Pediatric Burkitt's Lymphoma in Ghana

A Decision-Analytic Model and Preliminary Cost-Effectiveness Analysis

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Preface and Acknowledgements

The following work is a master's thesis, which marks the end of my studies in Health Economics, Policy and Management at the University of Oslo. The thesis, authored solely by me, is a contribution of the Evidence to Decisions global health collaboration at the Norwegian Institute of Public Health. It is written within the collaboration project between NIPH's Global Health department and the Ministry of Health of the Republic of Ghana. I have been employed as an advisor at NIPH for a portion of the duration of this master's thesis.

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Abstract

Title: Pediatric Burkitt's Lymphoma in Ghana: A Decision-Analytic Model and Preliminary Cost-Effectiveness Analysis

Methods: In the study performed in this thesis, academic literature for the clinical progression of pediatric Burkitt's Lymphoma was used to pilot a novel decision tree model to simulate the clinical progression and outcomes of the disease. A preliminary cost-effectiveness analysis was performed using this decision-analytic model. The parameters for the preliminary analysis were populated using data from Ghanaian sources when applicable, and sources from similar settings when necessary. Deterministic and probabilistic sensitivity analyses were performed in order to account for structural and parameter uncertainty, and to identify the parameters with the largest impact on the cost-effectiveness of pediatric Burkitt's Lymphoma treatment in Ghana.

Results: The decision-analytic model was able to produce outcomes similar to observed pediatric Burkitt's Lymphoma outcomes in Ghana. Deterministic sensitivity analysis indicated annual fixed costs, treatment abandonment and advanced-stage treatment efficacy to be among the most influential parameters. The preliminary cost-effective analysis produced an Incremental Cost-Effectiveness Ratio of $301 per DALY averted. In the probabilistic sensitivity analysis, 99.85% of iterations were under the threshold for being considered very cost effective, with the cost per DALY averted being less the $2202 GDP per capita of Ghana. Fixed costs of treatment and treatment abandonment were among the parameters with the highest impact on the cost-effectiveness of pediatric Burkitt's Lymphoma treatment in Ghana

Conclusion: Through this study, a novel decision tree model for the simulation of pediatric Burkitt's Lymphoma outcomes in Ghana was created. Through sensitivity analysis, this model was able to identify the parameters that had the largest impact on the cost-effectiveness of pediatric Burkitt's Lymphoma treatment in Ghana. The preliminary cost-effectiveness analysis based on this model indicated NHIS-funded treatment to be likely to be very cost effective compared to the current practice in Ghana.

List of Abbreviations

Abbreviations

HIC	High-Income Countries
LMIC	Low- and Middle-Income Countries
BL	Burkitt's Lymphoma
SSA	Sub-Saharan Africa
NHIS	National Health Insurance Scheme
HTA	Health Technology Assessment
EFS	Event-Free Survival
KBTH	Korle-Bu Teaching Hospital
KATH	Komfo Anokye Teaching Hospital
IT	Intrathecal
FNA	Fine Needle Aspiration
NEML	National Essential Medicines List
WHO-CHOICE	World Health Organization's Choosing Interventions That Are Cost-Effective
DALY	Disability-Adjusted Life Year
QALY	Quality-Adjusted Life Year
HYE	Healthy Years Equivalent
HRQoL	Health-Related Quality of Life
CEA	Cost-Effectiveness Analysis
CBA	Cost-Benefit Analysis
CUA	Cost-Utility Analysis
WHO	World Health Organization

GBD	Global Burden of Disease
ICER	Incremental Cost-Effectiveness Ratio
YLL	Years of Life Lost
YLD	Years Lived with Disease
PSA	Probabilistic Sensitivity Analysis
CEAC	Cost-Effectiveness Acceptability Curve
WTP	Willingness to Pay

Contents

Chapter 1

Introduction

Burkitt's Lymphoma (BL) is a Non-Hodgkin's lymphoma that primarily affects children. It is a very aggressive form of cancer, holding the title of the fastest growing tumor in humans (Molyneux et al., 2012). The disease is treatable in pediatric contexts using chemotherapy, seeing cure-rates of up to 90% in High-Income Countries (HIC). However, the outcomes seen in Low- and Middle-Income Countries (LMIC) are typically worse, with overall survival rates of 40% to 60% (Denburg et al., 2019). The reasons behind this disparity are complex. Two factors likely at play are the high abandonment rates seen in LMIC, as well as a lack of resources necessary to achieve the outcomes seen in HIC (Gopal & Gross, 2018).

The consequences of this disparity in outcomes are felt most severely in Sub-Saharan Africa (SSA), where the combination of the incidence rates of the disease and the outcome disparity leads to pediatric BL carrying a particularly heavy burden in these countries. Among these countries is Ghana, where one study estimated the incidence rate for pediatric BL to be between 0.59 and 1.1 per 100,000 children under 15 years of age (Hämmerl et al., 2019). Endemic BL, the form of BL seen in SSA, occurs in children, with the incidence peaking at around 6 years old (Molyneux et al., 2012). Pediatric cancers are not currently covered by the National Health Insurance scheme in Ghana, so pediatric BL treatment costs must be borne by the children's families. A study by Offor et al. (2018), where they retrospectively analysed patient data for the Korle Bu Teaching Hospital from 2007 to 2012, reported a 20% overall survival rate for the patients treated when excluding those lost to follow up. This rate may be lower in reality. This is because 67% of all patients were lost to follow up, and 75% of those who were lost to follow up abandoned the treatment due to inability to pay (Offor et al., 2018).

It is within this background and context that pediatric BL treatment was identified by the Ghanaian Ministry of Health as a potential target for reimbursement within their National Health Insurance Scheme (NHIS). In order to inform this decision, a Health Technology Assessment (HTA) of treatments for pediatric BL in a Sub-Saharan African context is being conducted by the Ministry of Health in Ghana and the Norwegian Institute for Public Health. The novel decision-analytic model presented in this thesis will be used in this HTA. Separately from this HTA work, a preliminary cost-effectiveness analysis of the treatment of pediatric BL in Ghana will be performed using publicly

available parameters.

There presently exist very few research articles that examine the cost-effectiveness of BL treatment in LMIC contexts, and there are no articles that examine the cost-effectiveness of BL treatment in a Ghanaian context specifically at the time of writing.

According to the ad-hoc literature searches performed for this thesis, there exist two cost-effectiveness studies that can be considered related research in the context of this thesis. Denburg et al. (2019) contains a cost-effectiveness analyses of BL within a country in Sub-Saharan Africa, and Renner et al. (2018) contains a cost-effectiveness analysis of the treatment of all pediatric cancers at one hospital in Ghana. Of the aforementioned cost-effectiveness analyses, both are based on clinical data and do not feature a decision-analytic model.

