotherapy the following day.

The cost of inpatient stay was attributed to the adverse events cost if there was evidence of such an event in the patient folder. Cost of hospitalisation due to surgery or radiation therapy was not included in the study

4.9.8 Adverse events

The costs associated with treating toxicity from chemotherapy were taken into account. For the purpose of this study, an adverse effect was defined as an additional condition or complication that occurred during the episode of care or immediately after treatment with chemotherapy. Clinical information available in the patient folders aided in the identification of the adverse events components. All patients were searched on the electronic database for an adverse effect related hospital admission. Patients found to have an episode of adverse events were recorded. The detailed information about the adverse event was obtained from the ward G7 hospital records.

The method developed to calculate costs relating to adverse events management included components such as medicines, doctor emergency consultations, laboratory tests and ambulatory services (Petterson *et al*., 2012).

Where information was available the cost of adverse events had the following components:

i. inpatient hospitalisation cost charged per day for the full length of stay. Hospitalisation cost was obtained by multiplying the cost of inpatient stay by the duration of inpatient stay. The cost of inpatient stay was charged as professional fee and facility fee per 12 hour intervals;
ii. cost of support medicines plus dispensing fee;
iii. cost of laboratory tests consisting of unit cost of test plus drawing of blood fee; and
iv. emergency consultation cost consisting of cost of emergency professional fee plus facility fee.

The cost of adverse events applied only to patients who had a record of serious adverse effect(s) during the episode of care. In this study the definition of a serious adverse effect was any unwanted or unexpected reaction requiring hospitalisation or emergency consultation caused as a result of treatment with chemotherapy.

4.10 Cost categorisation

The cost of breast cancer treatment and associated adverse events was broadly categorised based on the following:

i. stage on diagnosis i.e. I, II, III or IV based on Tumor-node-metastasis (TNM) staging (Davari *et al.*, 2013);
ii. early stage or late stage cancer. Early stage cancer i.e. stage I and II, and late stage being stage III and IV invasive disease (Pagano *et al.*, 2012; Will *et al.*, 2000);
iii. age 18-35 years, 36-50 years, 51-65 years or older than 65 years;
iv. chemotherapy treatment approach, i.e. adjuvant, neo-adjuvant or palliative based on type of treatment and clinical assessment as recorded in the folders;
v. primary or salvage therapy based on type of treatment and clinical guidelines; and
vi. type of chemotherapy regimen used according to the GSH treatment protocol.

Costs were categorised based on the clinical information obtained from the patient folders. Where information was not clearly stated in the folder, the clinical information available was used to categorise costs. Expert opinion was obtained, where necessary.

4.11 Cost template

The costing template was developed using an Excel® 2010 spread sheet. All patients who met the inclusion criteria were entered into the spread sheet. The cost template provided information derived from MI and information recorded on the data collection form. The data recorded on the cost template represented all utilised resources and direct medical costs that were related to breast cancer treatment according to the study aim and objectives. The data fields which were developed for this cost template are presented in Annexure 5. The cost template included all the relevant costs for calculating the cost of breast cancer treatment for an episode of care. The cost components explained in section 4.9 above were used to quantify the direct medical costs of treating breast cancer.

The second part of the cost template provided costs for management of adverse events. The cost components that contributed to the cost of treating adverse events are explained in section 4.9.8.

Two scenarios of costs were created from the developed cost template, i.e. Scenario 1 was created from costs obtained from the UPFS and Scenario 2 was created from costs obtained from the UPFS and the time and motion studies (Table 4). The same patients included in the cost template were used in the development of costs of treatment for Scenario 2 costs.

4.12 Cost calculation

The cost per episode of care was calculated for each patient using data that were collected as mentioned earlier. The UPFS was the main source of cost whilst the time and motion studies provided an alternative cost for scenario 2 according to Table 4 below. All cost components were added to give the episode of care cost scenario 1 and 2.

Table 4: The summary for calculation of costs per patient

Cost component	Cost calculation
Chemotherapy medicines	Scenario 1: • cost of medicines per cycle which was summed to provide the total cost for all cycles + • dispensing fee unit cost multiplied by the number of cycles Scenario 2: • cost of medicines + compounding fee (TM) + dispensing fee
Support medicines	Scenario 1 and 2: • cost of all support medicines + • dispensing fee where applicable added (refer to section 4.9.2)
Chemotherapy administration	Scenario 1: • professional fee per cycle (UPFS) multiplied by the number of cycles + • facility fee (UPFS) per cycle multiplied by the number of cycles Scenario 2: • cost for doctor and nurse's time per cycle per protocol (TM) + • facility fee (UPFS) per cycle multiplied by the number of cycles
Consultation visits	Scenario 1: • cost of doctor consultation (UPFS) multiplied by the number of consultations during the episode of care + • facility fee (UPFS) per consult multiplied by the number of consultations during the episode of care Scenario 2: • average cost of doctor consultation (TM) multiplied by the number of consultations during the episode of care + • facility fee (UPFS) per consult multiplied by the number of consultations during the episode of care
Laboratory tests	Scenario 1 and 2: • sum of unit costs for each test conducted + • drawing of blood fee calculated per each day laboratory tests were done (normally at every cycle of chemotherapy)
Scans and imaging	Scenario 1 and 2: • sum of unit costs for each procedure conducted + • sum of facility fee (UPFS) for each procedure conducted

UPFS- Uniform Patient Fee Schedule, TM- time and motion, Compounding fee- cost per dose of chemotherapy

4.13 Cost analysis

4.13.1 Cost at patient level

The developed cost template allowed for the cost of treatment of breast cancer to be calculated at patient level. All the cost components that formed part of the patient's care were added to give a total cost for each patient.

4.13.2 .Cost per episode of care

The following costs were calculated in the study:

i. each cost component had a cost at patient level;
ii. each cost component had a total cost for the study population, obtained by adding the cost for each patient;
iii. total cost per episode of care for each patient, obtained by adding all cost components relevant for the patient; and
iv. total treatment cost per episode of care for all patients in the study.

4.13.3 Average cost

The average cost of treating a breast cancer patient in this study was calculated. It was obtained by dividing the total cost of treatment by the number of patients in the study. Similarly, an average cost of each component per patient was calculated by dividing the total cost of each component by the number of patients who utilised the component.

4.14 Predictive model development

A decision tree model was developed to predict the cost of breast cancer treatment with chemotherapy. The cost of breast cancer treatment was grouped based on the stage of cancer. The probabilities of being diagnosed with any of the 4 stages of breast cancer and of a patient on chemotherapy to complete their prescribed episode of care period were used in the decision tree. The costs of treatment were linked to the likelihood of these events occurring at GSH. The same sample of 200 patients used in the development of the method was used in the decision tree model. The cost per event was obtained by multiplying the cost for the particular outcome by the outcome probability. These costs were compared with the costs of treatment from the developed method. The cost per episode of care was used in this analysis.

4.14.1 Model assumptions

The model made the following assumptions:

i. the patients' chemotherapy medicines did not change during the study period;
ii. there were no adverse events or complications with chemotherapy treatment; and
iii. resource use for all components were incurred at GSH.

4.15 Statistical analyses

The SPSS statistical package (version 4) was used to perform all computations. Descriptive statistics were used for all variables. Continuous variables were summarised in descriptive terms stating mean, median, cost range and standard deviation. Both means and medians were used to present cost of treatment due to some outliers which made the means differ from the median.

The Pearson's chi-square tests were conducted to test whether there was a significant relationship between the following treatment categories: (1) stage of breast cancer with treatment approach, (2) episode of care cost with treatment approach and (3) episode of care cost with chemotherapy regimen. *P*-values less than 0.05 were considered to be statistically significant.

A multivariate analysis of variance (Wilks' lambda) was used to test whether there are differences between the means of the categorised costs of treatment. The Wilks' lambda test was used in this study due to the following; (1) the groups which were examined were unequal in size, (2) small sample sizes of subgroups, (3) the groups were independent and not related, and (4) the groups had different mean values. The Wilks' lambda statistic was recorded with a *p*-value and the degrees of freedom. The computed *p*-values for the tests were compared with the α-value of 0.05. When the *p*-values were less than the α-value of 0.05, the tests conducted were considered to be statistically significant.

A multiple regression analysis was used to investigate the relationship between the cost of treatment of breast cancer and the predictor variables, i.e. clinical stage, age at diagnosis, status of treatment (complete or incomplete), protocol and treatment approach. The *f*-value and the regression coefficient of determination are presented in Table 33.

4.16 Ethics

Ethical approval of this study was obtained from the Research Ethics Committee of the University of the Western Cape (ref 14/9/48) and the Human Research Ethics Committee of the University of Cape Town, Faculty of Health Sciences (HREC ref 824/2014). The letters of approvals are attached on Annexure 6. Additional approval was granted by GSH to conduct the study in the Radiation Oncology Department of the hospital. Patient confidentiality was maintained at all times. Patient records were only accessible to the researchers directly involved in the study, i.e. Prof P. Valodia and N. Guzha. Patient data and records collected were kept in a password secure computer and data collection forms were kept in a locked cupboard.

CHAPTER 5

RESULTS

The main focus of this chapter is to illustrate the development of the methodology for costing of breast cancer treatment and the results obtained using the method developed. The predictive models and scenarios developed were also presented.

5.1 Demographics

Two hundred (200) patients diagnosed with breast cancer during the period of 2013-2015 were enrolled in the study according to the inclusion criteria. Demographic information was validated based on the data extracted from the electronic system and the patient medical folders.

Patients enrolled at the GSH Radiation Oncology department (ROD) were confirmed breast cancer patients. According to the information collected from the hospital electronic database, a total of 1 024 patients were registered by the ROD between the period 1 April 2013 to 31 March 2015. Of the patients diagnosed with breast cancer, 67.58% were treated with chemotherapy either alone or in combination with surgery, radiotherapy and/or hormone therapy. During the process of data collection 36 folders were missing. The reasons for missing folders were either because the folder was in another ward, the patient had died or the folder was misplaced. A total of 428 patients who received chemotherapy were eligible for inclusion in the study. Of these patients, a sample of 200 patients was selected by random sampling.

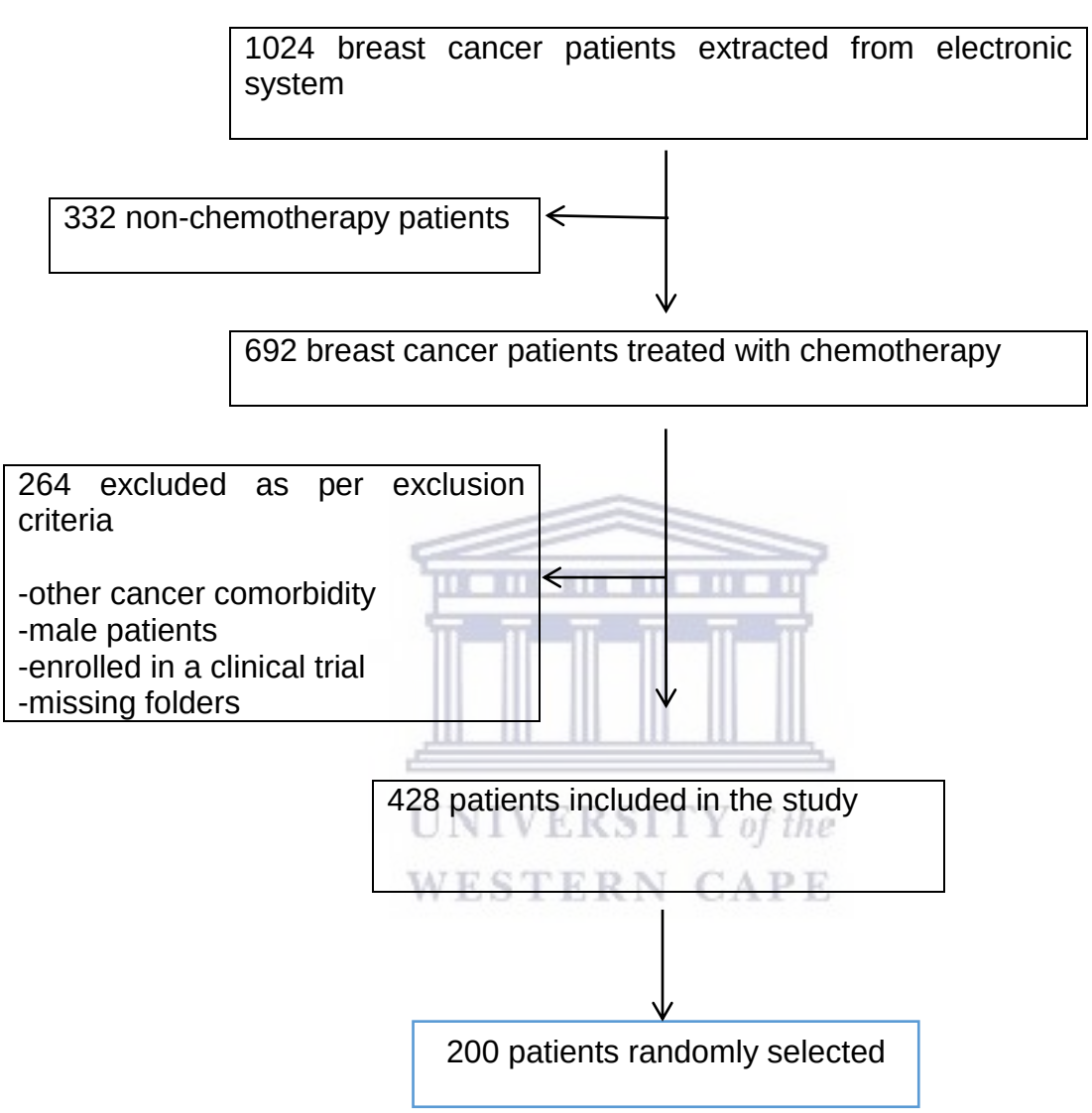


Figure 2: Patient selection

5.2 Patient clinical characteristics

A data set of 200 patients was used for this analysis. Table 5 provides information on the characteristics of patients enrolled into the study.

Our sample (n=200) represented various racial groups and patients were between the ages of 23 and 77 years. The mean age was 50 years (SD 11.6 years) and 66% of patients were above 45 years old. The various stages of breast cancer incidences are reported in Table 5. Of all the stages of breast cancer, the highest incidence (49%) was reported for stage II at the point of registration as reflected in Table 5. The lowest incidence (7%) was recorded for stage I breast cancer. Of the patients, 55% presented with a pre-existing comorbidity at diagnosis and of these 27% presented with 2 or more co-morbid conditions. The most frequent comorbidities were heart diseases (71 patients), endocrine diseases (25 patients), arthritis and pulmonary diseases (16 patients each) and retroviral disease (10 patients). Other less common comorbidities were depression, eczema and epilepsy.

The majority (84.5%) of the diagnosed breast cancers were invasive ductal carcinomas (IDC) with ductal carcinoma in situ also detected. Other unusual variants of breast cancer such as Paget's disease, mucinous and adenoid cystic carcinomas accounted for less than 2% of the diagnosed patients. Adjuvant chemotherapy was the most prescribed approach of chemotherapy treatment at GSH. Of the patients in the study, 61% had adjuvant chemotherapy while 30% had neo-adjuvant chemotherapy. Only 9% of patients received palliative chemotherapy treatment.