1.1 Objectives

There are two interrelated objectives to the research project described in this thesis. These objectives are as follows:

1. To pilot a decision-analytic model to simulate the clinical progression of pediatric Burkitt's Lymphoma in Ghana to be used to fulfil the research aim of this thesis and to be delivered to the Ghanaian Ministry of Health for future use.

2. Populate the model with appropriate parameter data in order to perform a preliminary cost-effectiveness analysis of NHIS-funded pediatric Burkitt's Lymphoma treatment compared to treatment with Current Practice in Ghana. This will also include deterministic and probabilistic sensitivity analyses.

The completion of these objectives will provide the information and context required to complete the research aims of this thesis.

1.2 Research Aims

The research aims of this thesis are the following:

1. To asses the cost-effectiveness of NHIS-funded treatment of pediatric Burkitt's Lymphoma compared to treatment with the Current Practice in Ghana protocol through the use of a piloted decision-analytic model.

2. To identify the parameters that have the largest impact on the cost-effectiveness of the treatment of pediatric Burkitt's Lymphoma in Ghana.

This thesis will constitute the first cost-effectiveness analysis of pediatric BL treatment in Ghana and the first decision-analytic model for the simulation of pediatric BL

treatment. The model developed in this thesis will be provided to the Ministry of Health of the Republic of Ghana for teaching, adaption and use in future analyses.

The study in this thesis is being performed in order to address the knowledge gap regarding the cost-effectiveness of pediatric BL treatment in Ghana, and the parameters that have the largest impact on the cost-effectiveness of pediatric BL treatment in Ghana. The novel findings of this thesis can be used to provide a starting point from which relevant stakeholders in Ghana can start to make an informed decision regarding the National Health Insurance Scheme (NHIS) reimbursement of pediatric BL treatment.

1.3 Thesis structure

This thesis is structured as follows:

Chapter 2 of this thesis details the background, diagnosis and treatment of BL. It also briefly describes the Ghanaian health system, so as to explain the details surrounding the characteristics of the decision-setting. This is also the chapter in which studies that explore research aims similar to the research aims of this thesis are introduced.

Chapter 3 outlines the theoretical framework behind the thesis, including cost-effectiveness analysis, decision-analytic models and sensitivity analysis.

Chapter 4 presents the methods applied in the piloting of the decision-analytic model and the subsequent preliminary cost-effectiveness analysis. This includes the justification for the model structure and assumptions, the selection of cost and effectiveness data, and the determination of cost-effectiveness. Also included are the methods applied for the deterministic and probabilistic sensitivity analyses.

Chapter 5 presents the results produced by the decision-analytic model, and the results from the preliminary cost-effectiveness analysis. This includes the costs and effects for both treatment situations, as well as the results from the deterministic and probabilistic sensitivity analyses.

Chapter 6 presents the discussion of the results, what the implications of the results are in a Ghanaian and wider context, the strengths and limitations of the study conducted in this thesis, and recommended areas of future research.

Chapter 7 presents the thesis's conclusion regarding the research aims of this thesis.

Chapter 2

Background

This chapter provides background information that is necessary in order to properly understand the context of the research undertaken in this thesis. This information includes details about the disease of Burkitt's Lymphoma, including diagnosis and treatment of the disease, as well as the burden BL poses for SSA and Ghana specifically. This chapter also examines existing research relevant to the research aim of this thesis.

2.1 Disease characteristics and Variants of Burkitt's Lymphoma

BL is a cancer of the lymphatic system that affects the B-cells of the lymph nodes, and is the fastest-growing tumor in humans. The disease is quickly fatal without treatment. Despite the aggressive growth-rate of the tumor, it is very reactive to chemotherapy in children (Okebe et al., 2011).

BL is a Non-Hodgkin's lymphoma that is primarily seen in children. It originates from the development of the c-myc proto-oncogene into an oncogene through a chromosomal translocation, and was notably one of the first types of cancer identified to develop via chromosomal translocation (Molyneux et al., 2012).

BL is normally categorized into three variants: endemic (African) Burkitt's Lymphoma, Sporadic (Non-endemic) Burkitt's Lymphoma and Immunodeficiency-associated Burkitt's Lymphoma (Molyneux et al., 2012). These variants all share the origin of c-myc oncogene activation, and are histologically indistinguishable from one another. (Guechongey et al., 2010). The differences among the variants are mostly characterized by how the diseases present and the area of the world in which those affected with the disease live (Offor et al., 2018).

2.1.1 Endemic Burkitt's Lymphoma

Endemic BL is named such because it is the variant seen in in areas where malaria is holoendemic, such as Sub-Saharan Africa. Epstein-Barr virus (EBV) and malaria are recognized as co-factors for endemic BL. There is a long-recognized link between the three diseases, with those who develop endemic BL usually being infected with one or both diseases (Molyneux et al., 2012). The endemic variant of BL occurs only in

children, with incidence peaking in children at age 6 (Hämmerl et al., 2019). It is the most prevalent form of BL, having an estimated incidence rate of between 40 and 50 per million children under 18 years of age (Molyneux et al., 2012). It is more common in boys, with males accounting for 2/3 of cases of BL (Hämmerl et al., 2019). The most common clinical presentations for BL are swelling in the jaw, swelling in the periorbital area and involvement of the abdomen (Molyneux et al., 2012).

The study conducted for this thesis evaluates pediatric BL in Ghana, which implies that the disease variant in question must be endemic BL, by definition. Therefore, for the purposes of this thesis, all references of pediatric BL within a Sub-Saharan African context should be assumed to be referring to the endemic variant.

2.1.2 Other Forms of Burkitt's Lymphoma

Sporadic BL is the form of BL that occurs outside of areas where malaria is holoendemic, primarily North America and Europe. It occurs most commonly in children, but can also be seen in adults. Sporadic BL most commonly presents in the abdomen (Molyneux et al., 2012).

Immunodeficiency-based BL is the form most commonly seen in individuals with health problems that cause immunodeficiency, and is most often seen in those who are infected by HIV/AIDS. Before antiretroviral therapy came to North America, BL was seen 1000 times more often in individuals infected with HIV/AIDS than in the general population (Molyneux et al., 2012). Those who present with HIV-associated BL tend to present with less obvious symptoms such as fever, night sweats and weight loss. BL in these individuals have more nodal involvement than those with other variants, and tend to get diagnosed in later stages (Atallah-Yunes et al., 2020).

2.2 Diagnosis of Pediatric Burkitt's Lymphoma

Proper diagnosis of pediatric BL is necessary in order to provide patients the treatment regimen best suited to their situation. Accurate diagnosis is important in order to differentiate BL from other types of Non-Hodgkin's Lymphoma that require a different therapeutic strategy (Ozuah et al., 2020). Due to differences in access to resources, methods for the diagnosis of pediatric BL differ between LMIC and HIC settings. These differences will be briefly examined in the following paragraphs.

Diagnosis of BL in LMIC commonly relies on the examination of tumor tissue morphology obtained via Fine Needle Aspiration (FNA) (Ozuah et al., 2020). This method, while less resource-intensive, is discouraged from use in HIC settings for BL diagnosis (Ozuah et al., 2020). This is likely because FNA does not provide sufficient tumor tissue for all of the investigations that should ideally be performed (Molyneux et al., 2012). FNA is, however, recognized as the minimum evidence needed to establish a pediatric BL diagnosis in LMIC settings (Gopal & Gross, 2018). Though diagnostic accuracy can be improved with the use of additional methods, studies estimate the specificity of morphology-only diagnoses to be around 50 % (Ozuah et al., 2020). Even in settings where additional diagnostic tests are available, access to these tests can be hindered by

patients' ability to pay (Offor et al., 2018). The difficulties in proper BL diagnosis in LMIC may contribute to the poor BL outcomes seen in these settings (Ozuah et al., 2020).

A method for diagnosis of pediatric BL commonly used in HIC contexts is outlined in Molyneux et al. (2012). The recommended method outlined in this document involves confirming the BL diagnosis via microscopy and immunocytological analysis. In order to do this, the paper recommends obtaining diseased tissue via excision biopsy of a lymph node, as well as performing a number of clinical investigations on the patient. These investigations include a full blood count, electrolyte measurements, liver function tests, Epstein-Barr Virus-status tests and chest radiography, among other investigations (Molyneux et al., 2012).

2.3 Staging of Pediatric Burkitt's Lymphoma

Clinical prognosis of and treatment decisions for BL are usually guided by disease stage. (Molyneux et al., 2012). Disease staging provides a method by which to tailor treatment to individual patients as well as provides a uniform way to compare individuals across contexts. The most common staging system for pediatric BL used in HIC and LMIC alike is the St. Jude/Murphy staging system (Molyneux et al., 2012). This is the system used in the treatment of pediatric BL in Ghana (Offor et al., 2018).

There are four stages in the St. Jude/Murphy staging system for pediatric BL, where Stage I and Stage II represent localized disease, Stage III represents disseminated disease, and Stage IV represents disseminated disease with central nervous system (CNS) or bone marrow involvement (Offor et al., 2018). The criteria for each stage in the staging system are clearly defined and can be seen in table 2.1. Although these staging guidelines are clearly defined for both HIC and LMIC practitioners, there can be heterogeneity in how diseases staging occurs in practice in LMIC contexts. Proper staging of advanced-stage pediatric BL requires microscopy of cerebrospinal fluid and evaluation of bone marrow samples. Because of the capacity required to accurately perform the tests needed for accurate staging of advanced-stage pediatric BL, the staging of advanced-stage pediatric BL in LMIC contexts is not reliably consistent (Ozuah et al., 2020).

Table 2.1: *St. Jude/Murphy staging system for Non-Hodgkin's Lymphoma. Table adapted from Molyneux et al. (2012). Staging system originally described in Carbone et al. (1971).*

Stage	Criteria for extent of disease
I	• A single tumor (extranodal) or single anatomic area (nodal), excluding the mediastinum and abdomen • A single tumour (extranodal) with regional node involvement, on same side of the diaphragm
II	• A single tumour (extranodal) with regional node involvement • Two or more nodal areas on the same side of the diaphragm • Two single (extranodal) tumors with or without regional node involvement on the same side of the diaphragm • A primary gastrointestinal tumor, usually in the ileocecal area, with or without involvement of associated mesenteric lymph nodes only, grossly completely resected
III	• Two single tumors (extranodal) on opposite sides of the diaphragm • Two or more nodal areas above and below the diaphragm • All the primary intrathoracic tumors (mediastinal, pleural, thymic) • All extensive primary intra-abdominal disease, unresectable • All paraspinal or epidural tumors, regardless of other tumor site(s)
IV	• Any of the above with initial Central Nervous System and/or bone marrow involvement

2.4 Treatment of Pediatric Burkitt's Lymphoma

Pediatric BL has been recognized to be very reactive to chemotherapy treatment since the earliest studies of the disease (Burkitt, 1968). BL is, in fact, considered to be the first childhood tumor to respond to chemotherapy alone (Molyneux et al., 2012). This sensitivity to chemotherapy still rings true in today, as chemotherapy treatment is still considered to be the gold standard for treating pediatric BL in all stages and contexts (Rocca et al., 2021). In the present day, pediatric BL is treated with a Cyclophposphamide monotherapy, or with a combination therapy that includes Cyclophosphamide in combination with other chemotherapy drugs of varying levels of intensity. The treatment regimen used in practice is based primarily on the resources available in the treatment setting (Gopal & Gross, 2018).

The first studies around pediatric BL treatment found Cyclophosphamide to be the chemotherapy agent that produced the most effect (Burkitt, 1972). Following this early research, treatment protocols in both LMIC and HIC had similar outcomes, and were based around a backbone of Cyclophosphamide (Ozuah et al., 2020). These low-intensity Cyclophosphamide-based treatment regimens are associated with cohort survival rates of 30-50% (Ozuah et al., 2020). Over time, research in HIC has led to the development of very intense chemotherapy treatments that see cohort survival rates of up to 90%. These high-intensity cytotoxic regimens are too resource intensive for LMIC settings, and have led to a distinct difference in what treatments are seen in practice in HIC compared to LMIC (Ozuah et al., 2020).

The treatment strategies currently in use for the treatment of pediatric BL can be divided into three categories. Most treatment strategies differentiate treatment based on the stage of disease, so treatment regimens are categorized by the intensity of the most intense treatment strategies. The treatment categories in order of treat-

ment intensity are: low-intensity treatment, anthracycline-based treatment and high-dose Methotrexate-based treatment (Gopal & Gross, 2018). High-dose Methotrexate treatments are recognized as the family of treatments that produce the best outcomes in HIC. However, clinical studies of this type of treatment in LMIC have shown worse results than lower intensity treatment, due in part to death from cytotoxicity (Ozuah et al., 2020).