Table 5: Clinical characteristics of study population

Patient characteristic	Number of patients (n=200)	Population %
Age at diagnosis		
18 - 35	22	11%
36 - 45	46	23%
46 - 65	113	56.5%
>65years	19	9.5%
Stage at diagnosis		
Stage I	14	7%
Stage II	98	49%
Stage III	65	32.5%
Stage IV	23	11.5%
Histology		
Ductal DCIS, IDC	169	84.5%
Lobular LCIS, ILC	13	6.5%
Paget's disease	1	0.5%
Mucinous	1	0.5%
Adenoma NOS	1	0.5%
Not mentioned	15	7.5%
Modality		
Adjuvant	123	61.5%
Neo-adjuvant	59	29.5%
Palliative	18	9%
Comorbidity		
0	91	45.5%
1	55	27.5%
2 or more	54	27%

DCIS – Ductal Carcinoman in Situ, IDC – Invasive Ductal Carcinoma, LCIS – Lobular Carcinoma in Situ, ILC – Invasive Lobular Carcinoma. NOS – Not Otherwise Stated

Prior to commencing chemotherapy treatment each patient's body surface area (BSA) was calculated. BSA is an important indicator of metabolic mass rather than weight alone in determining the dose of chemotherapy a patient should receive. The doctor or nurse calculated the patient's BSA at every cycle of chemotherapy to minimise under or over dosing of intravenous cytotoxic chemotherapy medicines. The average BSA in this study population was 1.83m^2 (Universal average for women is 1.7m^2) (Sacco *et al.*, 2010).

Each patient with breast cancer was tested for hormone involvement i.e. progesterone receptors, estrogen receptors and HER2, upon diagnosis of breast cancer. The result of each of the 3 tests was recorded in the patient folders. In some cases where the test result was missing or was not recorded in the patient folder, the test was recorded in the data collection form as missing. The missing test results for progesterone receptor (PR), estrogen receptor (ER) and HER2 were 6%, 3% and 4% respectively. When the results in Table 6 are translated to percentages, 50.5% of the tests conducted were positive for ER and 50% tested positive for PR. ER positive patients were prescribed tamoxifen. The positive and negative results of the HER2 tests were evenly distributed within the study sample, i.e. 33.5% positive and 34.5% negative. For the balance of the patients, 28% were equivocal (test in-between positive and negative) and 4% missing. Although 33.5% of the patients tested HER2 positive, trastuzumab was not available at GSH. Out of the 200 patients, there were 27 patients with a triple positive result and there were 39 patients with a triple negative result. Both groups of patients were treated with chemotherapy either as curative or palliative therapy. Furthermore, the patients with a triple positive or ER positive result were managed with hormone therapy in addition to chemotherapy. The cost of hormone therapy was not determined in this study as the focus was on chemotherapy cost.

Table 6: Results of the hormone receptor tests

		Number of tests[1] (n=200)		
	Positive	**Negative**	**Equivocal**	**Missing**
PR	100	88	-	12
ER	101	93	-	6
HER2	67	69	56	8

PR - progesterone receptor, ER - estrogen receptor, HER2 - human epidermal growth factor receptor 2
[1]Each patient had three tests done and each test result was recorded in the patient folder
[2]Number of patients whose tests were neither positive nor negative, it was reported as equivocal.

The Eastern Cooperative Oncology Group (ECOG) scale of Performance Status (PS) was used to assess how breast cancer affects the daily abilities of the patient, and as an important factor in determining appropriate treatment and prognosis. When a patient was diagnosed with breast cancer the doctors performed a physical examination in order to score each patient according to the status of symptoms and functions with respect to ambulatory status and need for care.

As seen in the patient folders, PS 0 means normal activity, PS 1 means some symptoms, but still near fully ambulatory, PS 2 means less than 50% active, and PS 3 means more than 50% of daytime in bed, while PS 4 means completely bedridden. According to Table 7, 51.5% of patients were PS 0 which means that they were fully active and normal functioning upon diagnosis. As the patients progressed with chemotherapy treatment, it was noticed that some moved to PS 1 and PS 2. It was assumed that the transition in performance could have been due to disease progression or presence of adverse events to chemotherapy treatment.

Tumour grade measured how well the cancer cells resembled the normal cells. A low grade tumour means well differentiated, resembling normal cells and thus better prognosis. Table 7 shows that 5.5% of the patients had grade 1 tumours, 33% had grade 2 tumours and 42% had grade 3 tumours. There were 19.5% of folders with missing tumour grade information.

Lymphovascular invasion measured the extent of spread of cancer cells to nearby lymph nodes. A positive (yes) result means that the likelihood of distant spread of cancer cells may be greater. Of the patients, 33.5% tested positive whilst 39.5% were negative. For the remaining 27%, the information was missing from the patient folders. The reason for the missing information in the folder could not be established. However, it was assumed that one patient is attended by different doctors and some doctors record all the results in the folders whilst others do not. It was also assumed that due to the busy nature of the hospital there was often not enough time to update all the laboratory results in the patient folders.

Table 7: Prognosis indicator statistics at GSH

Prognostic indicator	Number of patients (n=200)	Percentage (%)
PS score		
0	103	51.5%
1	77	38.5%
2	5	2.5%
3	2	1%
4	0	0%
X	13	6.5%
Tumor grade		
1	11	5.5%
2	66	33%
3	84	42%
X	39	19.5%
Lymphovascular invasion		
Yes	67	33.5%
No	79	39.5%
X	54	27%

PS- performance status (Sørensen, J.B et al. 1993), X means unknown or missing or not recorded in patient folder.

5.3 Cost components

5.3.1 Cost of chemotherapy

The cost of chemotherapy was calculated at patient level per each cycle of regimen received. The cost per cycle of chemotherapy varied for each patient depending on the type of regimen prescribed.

Table 8: Cost per cycle of chemotherapy regimens at GSH

Chemotherapy regimen	Average cost per cycle	Number of cycles prescribed, (n)
FEC	R615.77	6
EC	R587.05	4
FEC-P	R790.14	7 (3-4)[1]
EC-P	R718.93	7 (4-3)[2]
P	R874.76	6

C-Cyclophosphamide, E-Epirubicin, F- 5-fluorouracil, P-Paclitaxel
[1]3 cycles of FEC and 4 cycles of P, [2]4 cycles of EC and 3 cycles of P

The cost of chemotherapy medicines was R761 152.26 for the 200 patients. The dispensing fee was added to each patient for each day a prescription was handled at the pharmacy. The cost of chemotherapy and dispensing fee amounted to R801 311.26 for the 200 patients.

The three aspects of chemotherapy costs that were studied were the cost of medicines (chemotherapy), dispensing fee and administration of chemotherapy. All the individual costs were added to give the total cost related to chemotherapy use as shown in Figure 3. The cost of compounding of chemotherapy medicines by the pharmacist was determined by time and motion studies. The compounding fee was added to the method developed for scenario 2 as illustrated in Figure 4.

The R761 152.26 cost of the intravenous chemotherapy medicines represented the cost to the hospital incurred by the 200 patients during the study period (Figures 3 and 4). The dispensing fee of R36 per patient per prescription was 5% of the cost of chemotherapy medicines. The cost of chemotherapy medicines was 2.9 times more than the cost of administering the chemotherapy.

The cost of administering chemotherapy to the 200 patients was R262 749. The cost consisted of a professional and a facility fee. The professional fee was 2.15 times more than the facility fee. According to the UPFS, the professional fee consists of the cost of the nurses' fee and the cost of other health care professionals involved in the care of the patient. The cost of administering chemotherapy was a fee charged for providing the service to the patient and equipment used.

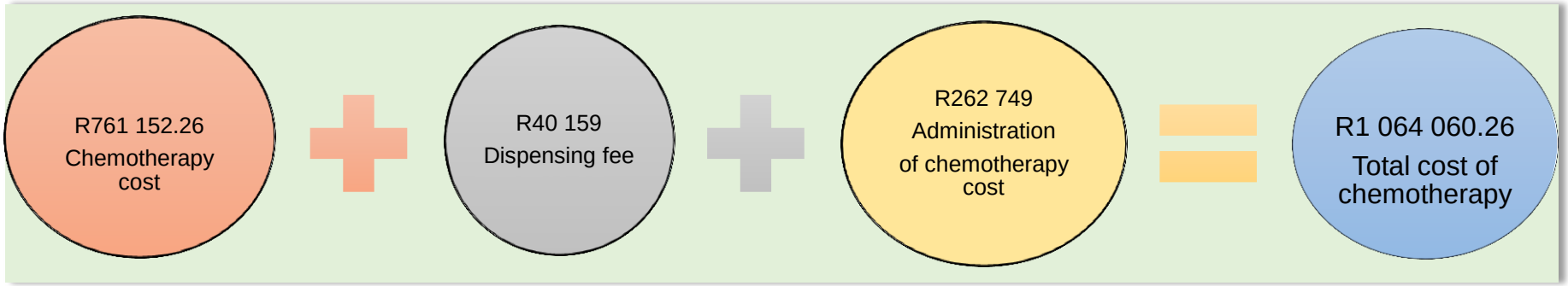


Figure 3: Component costs for chemotherapy as they appear in the model scenario 1 (n=200)

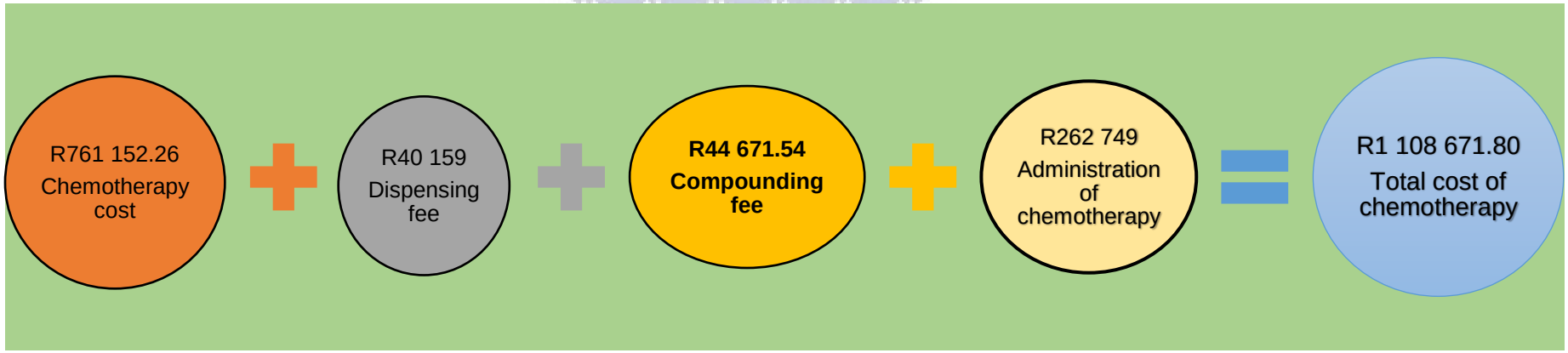


Figure 4: Component costs for chemotherapy as they appear in the model scenario 2 (n=200)

Table 9: Chemotherapy components for the treatment of breast cancer at GSH (n= 200)

Cost component		Costs for 10-12 month period				
	Cost (n=200)	% (n=200)	Average cost per patient	SD	Median	Min-Max
Chemotherapy and dispensing fee	R801 311.26	75.3	R4 006.56	R1 635.67	R3 880.81	R544.82 – R10 653.39
Administration of chemotherapy	R262 749.00	24.7	R1 313.75	R335.46	R1 404.00	R234.00 – R3 276.00
Chemotherapy total cost	R1 064 060.26	100	-	-	-	-

In the model for calculating the cost of treatment, other cost components relating to chemotherapy in the management of breast cancer were accounted for. Of the total cost, the cost components, i.e. chemotherapy, support medicines, consultation, laboratory tests, scans and imaging procedures accounted for 33.7%, 7.5%, 17.4%, 14.1% and 27.3% respectively. All the cost components costs are summarised in Figure 7, Section 5.4.3.

Table 10: Summary of other cost components studied for the treatment of breast cancer at GSH

Cost component	Costs for 10–12 month period					
	Cost (n=200)	% (n=200)	Average cost per patient	SD	Median	Min-Max
Chemotherapy total cost	R1 064 060.26[1]	33.7	-	-	-	-
Support medicines	R235 425.67	7.5	R1 177.13	R738.21	R1 089.87	R116.99 – R 7 385.48
Consultation	R549 562.00	17.4	R2 747.81	R736.31	R2 691.00	R897.00 – R4 784.00
Laboratory tests (routine)	R445 247.98	14.1	R2 237.43	R1 166.12	R1 997.01	R447.48 – R6 840.00
Scans and imaging (routine)	R860 582.00	27.3	R4 302.91	R1 674.10	R4 233.00	R527.00 – R10 064.00
Total cost	R3 154 877.91	100	-	-	-	-

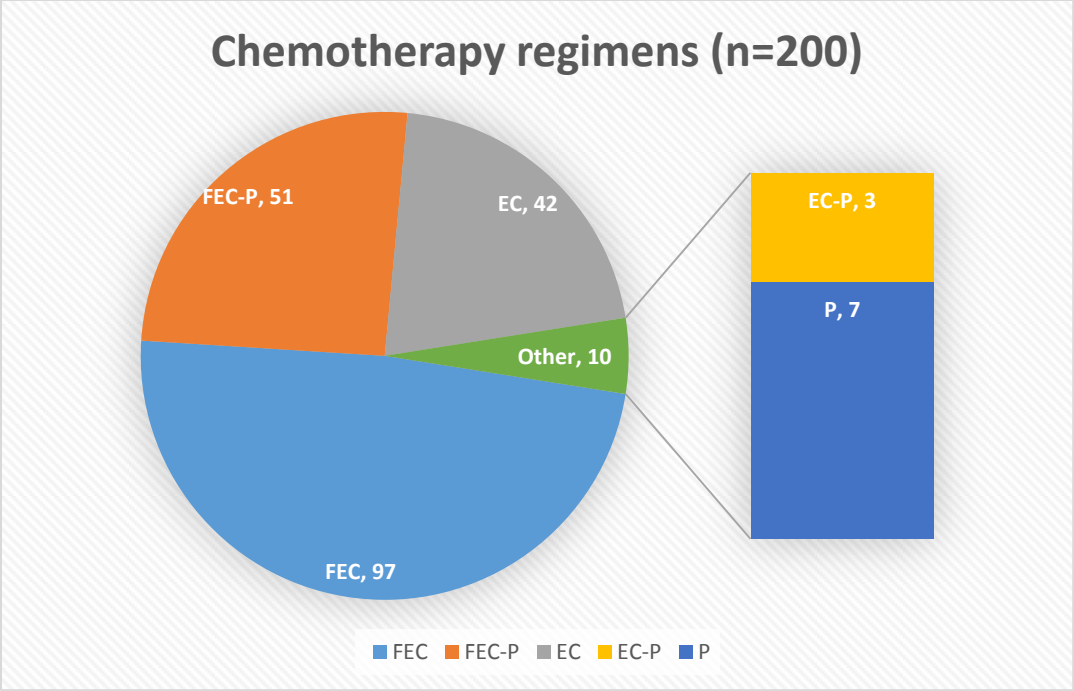
[1]Cost derived from Table 9 and includes the following components: chemotherapy medicine, dispensing fee and administration of chemotherapy

5.3.2 Cost of chemotherapy regimens as per GSH protocol

The chemotherapy medicines that were studied were categorised based on the type of chemotherapy regimen selected for the patient. The chemotherapy regimens were classified according to the identified patterns of prescribing (as seen in the patient folders) and the GSH breast cancer protocol provided. The GSH protocol had at least 6 regimens of different chemotherapy combinations (Table 2, Section 4.9.1).

In the study, it was found that 5 regimens were widely prescribed. The other regimen, i.e. cyclophosphamide and docetaxel was not used often probably due to cost and a high potential to cause adverse events. In the class of taxanes, paclitaxel was preferred as compared to docetaxel. According to the prices listed on MI database, paclitaxel 100mg injection for infusion costs R143.13 while docetaxel 80mg injection for infusion costs R825.78. Although the medical informatics database listed docetaxel on the price list, docetaxel was not used by any of the 200 patients in this study.