2.4.1 Pediatric Burkitt's Lymphoma Treatment in Sub-Saharan Africa

The current standard of treatment for pediatric BL in SSA is considered to be low-intensity Cyclophosphamide-based therapy, without treatment differentiation for disease stage (Ozuah et al., 2020). In some SSA contexts, treatment regimens utilizing anthracycline-based treatment plus Cyclophosphamide are used. In these types of treatment regimens, treatment is differentiated according to disease stage. Some SSA contexts utilize "named" treatment regimens, which are treatment regimens that use combinations of drugs whose combined effects have been tested in clinical trials. Some of these named regimens include the "CHOP" regimen, the "JOOTRH Protocol", and the "Malawi 2012-2014 Protocol" (Gopal & Gross, 2018).

Pediatric BL Treatment in Ghana

There are two treatment centers in Ghana that have specific centers for pediatric cancer care such as pediatric BL: Korle-Bu Teaching Hospital (KBTH) in Accra and Komfo Anokye Teaching Hospital (KATH) in the Kumasi Region (Boateng et al., 2020). The treatment regimen for pediatric BL at KATH is not publicly available. The treatment regimen for treating pediatric BL at KBTH can be seen in table 2.2. This regimen uses a low-intensity treatment for disease stages I and II, and an anthracycline-based therapy for disease stages III and IV (Offor et al., 2018).

Table 2.2: *This table shows the treatment protocol for pediatric Burkitt's Lymphoma at Korle-Bu Teaching Hospital. This treatment protocol is referred to as the "Current Practice in Ghana" Protocol throughout this thesis. The protocol in this table is adapted from Offor et al. (2018).*

Tumor Stage	Course of Treatment
Stages I & II	4 courses of IV Cyclophosphamide 40mg/kg every 2 weeks with intrathecal (IT) Methotrexate for central nervous system (CNS) prophylaxis during courses 1-3.
Stage III	A pre-phase dose of IV Cyclophosphamide 1400mg/m2 with IT Methotrexate, followed by a combination chemotherapy consisting of 6 cycles (Cyclophosphamide, Vincristine and Doxorubicin alternating with Cyclophosphamide, Vincristine and Cytarabine every 2 weeks) with IT Methotrexate given during the first 3 courses
Stage IV	For bone marrow involvement a modified version of a mature B-cell protocol for high income countries without Rituximab is used, and inclusive of four cycles of maintenance therapy, following reduction, induction and consolidation phases of therapy. For CNS disease, additional intrathecal therapy is included until cerebrospinal fluid (CSF) cytology is negative

2.5 The Burden of Endemic Burkitt's Lymphoma in Sub-Saharan Africa

Pediatric BL is the most common type of childhood cancer in areas where malaria is holoendemic, namely SSA (Molyneux et al., 2012). The exact incidence of BL in SSA is difficult to measure due to a lack of relevant data (Hämmerl et al., 2019). Magrath (2012) estimated the incidence of BL in SSA to be between 3-6 per 100,000 children. More recently, a study by Hämmerl et al. (2019) used the reported incidence of pediatric Non-Hodgkins Lymphoma according to the Globocan 2018 estimates, combined with SSA cancer registry data, in order to estimate the overall incidence of pediatric BL in SSA. This study estimated the incidence of pediatric BL in SSA to be 0.86 per 100,000 children under 15 years of age. The study notes, however, that this is likely an underestimate due to the urban bias seen in the registries used in the study (Hämmerl et al., 2019).

The long-term survival rates for pediatric BL in SSA are poor, with typical long-term survival rates of 40%-60% (Denburg et al., 2019). These rates are likely lower in reality, as there is likely a referral bias among patients who are able to make it to the tertiary centers for treatment. This is especially the case for children in rural areas, as treatment centers are often located in urban areas (Gopal & Gross, 2018). Pediatric BL in SSA is associated with high incidence rates, low survival rates, longer distances to treatment and patients and systems with less access to resources. These factors contribute to the burden of pediatric BL in SSA.

2.5.1 The Burden of Burkitt's Lymphoma in Ghana

Pediatric BL is the most common form of childhood cancer in Ghana (Offor et al., 2018). The incidence of pediatric BL in Ghana is impossible to derive using empirical data, as there is no national cancer registry in Ghana (Renner et al., 2018). Hämmerl et al. (2019) estimated the incidence to be between 0.59 and 1.1 per 100,000 children under 15. However, the methods for the estimate for Ghana specifically are not clear. Additionally the data itself was presented in an unclear manner, being only shown in a map figure, with the color of the country being the only indication of the value-range of the incidence (Hämmerl et al., 2019).

KBTH and KATH, the only public pediatric cancer treatment centers in the country, treat a combined average of 70 pediatric BL patients per year. These treatment centers are located in the Accra and Kumasi regions of Ghana. (Offor et al., 2018; Paintsil et al., 2015). Although there is no survival data available for pediatric BL patients at KATH, Offor et al. (2018) reported the current survival status of 173 pediatric BL patients. When censoring patients who abandoned treatment, 20% overall survival was reported. The time between treatment and death for these patients was not reported (Offor et al., 2018).

Treatment for pediatric BL is not covered under the Ghanaian NHIS, so the cost of treatment must be shouldered by the patients and their families (Renner et al., 2018). Additionally, because these treatment centers are the only centers for pediatric BL in the country, many patients are required to travel long distances in order to receive treatment. These factors lead to a notable financial burden on families. At KBTH, treatment delay was seen in 9 of 10 patients, with 75% of these patients delaying due to financial constraint (Offor et al., 2018).

These factors of burden of pediatric BL are present in Ghana to a problematic degree, having very high prevalence rates and poor outcomes, even when compared to other parts of SSA (Hämmerl et al., 2019; Offor et al., 2018). This leads to pediatric BL posing a substantial burden on both the healthcare system and society of Ghana.

2.6 Relevant Existing Research

Ad-hoc literature searches were performed in order to locate relevant existing research regarding this thesis's stated objectives of the construction of a decision-analytic model for pediatric BL in Ghana and the determination of the cost-effectiveness of pediatric BL in Ghana through the utilization of such a model.

The literature searches did not yield any existing decision-analytic models for the treatment of endemic BL treatment upon which to base the model in this thesis. The literature search also failed to yield any academic studies regarding the cost-effectiveness of endemic BL in Ghana. However, the literature searches did yield two academic publications that had study aims similar to the study aims of this thesis. The study by Denburg et al. (2019) examines the cost-effectiveness of pediatric BL treatment in Uganda, and the study by Renner et al. (2018) examines the cost-effectiveness of the treatment of all pediatric cancer in Ghana.

2.6.1 Research on the Cost-Effectiveness of BL in SSA

Denburg et al.

The study performed by Denburg et al. (2019) examines the cost-effectiveness of treating pediatric BL in Uganda. This is relevant to this thesis because Uganda is a country in SSA with endemic BL.

The study examined the cost-effectiveness of a low-intensity treatment regimen with a anthracycline-based second-line therapy compared to a "do-nothing" strategy. The study took a governmental perspective, though some family costs were included. The cost-effectiveness analysis was conducted in tandem with a clinical study. The authors were therefore able to calculate outcome data and variable cost data prospectively through a microcosting strategy, where the costs and effects for each patient were calculated individually, then combined and represented as mean values in the analysis (Denburg et al., 2019). Costs that were not able to be captured in individual patient costs, such as the fixed costs of operating the hospital, were calculated retrospectively.

Cost-effectiveness in this study was determined using the World Health Organization's Choosing Interventions That Are Cost-Effective (WHO-CHOICE) methodology. In this methodology, interventions with an Incremental Cost-Effectiveness Ratio (ICER) with a cost per DALY averted value of less than three times the GDP per capita of a country (3:1) are considered to be "cost-effective". Interventions with an ICER with a cost per DALY averted value of less than the GDP per capita of a country (1:1) is considered to be "very cost-effective" (Tan-Torres Edejer et al., 2003). This study found this treatment regimen for endemic BL in Uganda was very cost-effective, with a cost per DALY averted of $97 per DALY averted, and a cost per DALY averted to GDP ratio of 0.14. It should be noted that, while treatment abandonment was accounted for in this study, the proportion of patients completing treatment in this study is notably high at 97%. Treatment abandonment for childhood cancers in resource-limited countries are noted to occur at rates of up to 67%, implying the 97% completion rate seen in Denburg et al. (2019) is higher than expected for the region (Stevens et al., 2008). This is important to consider when interpreting the conclusions of this study, as the lack of treatment abandonment may indicate that the study primarily measures the efficacy of the treatment used, and does not necessarily capture the real-world situation.

2.6.2 Research on the Cost-Effectiveness of Pediatric Cancer in Ghana

Renner et al.(2018)

The study performed by Renner et al. (2018) examines the cost-effectiveness of treating childhood cancer at the pediatric cancer center at KBTH. This cost-effectiveness analysis represents a unique analysis within the literature, as it is the first to evaluate the cost and cost-effectiveness of operating and maintaining a pediatric oncology treatment center in an African setting (Renner et al., 2018). This is relevant to this thesis because pediatric BL is among the diseases treated in this treatment center.

The cost-effectiveness analysis was conducted using internal hospital data. The study

was expanded beyond a healthcare payer perspective, as the study incorporated patients costs in their calculations. The study broke costs into the following categories: medical personnel, non-medical personnel, hoteling of patients, medical services, and central administration and utilities. The study used hospital data to calculate one-year survival. The study then used the proportion of 1-year overall survival to 5-year overall survival seen in Swaminathan et al. (2008) to estimate 5-year survival in their study. This study found the operation and maintenance of the pediatric oncology treatment center at KBTH to be very cost-effective according to the WHO-CHOICE methodology, with a cost per DALY averted of $1,034. This result indicated a 0.68:1 ratio of cost per DALY averted to the GDP per capita at the time of the study.

2.7 The Ghanaian Healthcare System

The Ghanaian healthcare system consists of five levels of providers. These include health posts, health centers and clinics, district hospitals, regional hospitals and tertiary hospitals. Health posts serve as the primary care providers for rural areas (US Dept of Commerce, 2020). The quality of care in Ghana is considered to be relatively high for the region. Though, this depends significantly upon location, as health services are mostly concentrated in the urban centers of Accra and Kumasi. Physicians are scarce in rural regions of Ghana. Ghana is also known for their relatively successful National Health Insurance Scheme (Drislane et al., 2014). Despite a recent rise in non-communicable diseases such as childhood cancer, Ghana's health system priorities are largely focused on the control of communicable diseases (Boateng et al., 2020).

2.7.1 The Ghanaian National Health Insurance Scheme

The Ghanaian NHIS scheme covers 95% of the health problems seen in Ghana (Mensah et al., 2010). Conditions covered under the NHIS include malaria, HIV/AIDS opportunistic infection, cervical cancer, breast cancer and typhoid fever among others. Cancers other than cervical or breast cancer are explicitly excluded from the list of covered conditions (National Health Insurance Authority of Ghana, 2021). In order for treatment to be reimbursed, it must be listed on the Ghana National Essential Medicines List (NEML). However, not all medications on the NEML are eligible for reimbursement (Boateng et al., 2020). Membership in the NHIS requires the payment of an insurance premium, with members in the formal sector paying an automatically deducted premium based on income. Individuals in the informal sector or who are self-employed also have the option to pay premiums for membership in the insurance scheme. NHIS coverage extends to children of members (Mensah et al., 2010).

Chapter 3

Theory

This chapter outlines the theoretical frameworks upon which this study was based. The academic theory presented in this chapter was either directly utilized in performing the study for this thesis, or is necessary for understanding the current academic context of the research field.

3.1 Economic Evaluation

Decision-makers across the globe within healthcare all face a similar problem. Namely, healthcare resources are scarce, and decision makers are tasked with deciding how to distribute these scare resources among competing needs. Economic evaluation is a methodological approach that can be used inform decision-makers in their pursuits of solving this problem.

Economic evaluation at its core can be defined as an analysis that compares multiple courses of action of a given scenario by analysing and comparing the costs and effects of these courses of action (Drummond et al., 2015). Within healthcare, economic evaluations are used to compare alternative healthcare choices in terms of their cost and effectiveness, in order to inform decisions regarding best use of healthcare resources. Examples can include surgical or pharmaceutical interventions, disease screening programs and informational campaigns (Briggs et al., 2006).

3.1.1 Types of Economic Evaluation

Economic Evaluations can be broken down into three categories: Cost-Effectiveness Analysis (CEA), Cost-Utility Analysis (CUA), and Cost-Benefit Analysis (CBA) (Drummond et al., 2015). As costs are always measured in monetary terms, the distinction between these categories stems from differences in the measurement of the effects of the interventions in question. Decision makers can choose the category of economic evaluation that provides information in the way best suited to inform the healthcare decision in question.

Cost-Effectiveness Analysis

In a CEA, costs are related to effects in the form of change in natural units. Such units can include life years gained, change in mmHG blood pressure measurement or number of individuals who abandon treatment (Drummond et al., 2015). Because CEAs use natural outcome units, they are most useful in evaluating alternative approaches with the same outcome measure (Drummond et al., 2015). For example, if a decision maker is tasked with reducing falls in a hospital using a fixed budget, a CEA with "falls prevented" as the measured outcome would be informative.