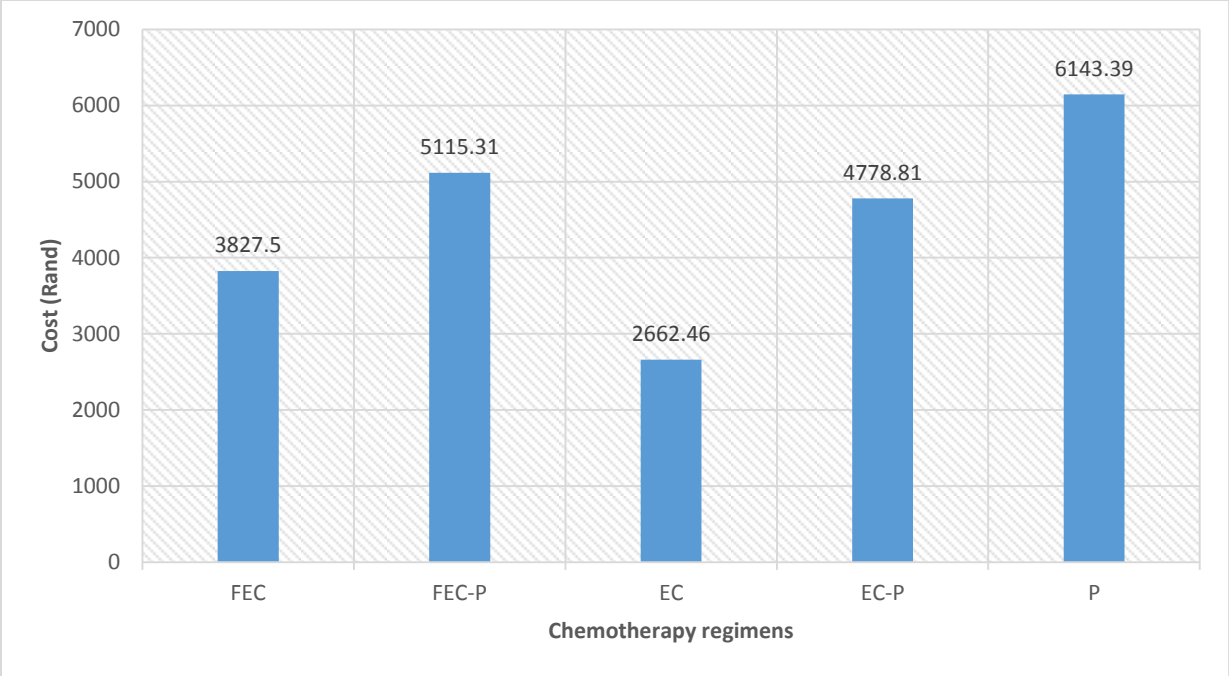
The therapeutic regimen, FEC, prescribed every 21 days cycle for 6 cycles, was the most frequently prescribed regimen (48.5%) for patients across all disease stages. The EC-P combination was least prescribed in 3.2% of patients.



C-Cyclophosphamide, E-Epirubicin, F- 5-fluorouracil, P-Paclitaxel

Figure 5: Number of patients who received chemotherapy regimens

The average cost of each regimen used is illustrated (Figure 6). The costs obtained from scenario 1 were used in this analysis. The scenario definitions are in section 4.12. The paclitaxel regimen (P) was the most expensive regimen of chemotherapy. The average cost per patient for P was R6 143.39. The most frequently prescribed regimen (FEC) was R5 115.37 per patient. The least expensive (R2 662.46) of all the regimens was the EC regimen.



C-Cyclophosphamide, E-Epirubicin, F- 5-fluorouracil, P-Paclitaxel

Figure 6: Average cost per patient of each regimen used at GSH

Table 11 shows the variation in cost of chemotherapy regimens, which were found to vary depending on the type of chemotherapy and dosage of medicines prescribed for each patient. The range of cost of each regimen was found to be fairly wide (refer to Table 11 for maximum and minimum cost per patient). This is because the recorded cost included both complete and incomplete protocols according to each patient's circumstances. About 14% of chemotherapy regimens at GSH were not completed as prescribed. The main reasons for discontinuation of chemotherapy were disease progression, toxicity (adverse events), patient refusal and death.

Table 11: Chemotherapy regimens as utilised by study population

Chemotherapy regimen	Number of patients, (percentage)	Average cost per patient	Minimum cost per patient	Maximun cost per patient
FEC	97 (48.5%)	R3 827.50	R544.82	R6 808.57
FEC-P	51 (25.5%)	R5 115.31	R1 302.29	R9 758.47
EC	42 (21%)	R2 662.46	R633.04	R6 533.98
EC-P	3 (1.5%)	R4 778.81	R3 675.10	R5 801.08
P	7 (3.5%)	R6 143.39	R2 983.90	R10 653.39

C-Cyclophosphamide, E-Epirubicin, F- 5-fluorouracil, P-Paclitaxel

The average cost of treating a patient on the FEC regimen differed by 37% when compared to paclitaxel. The cost of FEC-P and the EC regimens were higher (25%) and lower (30%), respectively, than the standard FEC regimen.

The prices of chemotherapy medicines obtained from the MI database were validated and checked for consistency. It was discovered that there were significant price variations for the same medicines, prescribed for the same patient, within the same episode of care and for the same dosage. Upon enquiry with the hospital pharmacy manager and the developer of the chemotherapy pricing system, the following reasons were given for the noted price variations. It was indicated that, (a) the chemotherapy medicines were prepared in batches and each patient was charged an average price for the same chemotherapy prepared in the batch on the particular day, and (b) the chemotherapy medicine prices were calculated based on the dosage of each patient according to the patient's BSA.

5.3.3 Cost of support medicines

The cost of support medicines was relatively inexpensive. The average cost per patient was R1 177.13 (SD R738.21) for the entire episode of care. The electronic data provided were characterised by minor price variations which were largely accounted for due to capture error. It was assumed that the quantity of medicines issued was captured incorrectly as the JAC medicines system automatically calculated the price of medicines using the captured quantities. When calculated per patient, the most costly class of medicines was the antibiotics (given in some cases to treat neutropenia) and the least costly was the antiemetics. The TPL of medicines was used to validate the price of medicines.

Table 12: The commonly prescribed medicines and their prices derived from the Medical Informatics (MI) and the Tender Price List (TPL)

Medicine and pack size available	MI	TPL
Metoclopramide 10mg x 30 tablets	R1.99	R1.58
Prednisone 5mg x 30 tablets	R2.72	R3.25
Betamethasone 500µg x 48 tablets	R124.05	Missing[1]
Ondansetron 8mg in 1 x 4ml injection	R6.75	R6.75
Ibuprofen 200mg x 21 tablets	R1.50	R2.12
Hyoscine n-butylbromide 10mg x 10 tablets	R4.90	R5.84
Paracetamol 500mg 10 x 10 tablets	R11.03	R11.28
Folic acid 5mg x 28 tablets	R1.78	R1.28
Tramadol 50mg x 80 capsules	R20.45	R22.76
Amikacin 500mg in 2ml injection	R16.96	Missing

[1] The cost of betamethasone tablets and amikacin injection were not available on the TPL provided

5.3.4 Cost of laboratory tests

The number of laboratory tests that were conducted routinely were 6 177 and 116 tests were conducted due to adverse events. The laboratory tests were conducted as a standard procedure at each cycle before chemotherapy administration and when the patient presented with adverse events. The average cost of laboratory tests per patient was R2 226.24 for the episode of care. The laboratory tests that were conducted outside the study site were not included in the analysis. A total number of 6 patients had all or some tests conducted privately. The maximum cost of laboratory tests per patient was R6 840.06 and the minimum cost per patient was R447.48. The average cost for laboratory tests conducted for adverse events management was lower (R551.82) than the average cost (R2 237.43) for the tests done during routine treatment period. This was because the adverse events tests were conducted during the period (1-2 months) when the adverse events occurred whilst the routine tests were greater in number and conducted over a longer period of time (10-12 months).

Table 13: Cost of laboratory tests (routine and adverse events)

Category	Number of tests	Cost of all tests	Average cost per patient
Routine laboratory tests	6 177 (n=199)	R445 247.98	R2 237.43 SD R1 166.12 (R447.48 – R6 840.06)
Laboratory tests for adverse events management	116 (n=10)	R5 518.14	R551.82 SD R589.14 (R108.76 – R1 642.11)
Total of all tests	6 293 (n=199)	R450 766.12	R2 265.16

A list of laboratory tests that appeared on the MI database and patient folders was compiled and tabulated below (Table 14).

Table 14: Laboratory tests conducted for breast cancer patients at GSH

Test	Procedure	Indication
Blood tests	FBC Platelet	Standard assessment for bone marrow metastasis
Liver function tests	Total bilirubin Albumin Alanine transaminase Aspartate transaminase Alkaline phosphatase Gamma-glutamyl transferase	Baseline tests to assess state of liver functioning and involvement
Renal function tests	Creatinine Calcium Urea Electrolytes	Assessment of possible obstructive renal symptoms
Menopause	Follicle stimulating hormone Luteinising hormone Estradiol	Assessment of menopausal status
Histology	ER (estrogen receptor) PR (progesterone receptor) HER2 (human epidermal growth factor receptor 2)	Determination of tumour type and grade

5.3.5 Cost of scans and imaging

As shown in Table 15, the cost of all scans and imaging procedures relating to both breast cancer treatment and management of adverse events was R871 843. The cost was measured over a period of each person's episode of care after the primary diagnosis of breast cancer. The cost per patient (R4 302.91) was calculated as an average. The facility fee represented 48% of the cost and the remainder included professional or procedure costs.

Table 15: Cost of scans and imaging procedures (routine and adverse events)

Category	Number of procedures	Cost of procedures	Average cost per patient
Routine scans	1477 (n=200)	R860 582.00	R4 302.91 SD R1 674.10 (R527.00 – R10 064.00)
Scans for adverse events management	24 (n=7)	R11 261.00	R1 608.71 SD R1 800.58 (R527.00 – R5 048.00)
Total of all tests	1 501 (n=200)	R871 843.00	R4 359.22[1]

1. The average cost per patient of all tests is calculated by dividing cost of procedures with 200 patients who had routine procedures and 7 of which had adverse events.

The facility and procedure fees for scans and imaging are listed in Table 16. The UPFS grouped the scans and imaging procedures in categories according to the facility and procedure costs. When the cost of routine tests is combined with cost of adverse events, the average cost of all tests was found to be more than the average cost of routine tests alone by 1.3%.

Table 16: Scans and imaging procedures conducted at GSH

UPFS category	Procedure	Facility fee	Procedure fee
B	Mammogram US breast US abdomen/ liver/ pelvis Chest xray CT scan body	R200	R327
C	Bone scan US guidance biopsy	R463	R800
D	US abdomen and pelvis CT scan head	R925	R1 599
Unknown group[1]	ERNA	R576	R286

CT – computed tomography, ERNA – Equilibrium Radio-Nucleotide Angiocardiography, US - ultrasound
[1] ERNA cost was not available in the UPFS gazette but obtained from the hospital electronic system.

The UPFS facility fee was an integral part of obtaining the cost of each component. The costs of providing the facility for the services that were rendered at GSH to the patients are listed in Table 17. The costs were fixed and charged for every patient who received the particular service.

Table 17: UPFS facility fees

UPFS component	Tertiary hospital unit cost
Dispensing fee per day	R36
Administration of chemotherapy	R87
Outpatient consultation	R95
Emergency outpatient consultation	R192
Inpatient General ward per every 12 hours	R774
Scans and imaging Mammogram CT scan of abdomen and pelvis	Varies depending on type of procedure R200 (minimum fee) R925 (maximum fee)
Drawing of blood	R31

Provincial Gazette for Western Cape No. 7245, 27 March 2014
CT – computed tomography

5.4 Developed cost method: Cost calculation

The development of the costing method was fully explained in Chapter 4. The costing method included data from Medical Informatics (electronic data) and from the patients' folders to ensure a complete data set. The results were presented as different scenarios depending on the different sources of costs. For the purpose of this study all costs are reported for the time period 2013 to 2015.

The costs obtained from the cost components were used in the development of the cost model. The model comprised of cost of chemotherapy and the associated cost components related to breast cancer management. When developing the cost model an incremental approach to costing was followed.

The starting point was understanding the cost of the chemotherapy medicines. The cost of chemotherapy medicines was categorised according to the 5 main regimens available at GSH. This cost of each regimen was obtained at patient level.

To the chemotherapy medicines, a dispensing fee of R36 was added. This was added according to the format explained in Section 4.9.2.

The support medicines were screened for relevance to the chemotherapy treatment by confirming the indication within the patient folders. The costs of support medicines and their respective dispensing fees were added to the model.

Thereafter, professional fees and facility fees obtained from the UPFS were added to each patient according to their individual history as collected from the MI and patient folders.

The professional and facility fees were for the following components: administration of chemotherapy, laboratory tests, doctor consultation, and scans and imaging procedures.

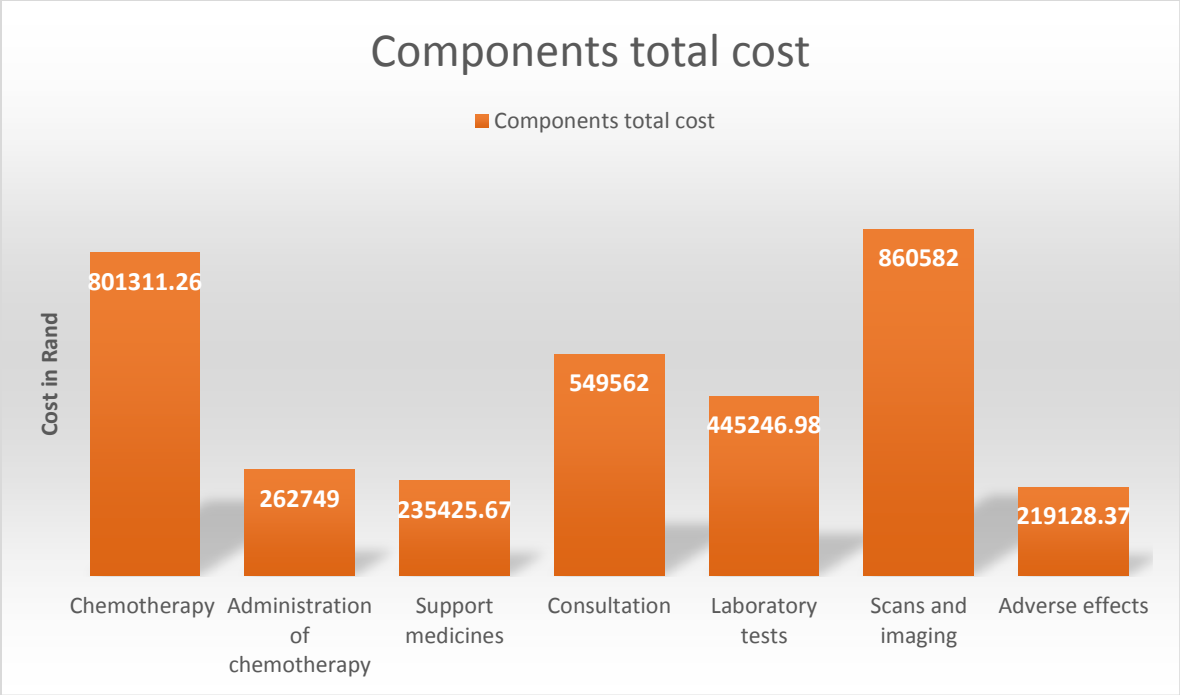
The sum of the cost components mentioned above resulted in the cost for episode of care per patient and the total cost of treatment of breast cancer with chemotherapy at GSH.