Cost-Utility Analysis

CUA is considered to be a variation of CEA, and the terms are often used interchangeably in academic literature (Drummond et al., 2015). The main distinction is that effects in CUAs are measured in terms of a generic measure of health gain instead of natural units specific to the decision problem. These generic health measures adjust life-years gained from an intervention for the Health-Related Quality of Life (HRQoL) of those years. HRQoL-adjusted outcome measures commonly seen in CUAs include the Quality-Adjusted Life Year (QALY), the Disability-Adjusted Life Year (DALY), and the Healthy Years Equivalent (HYE). Adjusting outcomes of interventions for quality of life in this way allows for results of CUAs to be compared across a variety of diseases, interventions and health system contexts (Denburg et al., 2019).

Cost-Benefit Analysis

In CBA, costs and effects are both related in monetary terms. This is done by translating natural outcome effects or generic health measure effects into a monetary value that can be interpreted alongside costs (Drummond et al., 2015). The translation of natural outcomes or generic health measure effects into monetary terms is done by evaluating the Willingness to Pay (WTP) for the given outcome within the given context. The results of these types of analysis are commonly presented as a ratio of cost per benefit, or as a sum of the total monetary benefit or loss associated with funding a given course of action (Drummond et al., 2015).

3.1.2 Disability-Adjusted Life Years

$$DALY = YLL + YLD \tag{3.1}$$

The disability-adjusted life year (DALY) measure was originally developed as a measure of disease burden for use in the World Health Organization (WHO)'s Global Burden of Disease (GBD) study (Drummond et al., 2015). The DALY is calculated by adding the Years of Life Lost (YLL) from a disease and Years Lived with Disease (YLD), as can be seen in equation 3.1. YLD is calculated by multiplying the years lived with a given condition by the disability weight of that condition. YLL can be calculated by subtracting the age at which an individual dies from the individual's life expectancy at the time of death (Fox-Rushby & Hanson, 2001). The DALY is a negative measure,

meaning that scenarios where a greater number of DALYs are accrued indicate a greater loss of health. Therefore, in CUA, the cost-effectiveness of an intervention is determined by the cost per DALY averted. DALYs can also incorporate discounting to adjust the future losses of life to their present values (Fox-Rushby & Hanson, 2001). DALYs can also incorporate age-weighting, which gives lower weight to the lives of the elderly and children. Age-weighting is not currently used in the DALY calculations in the most recent GBD study (Drummond et al., 2015).

3.1.3 Perspective in Economic Evaluation

The perspective from which an economic evaluation is performed determines what costs and effects should be taken into consideration when presenting results and making decisions, and is a key factor in economic evaluation (Hunink et al., 2014). The perspective used in an economic evaluation is determined by the circumstances of the decision problem and the needs of the decision maker. Examples of perspectives that can be taken in an economic evaluation include individual patient perspective, institutional perspective, governmental payer perspective and societal perspective (Drummond et al., 2015).

3.1.4 Incremental Cost-Effectiveness Ratio

$$ICER = \frac{\Delta Costs}{\Delta Effects} \tag{3.2}$$

The Incremental Cost-Effectiveness Ratio (ICER) is commonly used as the primary outcome measure of cost-effectiveness analyses. The ICER is an incremental outcome, representing the additional resources required per additional unit of benefit when comparing multiple alternatives (Briggs et al., 2006). The equation for the calculation of the ICER can be seen in equation 3.2. The ICER is reported in incremental cost per incremental desired unit of effect, such as incremental cost per QALY gained or incremental cost per DALY averted.

3.2 Decision-Analytic Modelling

Decision-analytic modelling, sometimes referred to simply as decision modelling, is a process in which a model is created using defined mathematical and statistical relationships between parameters in order to simulate the costs and outcomes of an intervention (Briggs et al., 2006). In selecting and building a decision-analytic model, a firm understanding of the decision problem and the clinical characteristics of the health problem in question is vital (Roberts et al., 2012). There are several types of decision-analytic models, all of which are better suited to certain types of decision problems. Types of decision-analytic models include: decision trees, Markov models, Microsimulation models, Dynamic models, and Discrete event simulation models (Kuntz et al., 2013).

3.2.1 Validation in Decision-Analytic Modelling

Validation in decision-analytic modelling consists of methods for determining the degree to which model predictions match reality (Eddy et al., 2012). Models often integrate data from multiple sources, and can utilize methods that are unclear for decision makers such as patients and policymakers (Hunink et al., 2014). Validation allows for the credibility of a model to be assessed by decision makers (Eddy et al., 2012). In Eddy et al. (2012), the authors define five categories of validation. These categories are: face validation, cross validation, external validation, internal validation, and predictive validation.

Face validation is performed by an expert, who analyzes the degree to which the assumptions and parameters of a model match the current academic and clinical understanding of the decision problem in question. Internal validation is a process by which the accuracy of the mathematics performed in the model is checked. External validation is achieved based on the degree to which model outputs match clinical outcome data. Cross validity is achieved based on the degree to which model outputs match the output of other similar models. Predicative validation is achieved based on the degree to which a model is able to predict clinical outcomes before they occur (Eddy et al., 2012).

3.3 Sensitivity Analysis

Sensitivity analysis defines a set of methodologies that can be used to account for the uncertainty inherent in a decision-analytic model. Drummond et al. (2015) presented two types of uncertainty seen in decision-analytic models: structural uncertainty and parameter uncertainty. Structural uncertainty in this context refers to the assumptions made when creating the model and performing the modelling itself, such as assumptions regarding mathematical relationships between parameters or decisions regarding study perspective or discount rates. Parameter uncertainty in this context refers to uncertainty inherent in populating parameters using sample data from a population, reflected by the variance between samples and the size of samples (Drummond et al., 2015).

Deterministic sensitivity analysis methods, such as one-way sensitivity analysis, involve the investigation one parameter at a time. These methods can be useful to see the effect of changing individual parameters on the ICER. This has utility in examining structural uncertainty by examining the effect changing certain parameter values or assumptions has on the model, as well as some utility in examining parameter uncertainty (Briggs et al., 2012; Fenwick et al., 2020). However, because of the complex interactions between parameters present in many decision-analytic models, deterministic analyses are not sufficient to properly account for uncertainty (Drummond et al., 2015).

Probabilistic Sensitivity Analysis (PSA) methods attempt to account for parameter uncertainty in a more robust manner than deterministic sensitivity analyses. Performing a PSA usually involves a process known as Monte Carlo Simulation. In a Monte Carlo Simulation, a random value is sampled for each parameter in the decision-analytic model based on the parameter distribution and uncertainty data assigned to each parameter. The outcomes from the Monte Carlo Simulation are then recorded in order to be compared. Normally in a PSA, 1,000 or more of these simulations are performed

(Drummond et al., 2015). Comparing the results of this large number of simulations allows for a more robust understanding of the impact of parameter uncertainty on the outcomes of the decision-analytic model in question (Briggs et al., 2006).