The professional fees for the administration of chemotherapy and doctor consultation were substituted with costs obtained from time and motion studies to give a second scenario of the cost. Furthermore, time and motion studies were utilised to calculate the cost of compounding of chemotherapy by the pharmacist. The aforementioned resulted in the cost of an episode of care for scenario 2.

Thereafter, information for patients who had adverse events to chemotherapy treatment was collected and added to the model.

5.4.1 Cost of components

The detailed costs of different components of treatment, following the primary diagnosis are displayed in Table 9 and 10. The highest component cost for the 200 patients was incurred for scans and imaging at a cost of R860 582. Support medicines were the least costly of all the cost components. The cost of all support medicines for all the 200 patients was R235 425.67. When evaluating the cost per patient for each component, the main cost drivers were the cost of scans and imaging and the cost of chemotherapy. The different cost components studied accounted for varying proportions of the total cost as shown in Figure 7.



The figure illustrates the total cost of each component as calculated for all 200 patients. The total cost sums up all the episode of care costs for each of the 200 patients.

Figure 7: The cost components of breast cancer treatment (n=200)

5.4.2 Cost of breast cancer per episode of care

The cost of treating breast cancer for the episode of care based on the variables and scenarios taken into consideration ranged from R12 664.76 to R16 259.72 per patient (Table 19).

The study population of 200 patients was made up of patients who completed their treatment cycles for chemotherapy and patients who did not complete due to reasons explained in Section 5.3.2.

Table 16 indicates the total cost of treatment for patients who completed treatment during their episode of care and those patients who did not complete treatment. Of the sample of 200 patients, the patients who completed treatment were 6 times more in number than the patients who did not complete their treatment with chemotherapy.

The total direct medical cost of treatment for 200 patients was R 3 154 877.90 (Table 18). The cost was calculated at patient level for a period of 10 - 12 months post diagnosis. The cost included all cost components for the management of breast cancer as studied in this research. Cost of diagnosis prior to enrolment at ROD was not included because the study excluded patients with an unconfirmed diagnosis and/or a negative diagnosis of breast cancer (Groot *et al*., 2006). The average cost of treatment for the episode of care period was R15 774.39 per patient (Table 19).

Table 18: The proportion of total costs by complete and incomplete chemotherapy treatment

	Number of patients (n)	Percentage (%)	Total cost (episode of care[1])
All patients	200	100%	R3 154 877.90
Patients who completed treatment	173	86.5%	R2 812 929.40
Patients who did not complete treatment	27	13.5%	R341 948.50

[1] The method included the costs associated with chemotherapy treatment and excluded cost associated with radiotherapy, surgery or hormonal treatment

5.4.3 Cost of management of breast cancer

The average costs of managing a patient diagnosed with breast cancer at GSH are reported in Table 19. The average cost was calculated based on each individual's duration of treatment. The average costs for patients who completed and who did not complete treatment were categorised separately. The average cost of treating a patient who manages to adhere to prescribed chemotherapy for the full duration of treatment was R16 259.72.

The cost of a small proportion (13.5%) of the study sample that did not complete the prescribed treatment was on average R12 664.76 per patient. The combined average cost of all the 200 patients in the study was R15 774.39.

The complete protocol cost allows the funder of care to estimate maximum budget for treatment of breast cancer whilst the incomplete protocols allows for the identification of true circumstances surrounding the treatment of breast cancer. The average and median per patient costs based on whether the protocol was completed or not are displayed in Table 19 below.

Table 19: Average cost of management of breast cancer per patient at GSH

	Average cost per patient	**Median cost per patient**	**Total cost**
	Approximately 10–12 month period		
Complete protocol (n=173)	R16 259.72 SD R6 077.37	R15 551.00	R2 812 929.40
Incomplete protocol (n=27)	R12 664.76 SD R6 417 75	R12 252.07	R341 948.50
All patients (n=200)	R15 774.39	R15 295.68	R3 154 877.90
Adverse events (n=27)	R7 782.53	R6 870.21	R210 128.37

5.4.4 Total cost of breast cancer

The total costs associated with breast cancer treatment are presented in Table 20. The costs are expressed as costs per episode of care calculated from the number of breast cancer patients treated with chemotherapy with different scenarios of cost. The cost of chemotherapy, administration of chemotherapy and consultation were presented in 2 scenarios.

The total cost of treatment was also presented as 2 different scenarios. The scenario definitions were explained in full in Section 4.12.

Scenario 1: Cost of components calculated with the UPFS fees as the main source of cost

Scenario 2: Cost of components calculated with UPFS fees and costs obtained from the time and motion studies.

The average cost per patient of scenario 1 was R1 442 (9%) more than the cost of scenario 2. It appears that the UPFS costs are more than the costs determined based on the actual time of consultation and administration of chemotherapy. However, a decent comparison can be drawn when the sample sizes in the study are increased and other types of cancers are also taken into consideration. Statistical tests were conducted on the total costs of breast cancer obtained from scenario 1 and scenario 2, based on the study sample. The two scenarios for the total costs of breast cancer were found to be statistically significant (p<0.001) using the Wilks' Lambda test. The results of the other tests conducted on the total cost of breast cancer are attached on Annexure 7.

Table 20: Total cost of scenario 1 versus scenario 2 for the treatment of breast cancer

Cost component	Total cost for 10–12 months period		Average cost per patient	
	Scenario 1	Scenario 2	Scenario 1	Scenario 2
Chemotherapy cost SD Median	R801 311.26 R1 635.67 R3 880.81	R845 982.80 R1 667.14 R4 120.33	R4 006.56 R3 880.81 R1 635.67	R4 229.91 R4 120.33 R1 667.14
Administration of chemotherapy SD Median	R262 749.00 R335.46 R1 404.00	R150 158.02 R199.65 R822.02	R1 313.75 R335.46 R1 404	R750.79 R199.65 R821.03
Consultation SD Median	R549 562.00 R736.31 R2 691.00	R329 036.66 R427.42 R1 612.07	R2 747.81 R2 691 R736.31	R1 645.18 R1 612.07 R427.40
All components[1] (n=200)	R3154 877.90	R2 866 433.11	R15 774.39	R14 332.17

[1]Total cost of all components included all other components of costs studied

The average cost per patient for administering chemotherapy was R1 313.75 for scenario 1 and R750.79 for scenario 2. According to the time and motion study results, it took an average of 16.87 minutes of nurses' time to administer chemotherapy. The time, however, varied according to the regimen of chemotherapy received. According to Table 21, it took an average of 19.54 minutes to administer FEC, 13.76 minutes for EC and 17.29 minutes for P. The EC regimen took less of the nurses' time than the P regimen. The single dose regimen P took 3.53 minutes more than the FEC regimen because the infusion rate of the P regimen was slower than the FEC regimen.

The costs of scenario 2 for administration of chemotherapy and doctor consultation were found to be less than the cost obtained with scenario 1. The chemotherapy cost

showed an increase in cost from scenario 1 to scenario 2. The cost of compounding of chemotherapy increased the total cost of chemotherapy by 5.3%. The pharmacists' time determined in this study reflected the actual cost incurred by the hospital during compounding of these chemotherapy medicines. It took an average of 9.76, 6.74 and 4.97 minutes to compound FEC, EC and P, respectively (Table 21).

Table 21: Time and motion study results

Task being measured	Average time per cycle (min)	Average cost per cycle
Compounding of chemotherapy	*Pharmacists' time*	
FEC	9.76	R44.16
EC	6.74	R30.49
P	4.97	R22.50
Consultation	*Doctors' time*	
First visit	20.50	R114.21
Follow-up	12.14	R67.61
Administration of chemotherapy	*Nurses' time*	
FEC	19.54	R38.48
EC	13.76	R27.10
P	17.29	R34.05
Administration of chemotherapy	*Doctors' time*	
Updating patient folder/ responding to query	1.32	R7.36

5.5 Cost categorisation

The cost of breast cancer treatment was categorised according to clinical stage, age at diagnosis, treatment approach and type of therapy as presented below (Tables 22, 23, 24 and 25).

5.5.1 Cost of breast cancer based on clinical stage

The cost of each component was determined at patient level. The presented costs include the costs of all patients despite the fact that the prescribed protocol of chemotherapy was complete or not. The cost per treated patient with stage I disease was R13 646.45, stage II was R15 095.71, stage III was R16 871.01 and stage IV was R16 862.29, as illustrated in Table 22.

An analysis of the stage at diagnosis revealed that the breast cancer patients who presented with stage III and IV had the highest cost of treatment.

The median costs were R13 237.48, R14 563.21, R16 296.85 and R15 684.84 for stages I, II, III and IV breast cancer respectively. The median costs showed an increasing trend in cost as the stage of breast cancer increases. When the ranges of the four stages were compared, stage IV had the highest minimum cost (R5 867.43) on the range and stage II had the lowest minimum cost (R3 480.81). The widest range incurred was for stage III.

Table 22: Cost of treatment per stage of breast cancer for all patients

Stage at diagnosis	Total cost per stage	Average cost per patient per stage	Range
I	R191 050.34 (n=14)	R13 646.45	R5 611.08 – R24 419.35
II	R1 479 379.41 (n=98)	R15 095.71	R3 480.81 – R37 705.02
III	R1 096 615.45 (n=65)	R16 871.01	R3 922.06 – R38 627.40
IV	R387 832.70 (n=23)	R16 862.29	R5 867.43 – R36 569.94

The total cost of treating early stage cancer was R1 670 429.75 and late stage cancer was R1 484 448.15. In this study early stage breast cancer was stages I and II disease while late stage breast cancer was stages III and IV disease. The Wilk's Lambda test found significant difference in cost between stage I and III, stage I and IV and stage II and III (p<0.001). However, there was no statistical significance observed between stages I and II and stages III and IV (p>0.05). As shown in figure 7, the variances of each stage of breast cancer were plotted using the one-way multivariate analysis of variance test (ANOVA).

An overlap of the variances and confidence intervals of stages of breast cancer mentioned above resembled the presence of statistical significant differences (X^2=491.77; df=9; p<0.001). The letters a, b and c in Figure 8, denote stages of breast cancer that are statistically significant and those that are not significant. The vertical bars with different letters, i.e. a and c or a and b, show statistical significance of cost between the respective stages. However, similar letters, i.e. a and a or c and c, show insignificant relationship.

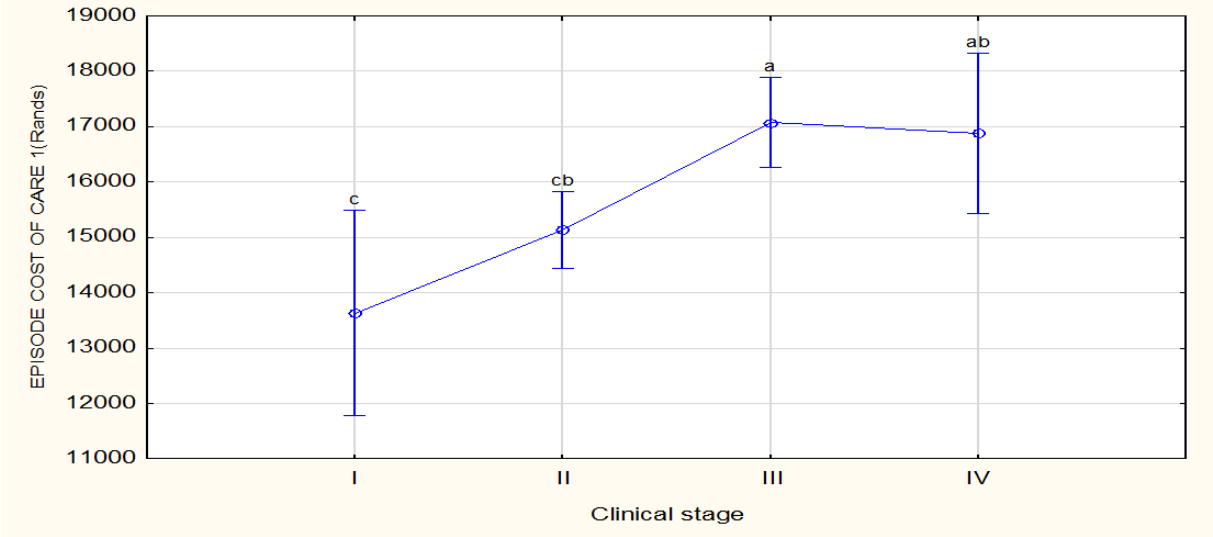


Figure 8: The Wilk's Lambda test for statistical significance differences of cost between the stages of breast cancer

5.5.2 Cost of breast cancer based on age at diagnosis

The patients were grouped into their respective age groups despite their type of chemotherapy received or the severity of their cancer. The highest incidence (113 patients) of breast cancer occurred in the 46-65 years age group whilst the lowest incidence (19 patients) occurred in the oldest age group, i.e. greater than 65 years old. The widest range of cost (R36 885.80) was incurred for the second oldest group.

The cost of treatment per age group is displayed in Table 23. The reported differences of the average costs per patient in each age group were found to be not statistically significant following a Wilk's Lambda test (p=0.15).

Table 23: Cost of treatment per age group

Age at diagnosis	Cost per age group	Cost per patient per age group	Range
18 – 35 (n=22)	R358 815.97	R16 309.82	R5 635.30 – R33 232.21
36 – 45 (n=46)	R737 405.26	R16 030.59	R4 047.22 – R40 932.99
46 – 65 (n=113)	R1 782 553.28	R15 774.81	R2 821.81 – R39 076.16
>65 (n=19)	R280 463.23	R14 761.22	R6 345.75 – R22 294.32

5.5.3 Cost of breast cancer based on treatment approach

The study population was tested for variation of cost based on the treatment approach as reported in Table 24. The results of this section showed that the most prescribed (62% of patients) type of treatment was adjuvant chemotherapy. The cost of treatment per patient with neo-adjuvant chemotherapy was greater than the cost of treatment for both adjuvant chemotherapy and palliative therapy. There were, however, small differences between the treatment approaches for the cost per patient as shown in Table 24.

Table 24: Cost of treatment per treatment approach

Treatment approach	Cost per modality	Cost per patient per modality	Range
Adjuvant	R1 902 382 (n=123)	R15 466.52	R2 618.81 – R40 779.16
Neo-adjuvant	R979 908 (n=60)	R16 331.80	R5 236.95 – R33 566.84
Palliative	R272 587.50 (n=17)	R16 034.56	R5 867.43 – R32 715.31

5.5.4 Cost based on primary and salvage therapy

Cost of treatment of breast cancer was classified based on primary and salvage treatment. Only 2% of the patients entered in the study had salvage therapy. Salvage therapy is given after the cancer has relapsed following treatment with standard therapy.

Table 25: Cost of treatment per primary and salvage therapy

	Number of patients (%)	Cost of protocols
Primary[1]	200 (100%)	R761 152.26
Salvage [2]	4 (2%)	R20 334.04
Total[3]	n/a	R781 486.30

[1]All 200 patients were treated with primary
[2]Cost of treatment of recurrent episode of disease only
[3]Total cost is the sum of all recorded episodes of treatment (primary plus salvage). Minimum number of episodes per patient recorded was 2.

5.6 Combined categorisation of costs

The categories of costs that were studied were further analysed in order to understand their relationship with each other with respect to costs and prescribing patterns at GSH.

5.6.1 Treatment approach versus stage of breast cancer

Table 26 illustrates the relationship between the stage of breast cancer and the treatment approach selected for the patient. The trend discovered was that all patients diagnosed with stage I cancer were treated with adjuvant chemotherapy. The majority (87.8%) of stage II patients were treated with adjuvant chemotherapy whilst a few (11.2%) were prescribed neo-adjuvant chemotherapy.

The advanced stage cancer, i.e. stage III and IV showed that neo-adjuvant and palliative, respectively, were the treatments of choice. Overall, adjuvant chemotherapy was the mostly prescribed type of treatment with 123 out of 200 patients receiving this approach of treatment. The Pearson's Chi-Square test indicated a significant association between stage of breast cancer and the approach of treatment (X^2=184.68; df=6; p<0.001). See Chi-Square test results in Annexure 7.

Table 26: Treatment approach versus stage of breast cancer

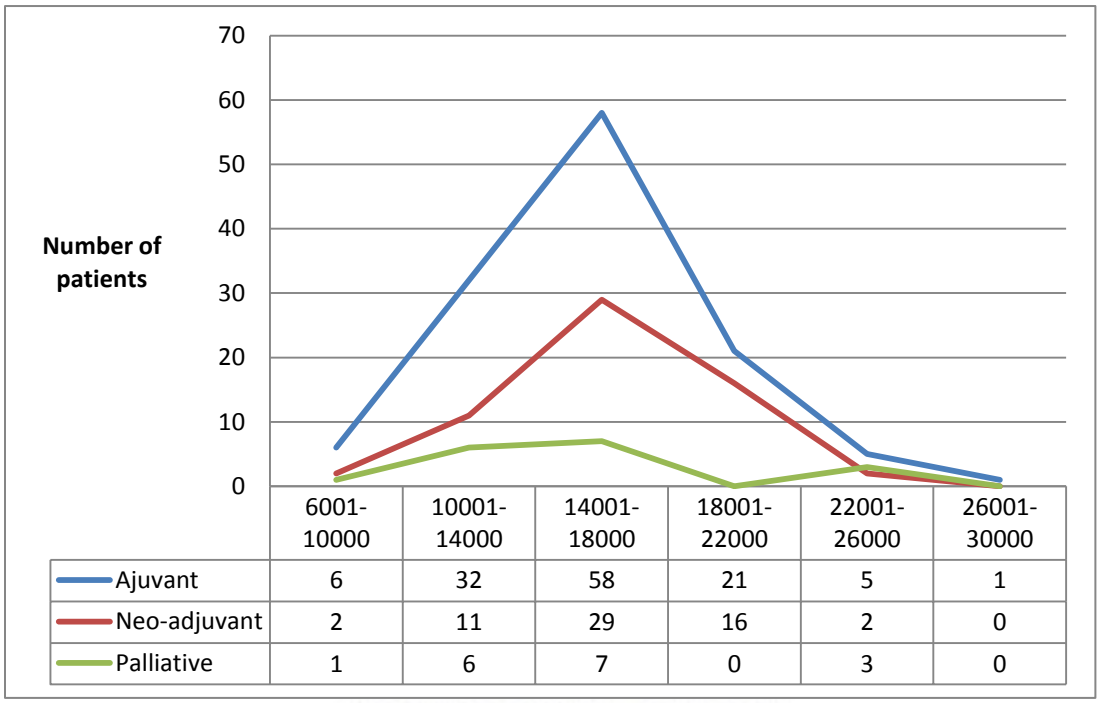
			Treatment approach			Total %
			Adjuvant	**Neo-adjuvant**	**Palliative**	
Clinical stage	**I**	Count % within CS I	14 100%	0 0%	0 0%	14 100%
	II	Count % within CS II	86 87.8%	11 11.2%	1 1%	98 100%
	III	Count % within CS III	18 27.7%	46 70.8%	1 1.5%	65 100%
	IV	Count % within CS IV	5 21.7%	3 13%	15 65.2%	23 100%
Total		Count % within CS all	123 61.5%	60 30%	17 8.5%	200 100%

CS – Clinical stage

5.6.2 Episode of care cost versus treatment approach

The episode of care cost per patient was plotted against the type of treatment prescribed for each patient. The most prominent feature observed across all modalities is that the average cost of an episode of care falls between R14 001–R18 000. The data also shows that most patients received adjuvant chemotherapy (61.5%), followed by neo-adjuvant (30%) and palliative therapy (8.5%).

The Pearson's Chi-Square test could not identify any significant differences between the cost categories (X^2=14.350; df=10; *p*=1.58). See Chi-Square test result in Annexure 7.



	6001-10000	10001-14000	14001-18000	18001-22000	22001-26000	26001-30000
Ajuvant	6	32	58	21	5	1
Neo-adjuvant	2	11	29	16	2	0
Palliative	1	6	7	0	3	0

Figure 9: The episode of care cost against treatment approach

5.6.3 Episode of care cost versus chemotherapy regimen

The distribution of episode of care costs were analysed against the chemotherapy regimens prescribed at GSH. It was found that 52,6%, 51% and 42,9% of patients, who were prescribed with the regimens FEC, EC and P respectively, had a total episode of care cost within the range R14 001 to R18 000 per patient. The episode of care cost for patients prescribed the regimen FEC-P and EC-P were in the ranges R10 001 to R14 000 and R18 001 to R22 000, respectively per patient.

The patients who had an episode of care cost within the lower ranges of cost were found to have not completed their treatment with chemotherapy. Only one person prescribed FEC had an episode of care cost in the highest range R26 001 to R30 000. This patient was in stage IV of breast cancer and was being managed with palliative chemotherapy. Overall, the most frequently prescribed regimens were FEC, EC and FEC-P. Table 27 illustrates the distribution of numbers of patients within the categories of episode of care costs utilising the listed regimens. The highlighted regions in Table 27 show the highest cost ranges for the episode of care for the particular chemotherapy regimen. The Pearson's Chi-Square test identified significant differences between the cost categories (X^2=52.34; df=20; p<0.000). See Chi-Square test results in Annexure 7.

Table 27: Episode of care cost versus chemotherapy regimen

		Episode of care cost (Rand)						**Total**
Regimen		6000-10000	10001 - 14000	14001 - 18000	18001 - 22000	22001 - 26000	26001 - 30000	
FEC	Count % within FEC % of total	2 2.1% 1%	19 19.6% 9.5%	51 52.6% 25.5%	21 21.6% 10.5%	3 3.1% 1.5%	1 1% 0.5%	**97** **100%** **48.5%**
EC	Count % within EC % of total	1 2% 0.5%	8 15.7% 4%	26 51% 13%	12 23.5% 6%	4 7.8% 2%	0 0% 0%	**51** **100%** **25.5%**
FEC-P	Count % within FEC-P % of total	6 14.3% 3%	21 50% 10.5%	14 33.3% 7%	0 0% 0%	1 2.4% 0.5%	0 0% 0%	**42** **100%** **21%**
EC-P	Count % within EC-P % of total	0 0% 0%	0 0% 0%	0 0% 0%	2 66.7% 1%	1 33.3% 0.5%	0 0% 0%	**3** **100%** **1.5%**
P	Count % within P % of total	0 0% 0%	1 14.3% 0.5%	3 42.9% 1.5%	2 28.6% 1%	1 14.3% 0.5%	0 0% 0%	**7** **100%** **3.5%**
Total	**Count** **% within A** **% of total**	**9** **4.5%** **4.5%**	**49** **24.5%** **24.5%**	**94** **47%** **47%**	**37** **18.5%** **18.5%**	**10** **5%** **5%**	**1** **0.5%** **0.5%**	**200** **100%** **100%**

C-Cyclophosphamide, E-Epirubicin, F- 5-fluorouracil, P-Paclitaxel

5.7 Cost of adverse events

The number of patients experiencing adverse events and the cost of adverse events were the highest for patients on palliative therapy. In the sample of 200 patients, 16 patients presented with adverse events to chemotherapy treatment which led to additional health resource utilisation. The number of these occurrences of adverse events is displayed in Table 28. Toxicity was scored according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.0). A toxicity grade was assigned to each symptom or adverse effect presented as listed in Table 28. The most commonly occurring adverse effect within this sample of this study was neutropenia while the cases of anaemia, erythema and severe pain were recorded once.

Severe pain, in this case abdominal pain, was documented by Andersen. (2013) as one of the common adverse events accompanied by chemotherapy usage. The cases of vomiting and diarrhoea were classified in two groups, i.e. grade 2 and 3 with 1 and 2 patients in each grade respectively. One patient presented with cardiac toxicity and the cost was not included in the study as it was not established whether the toxicity was due to chemotherapy or to a pre-existing heart condition.

Table 28: Occurrences and grade of adverse events

Adverse effect	Grade	Number of patients who had the adverse effect
Neutropenia	3	5
Thrombocytopenia/ anaemia	3	1
Cardiotoxicity	4	1, not included in costing model
Vomiting and diarrhoea	2 3	1 2
Cellulitis	2	2
Severe pain	3	1
Erythema	2	1
Unknown	Ungraded	4

The reason for admission to the hospital was recorded as an adverse effect in the patient's folder. The cost of treating a patient who presented with vomiting and diarrhoea was the highest (R43 904.29) and was followed by neutropenia (R36 465.82) as shown in Table 29. Some of the patients presented with a combination of adverse events (i.e. anaemia, vomiting and severe pain), however the main adverse effect was recorded as the reason for admission. For the sample of 200 patients the cost of managing adverse events was R210 128. This total cost included the cost of hospitalisation, IV antibiotics and antiemetics but did not include the cost of blood transfusion and blood products. For the treatment of adverse events the longest length of hospital stay was 15 days costing R42 672 for the hospital stay alone.

Table 29: Cost of each adverse effect and its component costs (per patient)

Category	Hospitalisation			Medicines cost, (R)	Laboratory tests cost, (R)	Scans and imaging cost, (R)	Emergency consult cost, (R)	Total cost per patient (R)
	Reason for hospitalisation	Length of stay, days	Cost of stay, (R)					
Patient 1	Severe abdominal pains, malaise	8	16002.00	848.79	1642.11	5048.00		23 540.90
Patient 2	Neutropenia	8	14224.00	328.76	1302.31		497.00	16 352.07
Patient 3	Unknown	3	5 334.00	49.79	589.7299		994.00	7 494.52
Patient 4	Neutropenia	11	33782.00	1042.18	1114.64	527.00		36 465.82
Patient 5	Vomiting, pleural effusion, shortness of breath	15	42672.00	178.29		1054.00		43 904.29
Patient 6	Unknown			86.72			497.00	583.72
Patient 7	Unknown	4		324.76			1491.00	1 815.76
Patient 8	Gastritis, vomiting	0.5	889.00	105.38		3051.00	497.00	4 542.38
Patient 9	Neutropenia	4	7 112.00	1533.77		527.00	497.00	9 669.77
Patient 10	Neutropenia	5	8 890.00	758.60	181.32			9 829.92
Patient 11	Vomiting, malaise, headache	15	26670.00	581.60	111.87	1054.00		28 417.47
Patient 12	Peripheral neuropathy	3	5 334.00	192.90	134.90		1491.00	7 152.80
Patient 13	Unknown			57.79			497.00	554.79
Patient 14	Anaemia	1	1 778.00	65.28	332.50		299.00	8 079.77
Patient 15	Neutropenia	3	5 334.00	204.20	108.76		497.00	6 143.96
Patient 16	Erythema, cellulitis, swelling, leg pain	3	5 334.00	246.40	1 642.11			5 580.40
	Total	**83.5**	**173355.00**	**6 605.23**	**5518.14**	**11261.00**	**7257.00**	**210 128.37**

Reason for hospitalisation was recorded for each of the 16 patients presenting with adverse events, the main reason for hospitalisation is underlined.

The costs of adverse events were categorised based on the patient's age and stage at diagnosis. Patients who were in stage I cancer and in the youngest age group 18–35 years did not have any record of adverse events. The rest of the cost distribution is explained in Table 30.

Table 30: Cost of adverse events according to age and stage of cancer at diagnosis

Stage at diagnosis	Cost of adverse events per stage	Average cost per patient	Age at diagnosis	Cost of adverse events per age group	Average cost per patient
I	R0 (n=0)	R0	**18 - 35**	R0 (n=0)	R0
II	R55 658.94 (n=5)	R11 131.79	**36 - 50**	R52 977.26 (n=6)	R8 829.54
III	R74 402.08 (n=5)	R14 880.42	**50 - 65**	R118 683.12 (n=8)	R14 835.39
IV	R80 067.35 (n=6)	R13 344.56	**>65**	R38 467.99 (n=2)	R19 234.00

Other less severe adverse events beside those recorded in Table 29 were reported in the patient medical files. While they were important clinically, their likelihood to influence the cost of treatment was negligible as they were managed with routine support medication. Examples of these side effects include mild nausea, mild vomiting, alopecia, oral thrush (candidiasis) and mild erythema.

5.8 Model for predicting the cost of treatment: Decision tree analysis

This model was developed as an alternative to validate the approach and method developed in this study for calculating the cost of treatment. The results of this model were based on actual treatment cost at GSH obtained in this study for an episode of care period (average 10-12 months). The probabilities of certain events occurring (patient completing treatment or not and stages of breast cancer) were calculated and summarised in Table 31. The costs obtained from the sample of 200 patients were used in the model development. The episode of care cost per patient included all cost components studied.

Table 31: Probability of patient being diagnosed with breast cancer according to status of treatment and stage of breast cancer

Event occurring	**Probability of event occurring**	
Patient completing treatment	0.87	
Stage I		0.08
Stage II		0.50
Stage III		0.33
Stage IV		0.09
Patient not completing treatment	0.13	
Stage I		0.04
Stage II		0.40
Stage III		0.30
Stage IV		0.26

The estimated cost of treating 200 patients with breast cancer was calculated using the probabilities of a patient being diagnosed with one of the four stages of breast cancer and the chance of a patient completing their chemotherapy treatment.