3.4 Determination of Cost-Effectiveness

Although the ICER is used as the outcome measure of CEA, the ICER alone is not sufficient to make normative claims about whether or not an intervention is cost-effective (Drummond et al., 2015). In order to make determinations regarding the cost-effectiveness of an intervention, a decision threshold must be utilized. In this context, a decision threshold is an ICER value representing the maximum additional monetary value a decision-maker is willing to pay for additional health gains (Drummond et al., 2015). In theory, CEAs are intended to ensure that decisions regarding the allocation of resources are cost-effective. That is to say, to ensure that the scarce resources used for one health intervention are not better suited by funding a different intervention. Therefore, cost-effectiveness thresholds should reflect the opportunity costs of additional health care spending (Woods et al., 2016). However, in practice, the data or resources required to calculate such opportunity cost-based threshold values is not always present (Drummond et al., 2015).

Chapter 4

Methods

This chapter is divided into two distinct parts, which are based upon the two stated objectives of this thesis. Part 1 of this chapter describes the methods used for developing the decision-analytic model for pediatric BL in Ghana. This includes inherent assumptions and decisions made in the model, and the academic evidence used in making these assumptions and decisions. Part 2 of this chapter describes the methods used to populate the parameters of the decision-analytic model in order to perform a preliminary cost-effectiveness analysis of the treatment of pediatric BL in Ghana. Part 2 also describes the methods used in the deterministic and probabilistic sensitivity analyses performed in this thesis.

Part 1: The Decision-Analytic Model

4.1 Development of the Decision-Analytic Model for Pediatric BL

According to the initial literature searches performed for this thesis, there are no currently existing decision-analytic models for pediatric BL. Therefore, in order to fulfil the research aims of this thesis, a novel decision-analytic model needed to be piloted. To inform this process, literature searches for the clinical progression of pediatric BL and literature searches for types of decision-analytic models were performed. The information from these literature searches was used to select an appropriate type of decision-analytic model, create appropriate decision nodes, chance nodes, end nodes and states for the decision-analytic model, and make clinically relevant assumptions in the model. Because the decision-analytic model used in this thesis will be delivered to the Ghanaian Ministry of Health to be used as a capacity-building tool to be used and expanded on in future projects, utility of use and flexibility was also considered in the selection of decision-analytic model type.

4.1.1 Selection of a Decision Tree as the Decision-Analytic Model

Nearly any type of decision problem can be represented by any type of model (Roberts et al., 2012). Some types of decision-analytic models are more suited to certain types of decision problems than others. It is therefore important to understand the decision problem at hand and the clinical aspects associated with it, and match it with the type of decision-analytic model that is best equipped to provide insightful information for solving the decision problem. Decision-analytic models are an attempt to represent reality, and ought to to capture that reality as accurately as possible while remaining as simple as possible in order to address the decision problem (Drummond et al., 2015).

Decision trees are a model type that is simple to conceptualize and good at separating components of a decision problem (Roberts et al., 2012). Decision trees are best suited for modelling decision problems that are able to be split into discrete pathways with concrete end-states (Drummond et al., 2015). Pediatric Burkitt's Lymphoma is a disease that is categorized into four distinct risk-stratified stages. These stages are treated differently according to the given regimen, and are associated with discrete stage-dependent outcomes. Additionally, because BL is the fastest growing tumor in humans, the outcomes can be represented in single time frame. Due to the orderly system diagnosis and discrete outcomes of pediatric BL, combined with the speed of progression of the disease, a decision tree type decision-analytic model was determined to the most appropriate type of decision-analytic model for this decision problem.

4.1.2 Structure and Characteristics of the Decision Tree Model for Pediatric Burkitt's Lymphoma

The structure of the decision tree model for pediatric BL in Ghana can be seen in its entirety in Figure 4.1. The model simulates the outcomes of a cohort with confirmed pediatric BL after one year of pediatric BL treatment. These outcomes are simulated through the progression of the cohort through the model via the chance nodes (represented by the green circles in Figure 4.1) to the end nodes (represented by the blue triangles in Figure 4.1). The chance nodes and treatment pathways were developed using a clinical understanding of pediatric BL, and have been designed to capture the clinical progression and outcomes of pediatric BL treatment in a mutually-exclusive and collectively-exhaustive manner.

The first-order chance node determines the proportion of the cohort diagnosed with Stage I, Stage II, Stage III, and Stage IV pediatric BL as per their definitions in the St. Jude/Murphy classification system. Because the disease stages are associated with discrete outcomes, it was determined to be important to differentiate modelled outcomes by stage in order to more closely simulate the real-world situation.

The second-order chance nodes determine the proportion of the cohort that abandons treatment or completes treatment given disease stage. Treatment abandonment in pediatric cancer treatment in SSA is common, and a major contributor to poor outcomes in LMIC contexts (Renner et al., 2018). Moreover, treatment abandonment is identified as an important factor in outcomes for pediatric BL in SSA specifically (Gopal & Gross,