The cost per patient per event was derived from the actual costs obtained from Tables 19 and 22 for the cost of episode of care. An example is given below for a patient diagnosed with stage I breast cancer at GSH:

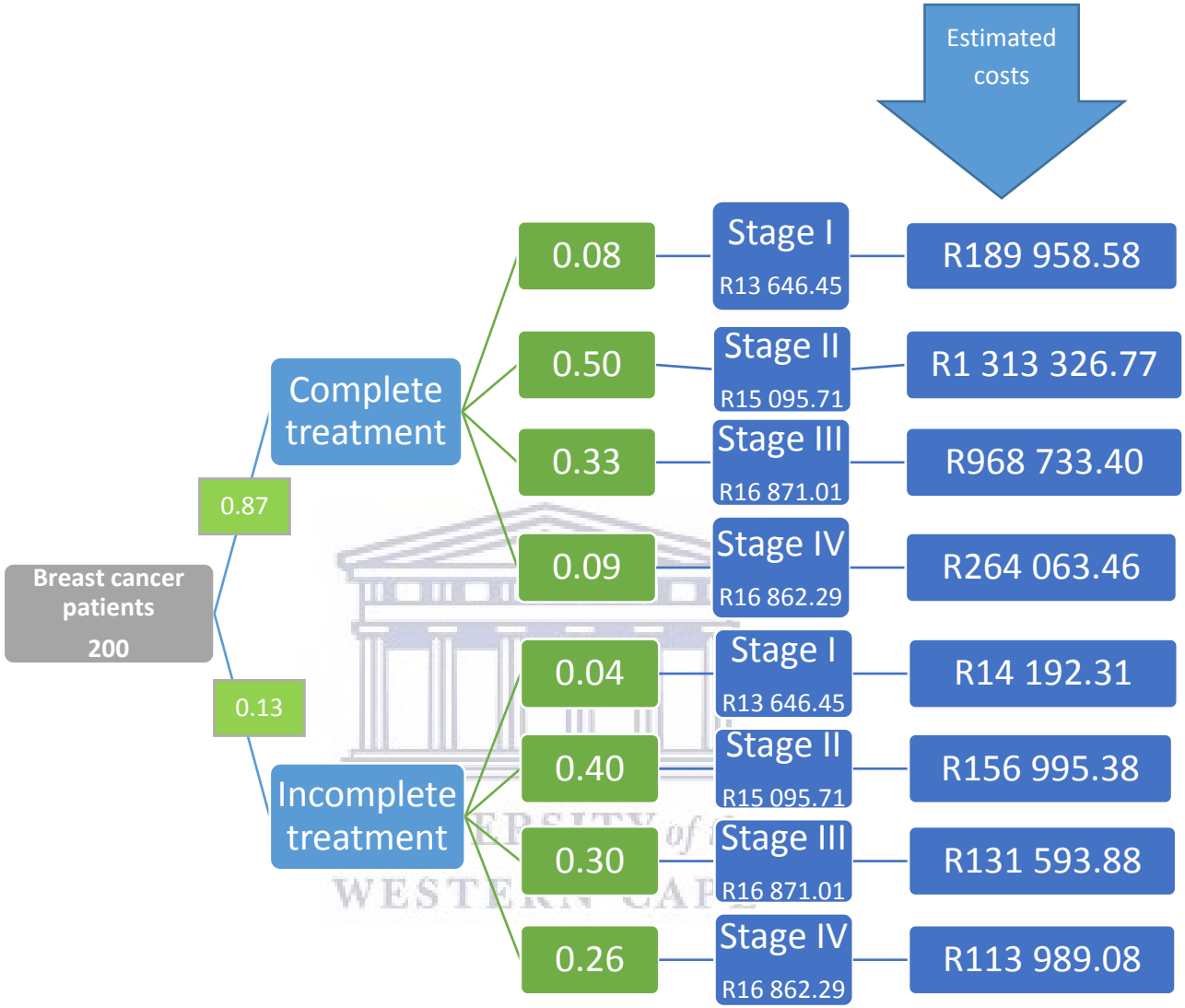
200 patients X 0.87 (probability of completing treatment) X 0.08 (probability of being stage I breast cancer X R13 646.45 (cost per patient per episode of care, Tables 19 and 22) = R189 958.58.

When the costs of the four stages of breast cancer were calculated for 200 patients, the sum represented the total cost for the population. The cost for treating breast cancer patients with chemotherapy when the patients were able to complete their full treatment during their episode of care was R2 566 022.21. Similarly, the cost of treatment of breast cancer patients with chemotherapy when the patients were unable to complete their treatment during their episode of care was R586 830.65. The total estimated cost was R3 152 852.86. It was found that the estimated cost was lower than the actual cost by 0.06% (R2 025.04). The result was expected as it estimated the cost of breast cancer using the same data set and averages obtained in this study. This indicated that the calculated probabilities in the model can be used to predict the total cost of treating a full episode of care for breast cancer patients for another data set at GSH provided that sample size, stage of breast cancer, treatment status and average episode of care cost (Table 19) are known.

Table 32: Estimated cost of treating breast cancer patients

Stage of cancer	Predicted total cost for complete treatment	Predicted total cost for incomplete treatment
Stage I	R189 958.58	R14 192.31
Stage II	R1 313 326.77	R156 995.38
Stage III	R968 733.40	R131 593.88
Stage IV	R264 063.46	R113 989.08
Total for all stages	R2 566 022.21	R586 830.65
Total for all patients (n=200)	R3 152 852.86	

Table 32 shows the estimated cost of treating a full episode of care for the patients diagnosed with the respective stages of breast cancer at GSH. The cost of treating a patient presenting with stage IV disease is the highest whilst stage I cancer is the least expensive to treat. The tree diagram (Figure 10) can be used in the calculation of these costs.



The figures in the green box reflect the probability of occurrence of breast cancer and the probability of completing the treatment or not for the various stages of breast cancer.

Figure 10: Decision tree analysis diagram with costs

5.9 Regression model analysis

A regression model was used to analyse dependent and independent variables of cost of breast cancer treatment. The multiple regression analysis was used to investigate the influence of some specific variables on the cost of treatment. Based on the results of this study, the dependent variable was the total cost of treatment, while the independent or predictor variables were clinical stage, age at diagnosis, status of treatment (complete/incomplete), protocol and treatment approach. For the purpose of the regression analysis only, 2 hypotheses were created,

H_o: There is no relationship between the independent and the dependent variables

H_a: There is a relationship between the independent and the dependent variables

The multiple regression equation was computed for the study as;

$$\text{TOTAL COST} = a + b_1(\text{CLINICAL STAGE}) + b_2(\text{AGE}) + b_3(\text{STATUS OF TREATMENT}) + b_4(\text{PROTOCOL}) + b_5(\text{TREATMENT APPROACH}) + e$$

where, TOTAL COST represents total cost of breast cancer treatment, a is the constant term and b_1 to b_5 represent the slopes of Y of the respective variables. The results of the analysis are presented in Table 33.

Table 33: Model summary for total cost of treatment of breast cancer

Model	R	R Square	Adjusted R Square	Std. Error of the estimate	Durbin-Watson	F-Statistics	Sig.
Total cost	0.341	0.117	0.094	1557.046	1.951	5.121	0.001

R- coefficient of determination, Durbin-Watson – tests for auto correlation in the sample, F- statistics – ratio of the mean regression sum of squares divided by the mean error sum of squares, Sig. – statistical significance

The probability of the F statistic (5.121) for the overall regression relationship is equal to 0.001, less than the level of significance of 0.05. Hence, the null hypothesis that there is no relationship between the cost of treatment and the predictor variables is therefore rejected. The alternative hypothesis that there is a statistically significant relationship between a set of independent or predictor variables and the dependent variable (cost of treatment) is therefore accepted. The coefficient of determination, R squared, which measures the level of variation in the dependent variable attributable to the independent variables is 0.117 (Table 33). The level of variation is therefore translated to 11.7%. This signifies a weak relationship between the dependent and independent variables and further implies that only 11.7% of the total variation in the cost of treatment is explained by the combined influence of some or all of the predictor variables. (Refer to section 4.6.1 for other reasons of cost variation).

The model summary confirms that there is a relationship between the total cost of treatment of breast cancer and the treatment variables. Hence, those that are statistically significant should be taken into account in the development of a method to determine the cost of breast cancer treatment. The variables were further tested individually to determine statistical significance towards the total cost of treatment of breast cancer. The results are explained in

Annexure 7.

The results of the multiple regression analysis shows there is a statistically significant relationship between cost of treatment of breast cancer and status of treatment (complete/incomplete) ($p<0.001$). This is because the probability of the T-statistic for its beta coefficients is less than the level of significance of 0.05 of the model. Therefore, it can be said that the status of treatment (complete/incomplete) significantly influences the cost of treatment.

Furthermore, statistically insignificant relationships were found between the dependent variable and the following individual independent variables; treatment approach, age at diagnosis, protocol and clinical stage. This is due to the fact that the T-statistics for their respective beta coefficients are greater than the level of significance of 0.05 of the model (i.e. sig. of independent variables > 0.05). Although it was expected that these variables would show statistical significance, the contrary result could have been due to the small sample size used in this study.

Additional results of the regression model including the scatter plots are attached in Annexure 7.

CHAPTER 6

DISCUSSION

According to our knowledge, there is no data currently available on the cost of an episode of care for breast cancer in the public sector in South Africa. This study was conducted to address this issue.

The aim of this study was to analyse retrospective data in order to develop a method to determine the direct medical cost of management of breast cancer with chemotherapy. In developing the method, the costs of chemotherapy per episode of care were determined from the funder perspective. All costs associated with chemotherapy were considered.

Previous studies conducted globally have looked at cancer costing models measuring direct medical costs (Davari *et al.,* 2013*;* Pompen *et al*., 2009; Maslove *et al.,* 2005), measuring direct and indirect medical costs (de Oliveira *et al.*, 2013) and conducting cost effectiveness analyses (Korpela *et al.,* 2011). Some of the above studies are similar to our study in measuring direct costs only.

6.1. Demographics and clinical characteristics

The study subject characteristics are reported in Table 5. The findings of this study showed that 11% of the patients were younger than 35 years of age and the majority (56%) of patients were aged between 46 and 60 years; the mean age at the time of diagnosis was 50. The findings concur with another study conducted in Asia, which estimated the mean age at diagnosis of breast cancer to be between 43 and 49 (Davari *et al*., 2013). A study by Hoang Lan *et al*. (2013), found the mean age of their study subjects to be 51 years and the most frequent age group was from 40 to 49 years and comprised 36.4% of patients. These show that breast cancer was prevalent in middle age women during the study period. This is the general trend of breast cancer in developing countries, which is contrary to the trend displayed in the developed countries where breast cancer patients are postmenopausal, i.e. 60 to 70 years old (Hoang Lan *et al*., 2013; Anyanwu, 2008). Of the patients in our study, approximately one-third presented with locally advanced and one-fifth with metastatic disease at the time of diagnosis, similar to what was found by Kaliks *et al*. (2013), whose study was also conducted in a low-middle income country.

It is reported that on average 10-20 women are diagnosed with breast cancer at GSH every week (Western Cape Government online. 2017). In our study, we found that, over a 2 year period 1 024 patients were registered in the Radiation Oncology department (ROD) following diagnosis of primary breast cancer. Therefore, according to the electronic database (MI), it is estimated that 512 patients were diagnosed with breast cancer per year at GSH. This is consistent with the report of 2017 on the Western Cape Government website which also estimates at least 520 new diagnoses per year. It was found in this study that the proportion of those who will go on to be treated with chemotherapy is 68%.

6.2. Developed method

The main focus of this study was to develop a method to determine the costs of breast cancer treatment and management of associated adverse events. The developed method measured resource use at patient level according to the data that were available from the hospital's data sources. The method measured costs of chemotherapy and resources linked to chemotherapy use, as was partially done by Boutayeb *et al*. (2010). In their study conducted in Morocco, Boutayeb *et al*. (2010), collected data for cost of treatment of breast cancer for early breast cancer. Non-chemotherapy resources, for example, scan and imaging procedures, had to be linked to an event involving chemotherapy and had to be in the same timeline as the patient's episode of care.

It was established that the methodology for costing breast cancer treatment differs according to the nature and the aim of the study. A study by Maslove *et al.* (2014), utilised a similar methodology, as in our study, of quantifying resource use data for treatment of breast cancer. The only difference was that their method included the cost of patients admitted to hospital for the purpose of chemotherapy administration. In our study, chemotherapy administration was conducted as an outpatient ambulatory procedure. The patients who were admitted for chemotherapy administration were boarding in a general ward for convenience when the chemotherapy administration would be conducted the following day. This category of cost was viewed as an indirect cost because the patients were individually screened for level of income and radius of their home from the hospital. It was therefore argued that cost of an admission under those circumstances could not be included together with direct medical cost of management of breast cancer.

The cost of hospitalisation in this circumstance was separated from hospitalisation due to management of adverse events which was classified under direct medical costs in this study.

It is important to note that the method developed could be applied to other costing projects of relevant hospitals. However, the results of this study are an analysis of costs incurred at GSH for the particular period of study. The results therefore, cannot be extrapolated to other breast cancer treatment centres. However, the methods could be modified for other treatment centres.

It is worth pointing out that the method of patient extraction from the electronic system revealed that the EPR was a better platform for breast cancer patient selection compared to MI. The system provided a summary of demographic and clinical information for the patients, i.e. approach of treatment, treatment plan and histology/ type of breast cancer. A database of this nature for breast cancer patients could aid future researchers in collecting relevant data without having to consult patient medical folders for this additional clinical information. Therefore, it is a recommendation of this study that either an update of this database be implemented by the hospital policy makers or the MI database could be merged with the EPR database. Merging the databases would provide comprehensive data on all breast cancer patients.

6.2.1. Time and motion study

This study showed that the pharmacist time spent during the process of compounding chemotherapy was not clearly accounted for by the hospital costing system. A component of cost called the 'compounding fee' was developed in our study and determined by time and motion studies. The compounding fee was added to the medicine cost and dispensing fee to provide a total cost of chemotherapy medicines. This component that is part of the pharmacists' scope of practice is noteworthy and therefore it was important that it was accounted for (Oglesby *et al*., 2009). It appears that the UPFS did not account for the compounding of chemotherapy separately as it is done in the private sector.

The National Patient Advocate Foundation, (2005) in their study introduced another methodology of a time and motion study motivated by the beta test which determined a potential miss of information if time and motion was based only on the top identified drugs (Brixner *et al*., 2005). The survey assessed all tasks conducted by the pharmacist in a specified period of time (i.e. in one shift). A list of duties a pharmacist was responsible for on a typical day of work was developed and if a task not listed was performed, it was noted separately. The methodology improved their quality of results. A broader analysis is crucial when resources are sufficient. However, in a time and motion study that focuses on breast cancer chemotherapy alone without concomitant drugs (other than support medicines), it would be an unnecessary time and resource consuming exercise to measure all tasks performed by the pharmacist related to all chemotherapy drugs and support medicines. Hence, our study focused on the task of compounding chemotherapy medicines for breast cancer only.

Even though no studies were found for comparison, the findings of this study will provide the funder of care (the government) with an insight of another (apart from the UPFS, scenario 1) methodology of calculating costs of components of treating breast cancer at GSH. The nurses' time taken to administer chemotherapy was reported as an average per patient on the cost template. The time and motion study provided the cost for this task which was independent from other nurses' duties. This provides a reliable assessment of the time spent by the nurse on chemotherapy tasks and the cost involved. According to the current costing approach based on the UPFS, patients are charged a set fee for the administration of chemotherapy.

The calculation of treatment cost is of particular importance in developing countries where the reality of economic constraints can often influence access to appropriate treatment. This study agrees with the notion stated by Alleyne-Mike, (2013) which supports a treatment option that is economically feasible without undue compromise to patient survival.

When the method for the time and motion study was compared with a method conducted by Haywood *et al*. (2012), one advantage of our study methodology was that the time recordings were conducted by the researcher. The method therefore did not rely on self-reported information to elicit the amount of time spent on nurses' tasks, thus reducing the risk of bias and systematic misreporting of time spent. The recording of actual times provided an opportunity to measure actual resource use as distinguished from calculating costs from the protocol based method as developed by Haywood *et al*. (2012). A possible limitation of our approach was that our method did not reflect the time differences in resource use within a particular task. The time difference, however, was considered to be small hence the times were recorded for the full task period.

One component that is often omitted when conducting time and motion studies for breast cancer treatment is the time specialists spend with the patient during chemotherapy administration (Haywood *et al*., 2012). Although small, the direct contact between specialist and patient seemed to exist where necessary at GSH. Unless the patient had severe adverse events or the nursing sister had a query about the patient, it was assumed that there was no reason for the doctor to see the patient during chemotherapy administration but rather only at a scheduled consultation after every cycle of chemotherapy. These assumptions were factored into the cost calculation by adding an average time (1.32 minutes) spent by the doctor with the patient. One of the strengths of our study lies in the determination of this cost. In the study of Haywood *et al*. (2012), they failed to quantify this cost as their model was not based on actual patient data or time and motion studies.

6.2.2 Scenario analysis

The scenarios 1 and 2 developed in this study were explained in full in section 4.12. Many studies have agreed that the cost of administration of intravenous chemotherapy and resource use has not been studied widely enough (Haywood *et al*., 2012; Gordon *et al*., 2011). Therefore, in our study the cost of treatment was measured using 2 different scenarios. There was no reference in literature that studied these scenarios before. The first scenario was developed with the standard method of costing utilising the UPFS. For the second scenario, where possible, the time and motion studies replaced some UPFS costs. When the 2 scenarios developed for the method of costing were compared, it was found that there was a negligible difference in costs obtained. The costs of chemotherapy administration and doctor consultation based on scenario 2 were found to be less than the costs based on scenario 1 by 9%.

The cost of compounding chemotherapy increased the total cost of chemotherapy by 5.3%. This increase in cost was expected as our assumption was that the compounding fee was not taken into account by the UPFS. Hence, our study considered this additional cost.

The costs of scenario 2, i.e. chemotherapy administration and doctor consultation were found to be less than those of scenario 1. Two important differences must be considered when comparing results of this study. First, the study did not use the same patient data in which the researchers applied costs. The patient data from the retrospective analysis was extracted and cost averages obtained from the time and motion studies on prospective resource utilisation data were applied to derive the cost of respective components. Second, it was discovered that the salary of the nurse used to calculate the cost in scenario 2 may not be the best method. The nurses on duty have different levels of qualification and years of experience and hence different cost associated with this. Notwithstanding the fact that there are other personnel involved, i.e. sister-in-charge over-seeing the practice in the clinic and student nurses whose roles could not be accounted for in the costing exercise. The impact of a time and motion study was crucial in measuring resource use and actual time spent as explained in section 6.2.1. It is worth noting that, although the figures obtained are invaluable for analysis, the model can be altered or modified to reflect the local clinical practices. For example, changing the type of medical staff involved in the administration of chemotherapy from nursing sister to sister-in-charge or from urban nursing sister to rural nursing sister (as they might have different salary scales) could be achieved in the same model developed in this study.

6.3 Cost of breast cancer treatment and adverse events

For most cost components measured, mean costs were higher than the median costs, which suggested that the majority of patients had a lower than average treatment cost, whereas a small group generated high costs (Pompen *et al.*, 2009). The minimum costs of treatment for some components were as low as R447.48 for laboratory tests and R527 for scans and imaging procedures. However, there were some patients who did not receive some services at all. These were excluded from the cost template.

6.3.1 Episode of care cost

The strength of this cost study lies in the determination of actual costs of treatment at patient level for an episode of care. Utilisation data in the routine setting allowed costing of chemotherapy in an accurate way without making assumptions of usage (Haywood *et al*., 2011). This was crucial in contrast to other studies that make assumptions of cost based purely on the protocols being followed (Pettersson *et al*., 2012).

The episode of care costs for the patients in this study could not be compared to other cost studies conducted internationally. Although the study conducted in Morocco also calculated the cost of breast cancer, the treatment protocols were different and the period when the study was conducted was different (Boutayeb *et al*., 2010). Another study conducted in Vietnam by Hoang Lan *et al*. (2013), measured the direct medical costs for a 5-year treatment course, thus limiting the chances for comparison of costs due to different timeframes. In most cases, the study characteristics were similar, i.e. retrospective patient-level data, analysis conducted from the health payers' perspective and measuring direct medical costs per episode of care.

However, the costs were derived from the health insurance industry or the costs were not direct costs for breast cancer treatment (Hoang Lan *et al*., 2013, Pagano *et al*., 2012).

In some cases, the costs of breast cancer were obtained for chemotherapy, surgery and/or radiotherapy (de Oliveira *et al*., 2013) instead of cost of chemotherapy alone. This further compromised the chances for comparison of costs. These studies, helped in shaping the methodology of our study and provided a basis for comparison of categorised costs, for example, cost based on age and stage of disease. However, the purpose of this study was to develop a method for GSH to determine the cost of breast cancer. It is recommended that due to the small sample sizes per subgroup in the analyses these costs should be used with caution for budgeting purposes or any other decision making purposes.

Although not many direct comparisons could be achieved, the total costs of this study were found to be generally less as compared to studies conducted in Canada (de Oliveira *et al*., 2013) and the USA (Boutayeb *et al*., 2010). The reason for this could be due to differences in population, cancer incidence, socio-economic status and health funding systems. However, the study conducted in Vietnam estimated the cost of breast cancer treatment over the first 9 months of treatment to be $632.85 (approximately R8 950) and the range was $11.70 - $3 955.40 (approximately R165 – R55 935) (Hoang Lan *et al*., 2013). In our study, the episode of care cost was R15 774.39 and the range was R3 480.81 to R38 627.40.

All patients evaluated in this analysis received first-line treatment with chemotherapy according to the GSH treatment protocols provided.

The episode of care period was confirmed to be complete when a patient successfully completed the treatment with chemotherapy and a 6 month follow up period was free of post-chemotherapy adverse events.

The reason for the choice of the prescribed chemotherapy was only known by the prescribing doctor. However, it could be related to the extent of disease, presence of co-morbid conditions and likelihood to cause adverse events.

The data were collected according to the period when each patient was attending the hospital. The cost of episode of care in this case is significant in measuring the cost per patient (Cipriano *et al*., 2011).

6.3.2 Cost drivers and cost of components

The major cost driver in this study was the category of scans and imaging with cost of chemotherapy and dispensing fee following closely thereafter. Procedure and facility per patient fees for scans were exceptionally high when compared to other component costs (Figure 7). The reason could be attributed to the use of high technology machines which required a specialist radiographer and experienced personnel to interpret the results. Some studies found that maintenance of these machines is a challenge in developing countries (Shah *et al*., 2015). Although this component is a high cost to the funders of care, it can be argued that the role of imaging testing in breast cancer diagnosis and measuring the effectiveness of treatment is equally crucial.

The chemotherapy medicines costs were the second highest among all the cost components. The huge variation in cost of chemotherapy within the same patient's episode of care receiving the same medicines and the same dosage was observed.

The variation in chemotherapy prices was mainly accounted for by the variation in the batch size compounded on the particular day.

Following a consultation with a member of the Pharmacy Department at GSH, it was discovered that the hospital electronic software was designed to calculate the cost of each medicine based on the number of items dispensed of that particular medicine in a day. Hence, the more of a specific medicine that was compounded on a particular day, the cheaper the medicine was priced. According to the Pharmacy Department at GSH, the JAC system calculates a price based on ingredients used in that batch, the price of the ingredient and the batch size that was made on the day.

For example, for an infusion containing 330mg paclitaxel for one patient on a particular day, the cost for the dose of 330mg paclitaxel was R989.88. However, if on another day a batch of 6 infusions were prepared for different patients, i.e. 1800mg of paclitaxel in total. The total cost was spread across all 6 patients resulting in a lower cost of R611.08 per patient. Unlike the private sector, linear pricing is not applied.

6.3.3 Cost of adverse events

A significant addition to the treatment costs was due to treatment of adverse events, especially neutropenic infections. Of these occurrences, adverse events requiring hospitalisation accounted for 60% increase in the treatment cost. A study by Lathia *et al*. (2010), reported that the high treatment cost of febrile neutropenia was mainly due to the cost of hospitalisation, which is consistent with the results of our study.

In our study, the calculated mean cost of R9 669 per hospital stay for an episode of febrile neutropenia was found to be very low when compared with £4 688 (approximately R86 900) of a Canadian study by Lathia *et al*. (2010).

Although the components added by Lathia *et al*. (2010), were not known, the cost differences could be accounted for due to differences in the level of therapy provided by the two hospitals, the socio-economic status and the purchasing power parity of the two countries. At GSH, the length of stay in hospital was found to be the main cost driver. The patients were admitted to the general ward where the cost was charged per 12 hour day.

The number of events and the subsequent cost of adverse events at GSH may be greater than that reported as some events may not have been recorded in the folders. It was also found that some patients died before the cause of the adverse events could be established. Often the words, “chemotherapy reaction?”, were annotated in the patient folders as the doctors were also not aware of the cause of adverse event presented by patient.

The study by Korpela *et al*. (2010), analysed cost of toxicity in the treatment of metastatic breast cancer and estimated a 20% increase in direct medical costs as measured over a period of 6 months treatment. When critically analysed a similar assumption on the increase of treatment costs could be made on our data, however taking into consideration the stage IV patients only. It is also highly likely that patients who are more prone to severe adverse events are late stage patients with metastatic disease. In our study 6 patients in stage IV had adverse events while the majority (10) were in other stages of breast cancer.

6.3.4 Categorisation of costs

The findings of this study revealed that the treatment costs were not the same for all breast cancer patients. The costs were dependent on a variety of factors i.e. age, stage at diagnosis, adverse events and complete or incomplete treatment. Older patients were assumed to be costly to treat since there was a greater probability to develop infection or presence of other diseases (Astim *et al*., 2011). It was found in this study that the average age at diagnosis was 50 years and almost 50% of patients were older than 50 years. This finding coincides with the fact that the risk of developing breast cancer increases with age and breast cancer patients are often diagnosed late in life (Davari *et al*., 2013). The life expectancy, however, lowers in the greater than 65 years old group. The prognosis is often poor in older patients due to various reasons i.e. presence of comorbidities, late diagnosis and risk of developing liver or kidney damage with some chemotherapy medicines. The 46 to 65 years age group accrued the highest cost of treatment due to the high number of patients in this age group (Table 23). Although the age at diagnosis does not seem to have a significant impact on the direct medical cost of treatment ($p>0.05$), there is a chance that the indirect cost of treatment could be affected (Davari *et al*., 2013). However, further study is needed.

It was found in our study that the stage of cancer at diagnosis was probably the most crucial parameter in defining the cost of treatment. Several studies in the literature (Hoang Lan *et al*., 2013: Rojnik *et al.*, 2008; Wong *et al.*, 2007; Yilmaz *et al.*, 2007) supported the fact that the progress of disease was the main factor influencing the cost of treatment because the medical intervention was decided according to extent of spread and stage of disease.

Patients with stage I disease had lower costs compared with patients presenting with more advanced disease (Gordon *et al.,* 2011).

The cost of late stage was increased by the likely occurrence of adverse events, treatment complications and palliative care (Hoang Lan *et al*., 2013). In this study, 1 patient in stage IV had an episode of care cost of R20 353.07 versus the average cost in that stage group of R16 862.29. The patient received 14 cycles of paclitaxel as palliative chemotherapy and supportive pain medication.

In Iran, Davari and colleagues, (2013) reported medication cost to be the main cost component for the patients treated in stage III and IV of breast cancer. However, if the cost of treatment is measured over a long-term period, i.e. 5 years, it could be argued that the cost of treatment is higher in early stages as the chances of survival are higher (Hoang Lan *et al*., 2013). However, the opposite could be true. If diagnosed early there is a greater chance of remission and treatment free life in early stages of breast cancer. In our study, the cost of treatment was determined for an episode of care period rather than per year or per 5 years. The cost of treatment was therefore expected to be higher in late stage than in early stage breast cancer. At GSH the costs per patient of stage III for breast cancer were found to be more than the cost of stage I by 19%. The difference in treatment cost among the stages was statistically significant (*p*-values <0.05).

The stage of breast cancer at diagnosis served as a defining factor for relative mortality rates of the patients and a determinant for breast cancer treatment options. The survival rates can be high if the diagnosis is made at earlier stages of breast cancer.

However, diagnosis at GSH was often made late as indicated by at least 44% of patients diagnosed with late stage cancer. The authors, Astim *et al*. (2011), recommend the allocation of funds for regular mammography screening for all women over the age of 40.

The results of their study proved that resource use and costs of treatment are minimised when breast cancer is diagnosed at an early stage and age (Astim *et al.,* 2011).

When the patients who were prescribed paclitaxel alone were compared with those who were prescribed FEC therapy, the former accrued higher medicine cost. The difference was mainly due to the cost of the individual medicines, paclitaxel being more expensive than the individual medicines in the FEC protocol. As seen also in a study conducted in Australia, no single regimen of breast cancer treatment was consistently more expensive than others (Haywood *et al.*, 2012). The FEC protocol was the most frequently prescribed regimen at GSH whilst paclitaxel or related regimens were reserved for recurrent disease and extreme cases of hypersensitivity to any of the FEC ingredients.

6.4 Predictive model developed

Even though no studies were found for comparison, this method allows the funder of care to estimate cost of treatment based on actual costs obtained from this study.

The rationale for a decision tree analysis was for the development of a method to predict the costs of treatment using the formula developed. It was established that the method could be used to calculate the estimated total cost of treatment of breast cancer patients at GSH. Given that, the factors, i.e. clinical stage of breast cancer, treatment status (whether treatment will be completed or not completed) and sample size are known.

The decision tree used for determining the total cost of treatment utilise probabilities (Table 31) and the average costs of treatment obtained in this study (Table 19). The probabilities can be used to determine completed or incomplete protocols for the costing of chemotherapy. One advantage of this model is that some local factors can be incorporated into the model. Information about local resource use and unit costs can be incorporated and the model can be altered to reflect local clinical practice when calculating the costs for other hospitals and treatment centres.

The results of our multiple regression analysis singled out 1 (status of treatment) out of 5 independent variables to be statistically significant to the cost of treatment. The multiple regression analysis conducted by Imamura *et al*. (2017), identified 3 factors (age, cost of chemotherapy and cost of support medicines) that significantly contributed to an increase in the cost of treatment per cycle. An adjusted R squared value of 0.680 was obtained for their study which was conducted over a 5 year period, as compared to 0.117 obtained in our study. As part of their methodology, Chang and co-workers (2004), excluded patients with extreme outlier of the direct costs of treatment (> $250,000 or $0 per month) from the multivariate analysis. When compared with our analysis, where the outliers to the calculated costs of treatment were not excluded, it can be argued that the results of our regression analysis could have been improved.

6.5 Limitations of the study

The study had the following limitations:

i. The sample size of 200 patients was not large enough to conduct proper statistical analyses. The sample was used in the development of costing methods.

ii. Several patient folders were missing from the hospital medical records. The patients' profiles that were incomplete were due to missing folders and these patients were replaced by other patients selected by random sampling.

iii. The cost of the same chemotherapy medicines for the same patient who was receiving the same dosage per cycle varied across the data set. The difference in costs was due to the hospital batch system that was calculated by the JAC system.

iv. During time and motion studies more than one nurse was in contact with the patient being observed. Since the nurses were all under the supervision of the sister-in-charge, it was assumed that the nurse with the highest rank had the ultimate responsibility for the patient and hence the cost was determined accordingly.

v. Some patients collected their breast cancer support medicines or had laboratory tests conducted from other private hospitals/ pharmacies whilst receiving chemotherapy treatment at GSH. These events were not included in the method developed and this probably influenced the average cost of treatment per patient.

vi. The cost of treatment as found by this study methodology might be lower than the estimated cost for the hospital. The trends in cost could have been different had we included surgery related costs, radiotherapy and same day procedures such as lumpectomies.

CHAPTER 7

CONCLUSIONS AND RECOMMENDATIONS

The study provided the costs of breast cancer and the cost of its associated adverse events. The costs obtained in this study could assist in the budget allocation and the financial decision making process of funders of care such as the government.

The main value of the present study is its detailed method development and assessment of treatment costs incurred during the episode of care period for breast cancer patients treated at GSH.

7.1 Conclusions

i. The method of costing breast cancer treatment at GSH was successfully developed. The total cost of treatment of 200 breast cancer patients managed with chemotherapy was R3 154 877.90. The average cost per patient for an episode of care was R15 774.39. The average cost for patients who completed treatment was 1.3 times more than the average cost for patients who could not complete treatment.

ii. The cost of treating breast cancer for the episode of care based on the variables and scenarios taken into consideration ranged from R12 664.76 to R16 259.72 per patient.

iii. The total cost was made up of costs of various components. The cost components were chemotherapy medicines, chemotherapy administration, support medicines, doctor consultation, laboratory tests, and scans and imaging procedures.

iv. The main cost drivers on a per patient basis were scans and imaging and chemotherapy medication costs.

v. The method of costing was developed with 2 scenarios, i.e. scenario 1 (costs derived from UPFS) and scenario 2 (costs derived from UPFS and time and motion studies) to determine the episode of care cost.

vi. Out of the 200 patients in this study, 16 patients had a record of adverse events to chemotherapy treatment. The total cost of managing adverse events for these 16 patients was R210 128. The adverse effect with the highest cost of treatment was vomiting (R43 904.29). The cost components used in the evaluation of adverse events cost were hospitalisation, laboratory tests, support medicines, emergency doctor consultation, and scans and imaging procedures.

vii. The cost of treatment of breast cancer was calculated according to the GSH chemotherapy protocol. The average cost per cycle per patient of each regimen on the protocol was R615.77, R587.05, R790.14, R718.93 and R874.76 for the FEC, EC, FEC-P, EC-P and P regimens, respectively.

viii. The cost of breast cancer treatment was categorised according to stage, age, treatment approach and whether treatment was either primary of salvage. The total cost of patients of stage I, II, III and IV breast cancer were R191 050.34, R1 479 379.41, R1 096 618.43 and R387 832.70, respectively. The average age at diagnosis was 50 years old, while the age group with the most number of patients was the 46-65 years category.

ix. Time and motion studies were conducted for the following categories, i.e. pharmacist compounding fee, administration of chemotherapy and doctor consultation. It took on average 9.76, 6.74 and 4.97 minutes of the pharmacist time to compound the FEC, EC and P chemotherapy regimens.

The total cost of medicines was increased by 5.3% when the compounding fee was factored into the total cost for chemotherapy. It took on average 16.87 minutes of the nurses' time to administer chemotherapy to 1 breast cancer patient at GSH. The costs of administration of chemotherapy and doctor consultation obtained from the time and motion studies were less than the costs recorded on the UPFS.

x. The predictive model developed in this study was the decision tree model. This model was specifically designed for breast cancer patients at GSH. The costs obtained from this models apply to GSH only, however, the model could be applied to other public hospitals which have an electronic database and accessible patient folders.

7.2 Recommendations

i. Chemotherapy compounding fee: the hospital billing system may incorporate the compounding fee of chemotherapy medicines on all the patients receiving chemotherapy via infusion. The cost of pharmacists performing this task is already being incurred by the hospital but it is not accounted for. It was found in this study following time and motion studies that the cost of chemotherapy medicines increased by 5.3% when the cost of compounding was added.

ii. The episode of care cost was calculated per patient and based on whether the patient completed or could not complete treatment. These episode of care costs can be used for budgeting when funding breast cancer treatment at GSH.

iii. EPR development: the Electronic patient records are being under utilised at GSH. The capacity and capabilities of the MI database could be improved by merging the electronic database with the EPR database. In order to fully appreciate its relevance, the database needs to be regularly updated the same way the MI is updated. The EPR however, is specific for breast cancer patients only. Furthermore, the database could be enhanced to include other cancers as well.

iv. Chemotherapy costs per patient: it was found in this study that the chemotherapy costs vary substantially. The variations were noticed for example, for the same patient, receiving the same dose of chemotherapy and within the same episode of care. The automatic calculation of these costs on the JAC system need to be reviewed to improve the pricing of these medicines.

v. Models developed: the method and models developed in this study can be used by GSH in estimating episode of care costs for breast cancer patients being treated with chemotherapy. The same methods can be applied at other breast cancer treatment centres to estimate the episode of care costs.

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Annexure 1: GSH Data collection form

SAMPLE: GSH Breast cancer data collection form Date……..

Patient's surname……. Folder number…….

Patient's name…… Age……

Date of birth ……..…… Gender M/F……..

Weight (kg) …….. Height (cm)……..

BSA…… BMI ……..

INCLUSION CRITERIA

18 years and older: □ **YES** □ **NO**

Treatment with chemotherapy**:** □ **YES** □ **NO**

Cancer diagnosis: □ Breast

HISTOPATHOLOGIC TYPE:

Cancer type	**Detail**
Breast	IDC: □ DCIS: □ LCIS: □
	Paget's disease: □ Other: □
	Detail:

Date of first consultation (Primary)…… Date of first consultation (relapse)……

Date of first diagnosis (Primary) …… Date of first diagnosis (relapse) ……

Stage of disease: T score…… N score…….. M score…… Clinical stage: 1 2 3 4 X

Grade: □ 1 □2 □ 3 □ X

PS/ ECOG score: □ 0 □ 1 □ 2 □ 3 □ 4

Lymphovascular invasion: □ **YES** □ **NO** □ **X**

Nuclear grade: □ 1 □ 2 □ 3 □ X

Metastasis: □ Yes □ No - If yes: □ Lung □ Liver □ Brain □ Bone other _____

If YES: site of initial occurrence_____

Receptor status: □ **ER+** □ **ER-** □ **PR+** □ **PR-** □ **HER2+** □ **HER2-**

TREATMENT:

□ Surgery □ Radiotherapy □ Chemotherapy □ Hormone □ Other _____

Sequence Key:

1. Surgery
2. Chemotherapy
3. RT
4. Hormone
5. Other

Treatment sequence: _____

□ Adjuvant therapy □ Neo-adjuvant therapy □ Palliative

Date of first treatment for chemotherapy (Primary): _____

Date of first treatment for chemotherapy (Relapse): First _____Second _____

Date of first treatment for radiotherapy (Primary): _____

Date of first treatment for radiotherapy (Relapse): _____

Chemotherapy medicine	Prescribed Dose /m^2	Date of administration	Quantity Administered per cycle	Cycle number	Number of cycles	Cycle length	Route PO/ IV

Other supporting medicines	Route PO/ IV	Dose	Frequency	Duration	Date

Reasons for early termination of chemotherapy treatment

□ Disease progression □ AE □ Patient refusal □ Death □ Other _____

ADVERSE EVENTS

_____
_____
_____
_____

Treatment of AE:

_____
_____
_____
_____

Rechallenge done □YES □ NO Event reappeared □ YES □ NO

ADVERSE EVENTS OUTCOME	
	Death
	Life-threatening
	Disability
	Hospitalisation
	Congenital anomaly
	Other:

LABORATORY TESTS FOR DIAGNOSIS/ STAGING

TEST	DATE	COMMENT

OTHER FOLLOW-UP TESTS FOR MONITORING TREATMENT

TEST	DATE	COMMENT

COMORBIDITIES:

_____
_____

Outpatient visits	Date of visit	Reason of visit	Duration
1			
2			
3			
4			
5			

Hospitalisation	Date of admission	Date of discharge	Duration	Reason for hospitalisation
1				
2				
3				
4				
5				

Annexure 2:

TIME AND MOTION STUDY: pharmacist compounding time for breast cancer chemotherapy

SAMPLE: DATA COLLECTION FORM Date…….

Pharmacist grade: ……. **Status**: Full time/ Part time

KEY: GSH CHEMOTHERAPY COMPOUNDING PROCESS

Step 1 – Pharmacist interprets the prescription, checks its validity, enters into JAC system, print labels

Step 2 – Takes folder for oral medicines, selection and assembling of chemo products & consumables from shelf into the aseptic unit, cleans work area

Step 3 – Actual compounding/ mixing of IV chemotherapy, labeling, final check and sign off

Regimen 1: FEC (5-FU, Epirubicin, Cyclophosphamide)

	Stage 1 (min)	Stage 2 (min)	Stage 3 (min)			Total time (min)	Comments
			F	E	C		
Patient 1							
Patient 2							
Patient 3							
Patient 4							
Patient 5							

Regimen 2: EC (Epirubicin, Cyclophosphamide)

	Stage 1 (min)	Stage 2 (min)	Stage 3 (min)		Total time (min)	Comments
			E	C		
Patient 1						
Patient 2						
Patient 3						
Patient 4						
Patient 5						

Regimen 3: Paclitaxel

	Stage 1 (min)	Stage 2 (min)	Stage 3 (min)	Total time (min)	Comments
Patient 1					
Patient 2					
Patient 3					
Patient 4					
Patient 5					

Annexure 3:

TIME AND MOTION STUDY: Doctor-patient time for breast cancer consultation

SAMPLE: DATA COLLECTION FORM Date:

Doctor's grade: ……. **Status**: Full time/ Part time

Patient RT number	Stage	Time patient enters Dr's office, (min)	Time patient leaves Dr's office, (min)	Time spent in Dr's office, (min)

Annexure 4:

TIME MOTION STUDY: Nurses' time in administration of chemotherapy

SAMPLE: DATA COLLECTION FORM Date:

Nurse's grade: ……. **Status**: Full time/ Part time

	Regimen type	Time for patient education, (min)	Time for actual administration, (min)	Comments

Annexure 5: List of fields for data collection

FIELDS	EPR	MEDICAL INFORMATICS	FOLDERS
Patient name & surname	x	x	x
Hospital number	x	x	x
Folder number			x
BSA			x
Weight			x
Date of birth	x	x	x
Date of death	x	x	x
Gender	x	x	x
Diagnosis	x	x	x
Date of diagnosis			x
Stage at diagnosis	x	x	x
Medicine record: type of chemotherapy		x	x
Dose			x
Number of cycles			x
Cycle length			x
Route of administration		x	x
Date of administration/ issue		x	x
Cost of chemotherapy			
Name of other medicines administered		x	x
Dose		x	x
Frequency		x	x
Date of administration/ issue		x	x
Outpatient visit: Date of consultation		x	x
Department		x	x
Reason for consultation			x
Inpatient admission: date of admission		x	x
Date of discharge			x
Duration of admission			x
Reason for hospitalisation			x
Ward		x	x
Date of lab test		x	x
Lab tests: name of test		x	x
Cost of test		x	
Scans: name of procedure			x
Date			x
Cost of procedure			
Adverse events reported			x
Treatment of adverse events			x

Annexure 6: Ethics approval certificates

Western Cape Government
Health

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E-mail: praneet.valodia@cancernet.co.za

Dear Professor Valodia

RESEARCH PROJECT: Development of a Model to Predict the Cost of Management of Cancer with Chemotherapy at Groote Schuur Hospital (Masters Candidate N. Guzha)

Your recent letter to the hospital refers.

You are hereby granted permission to proceed with your research.

Please note the following:

a) Your research may not interfere with normal patient care.
b) Hospital staff may not be asked to assist with the research.
c) No hospital consumables and stationary may be used.
d) **No patient folders may be removed from the premises or be inaccessible.**
e) Please introduce yourself to the person in charge of an area before commencing.
f) Please provide the research assistant/field worker with a copy of this letter as verification of approval.
g) Confidentiality must be maintained at all times.

I would like to wish you every success with the project.

Yours sincerely

signed by

DR AGATA KRAJEWSKI
***(Acting)* CHIEF OPERATIONAL OFFICER**
Date: 15th January 2015

C.C. Mr. L. Naidoo, Dr R. Kirsten, A/Professor J. Parkes

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UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

Room E52-24 Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6338 • **Facsimile** [021] 406 6411
Email: shuretta.thomas@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

03 December 2014

HREC REF: 824/2014

Prof P Valodia
School of Pharmacy
University of Western Cape
Private Bag X17
Bellville
7535

Dear Prof Valodia

PROJECT TITLE: DEVELOPMENT OF A MODEL TO PREDICT THE COST OF MANAGEMENT OF CANCER WITH CHEMOTHERAPY AT GROOTE SCHUUR HOSPITAL (Masters Candidate - N Guzha)

Thank you for your letter to the Faculty of Health Sciences Human Research Ethics Committee dated 25 November 2014.

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

Approval is granted for one year until the 30th December 2015.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period:
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

Please quote the HREC REF in all your correspondence.

We acknowledge that the student, Nyasha Guzha will also be involved in this study.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE
Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938

University of the Western Cape Ethics Approval

Prof P Valodia (School of Pharmacy)

Study project: Development of a model to predict the cost of management of cancer with chemotherapy at Groote Schuur Hospital

Registration no: 14/9/48

Ethics: *Approved*

- Permission may be needed from GSH Research Ethics Committee

Annexure 7: Statistical analyses

Statistics tests conducted on the TOTAL cost of breast cancer treatment

Test	F (Observed value)	F (Critical value)	DF1	DF2	*p*-value	alpha
Wilk's Lambda	6.112	1.392	552	64	< 0.0001	0.05
Pillai's Trace	5.155	1.375	552	69	< 0.0001	0.05
Hotelling-Lawley trace	7.051	1.457	552	50	< 0.0001	0.05
Roy's greatest	14.440	1.794	184	23	< 0.0001	0.05
Chi-square asymptotic approximation	The test could not be computed as at least one of the determinants of the within-class covariance matrices is null					
Fisher's Ftest						
Kullback's test						

DF- degrees of freedom

Tests interpretation: P value less than alpha value means test is statically significant

Chi-Square Tests for costs based on clinical stage

	Value	Degree of freedom, df	Asymp. Sig. (2-sided) p-value
Pearson Chi-Square	184.675	6	.000
Likelihood Ratio	141.440	6	.000
N of Valid Cases	200		

Chi-Square Tests for treatment approach versus stage of breast cancer

	Value	Degree of freedom, df	Asymp. Sig. (2-sided) p-value
Pearson Chi-Square	14.350[a]	10	.158
Likelihood Ratio	15.476	10	.116
Linear-by-Linear Association	.256	1	.613
N of Valid Cases	200		

Chi-Square Tests for episode of care costs versus treatment approach			
	Value	Degree of freedom, df	Asymp. Sig. (2-sided) p-value
Pearson Chi-Square	52.396[a]	20	.000
Likelihood Ratio	53.631	20	.000
Linear-by-Linear Association	2.680	1	.102
N of Valid Cases	200		

Regression analysis results

Model Summary[b]					
Model	R	R Square	Adjusted R Square	Std. Error of the Estimate	Durbin-Watson
1	.341[a]	.117	.094	1557.0462198	1.951

[a]Predictors: (Constant), Treatment approach, age at diagnosis, complete or incomplete, protocol, clinical stage
[b]Dependent Variable: Total cost Scenario 1

TOTAL COST[a]						
Model		Sum of Squares	df	Mean Square	F	Sig.
1	Regression	62072861.388	5	12414572.278	5.121	.000[b]
	Residual	470332228.555	194	2424392.931		
	Total	532405089.943	199			

[a]Dependent Variable: Total cost Scenario 1
[b]Predictors: (Constant), Modality, Age at diagnosis, Com/ incomplete , Protocol, Clinical stage

Summary of regression coefficients for treatment of breast cancer

Model	Unstandardised Coefficients		Standardised Coefficients	T	Sig.	95.0% Confidence Interval for B		Correlations
	B	Std. Error	Beta			Lower Bound	Upper Bound	Zero-order
(Constant)	2247.719	748.495		3.003	.003	771.488	3723.951	
Protocol	68.547	112.444	.043	.610	.543	-153.223	290.317	.031
Com/ incomplete	1562.857	326.786	.327	4.783	.000	918.347	2207.367	.314
Age at diagnosis	-6.936	9.550	-.049	-.726	.469	-25.771	11.899	-.062
Clinical stage	306.642	189.234	.148	1.620	.107	-66.577	679.862	.063
Treatment approach	-88.542	235.442	-.035	-.376	.707	-552.896	375.812	.000

Regression coefficients[a]					
Model		Correlations		Collinearity Statistics	
		Partial	Part	Tolerance	VIF
1	(Constant)				
	Protocol	.044	.041	.913	1.096
	Com/ incomplete	.325	.323	.972	1.029
	Age at diagnosis	-.052	-.049	.985	1.015
	Clinical stage	.116	.109	.546	1.831
	Modality	-.027	-.025	.522	1.917

[a.] Dependent Variable: Total cost Scenario 1