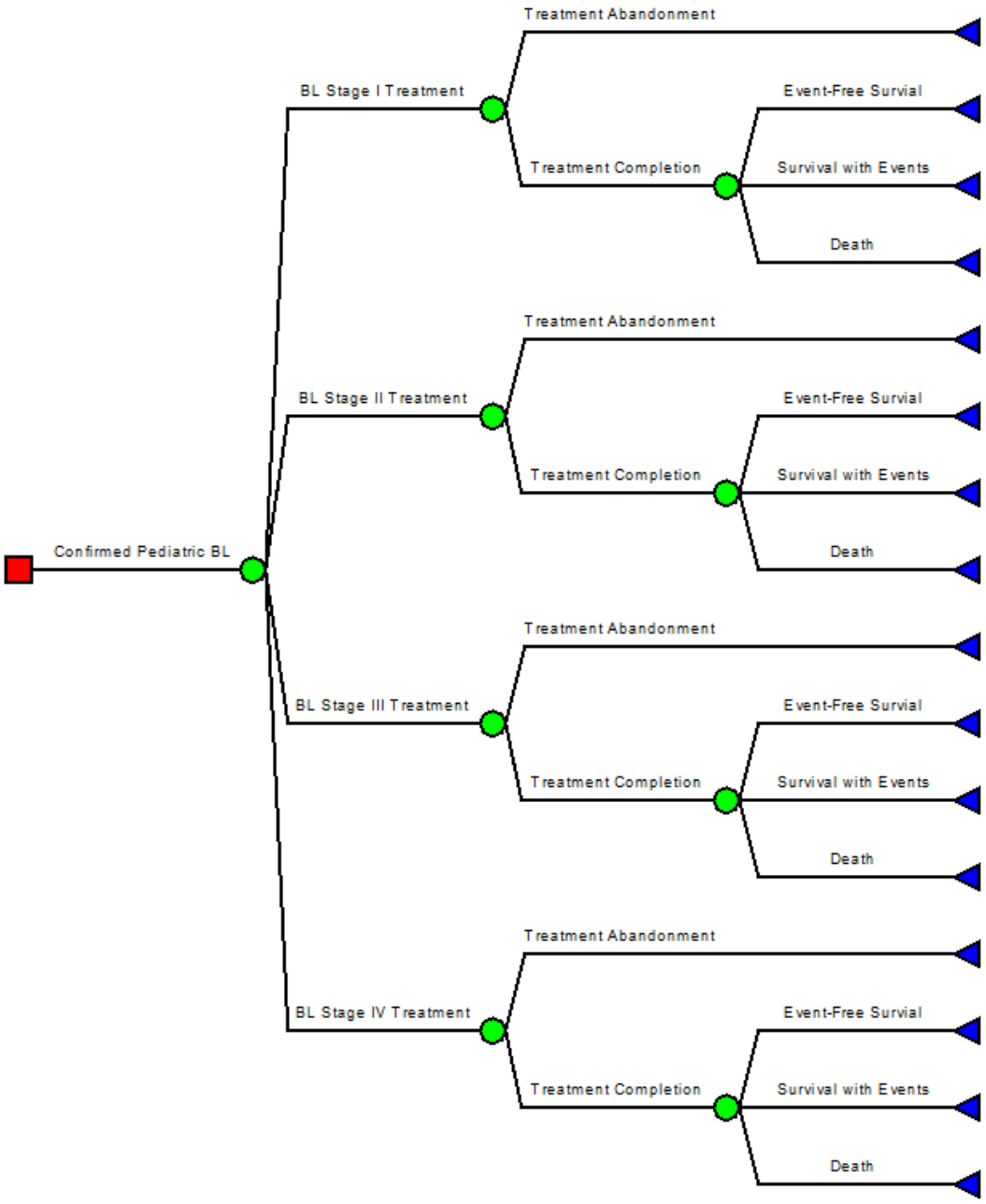

Figure 4.1: *This figure depicts the Decision Tree decision-analytic model for the treatment of pediatric Burkitt's Lymphoma in Ghana developed in this thesis. The red square is a "decision node", and represents the point where the cohort begins in the model. The green circles represent "chance nodes", which are points where chance determines what happens to the starting cohort. The blue triangles represent "end nodes", which represent a final outcome of a decision path. The simulated cohort proceeds through the branching pathways based on the probabilities associated with the chance nodes, and ends in one of the 16 discrete end-states represented by the end nodes. The pathways after the first chance node are defined by which stage of pediatric BL a patient is determined to have, based on the St. Jude/Murphy Classification system. After the second chance node, "Treatment Abandonment" is defined as stopping treatment without returning. After the third chance node, "Event-Free Survival" is defined as individuals who survive without "events", which includes relapse or extreme symptoms, as normally reported in clinical studies of the effectiveness of cancer treatments. This figure was generated using the open-source modelling software Amua.*

2018). Despite being such an important determinant of outcomes, treatment abandonment is not reported consistently across clinical studies in LMIC contexts (Gupta et al., 2013). The second-order chance nodes and subsequent pathways in this model were therefore created to ensure that the impact of treatment abandonment was captured in this model, and that this impact could be examined as an isolated variable.

The third-order chance nodes determine the proportion of the cohort that experiences Event-Free Survival (EFS), survival with events, and death following pediatric BL treatment. EFS has a heterogeneous definition across studies, but generally measures the proportion of a cohort that survives treatment without relapse or progression of disease. Event-free survival, as well the related statistic progression-free survival, are often used as proxies for overall survival in clinical studies (Zhu et al., 2020). Due to pediatric BL's low relapse rate after the first year, 1-year EFS is considered a reasonable indicator of long-term survival in pediatric BL (Molyneux et al., 2012). EFS was, therefore, included as an end-state in this model to represent long-term survival. The state "Survival with Events" was included to capture the proportion of the cohort who has experienced an event as described in the literature, and is not likely to survive long-term.

4.1.3 Fundamental Model Assumptions

As with any decision-analytic model, this decision tree model for pediatric BL in Ghana makes assumptions in order to represent the decision problem.

As the model starts with individuals with confirmed pediatric BL, it is assumed that the starting cohort has the disease. This means that the model does not account for the sensitivity or specificity of the diagnostic methods used. The model assumes that all in the cohort who abandon treatment die. This assumption is made because of the length of cycle combined with the speed of normal disease progression. This assumption is made in related literature examining the cost-effectiveness of pediatric BL or other childhood cancers (Denburg et al., 2019; Renner et al., 2018). As the model separates deaths from treatment abandonment from outcomes associated with the effectiveness of the treatment itself, the model assumes that abandonment is not included as an event in EFS. Care should be taken that the parameters for the third-order chance nodes are populated with effectiveness data that censors abandonment, or evaluates a cohort with minimal to no abandonment.

Part 2: The Economic Evaluation

The decision-analytic model described in Part 1 of this chapter was used to perform a preliminary economic evaluation of the treatment of pediatric BL in Ghana with an NHIS-funded treatment regimen compared to treatment with the regimen that is current practice in Ghana, which does not include NHIS reimbursement. As this decision-analytic model simulates outcomes for a single intervention, two identically structured decision tree models were created. One model was populated with parameters to simulate treatment with current practice in Ghana, and one model was populated with

parameters to simulate treatment with an NHIS-funded treatment regimen. The outcomes for these two models were then compared in order to produce an outcome in the form of incremental cost per DALY averted. Additionally, deterministic and probabilistic sensitivity analyses were performed.

According to the literature reviews performed for this thesis, this study constitutes the first cost-effectiveness analysis of pediatric BL in a Ghanaian context, and the first cost-effectiveness analysis of pediatric BL in a SSA context to utilize a decision-analytic model. This part of the chapter outlines the research methods utilized to carry out the second objective of this thesis seen in section 1.1 and fulfill the research aims seen in section 1.2.

4.2 Type of Economic Evaluation

The economic evaluation undertaken in this thesis constitutes a cost-effectiveness analysis according to the WHO-CHOICE definition, and a cost-utility analysis according to the definition from Drummond et al. (2015), as the evaluation measures costs in monetary units and outcomes in the HRQoL-adjusted measure of DALYs (Drummond et al., 2015; Tan-Torres Edejer et al., 2003). The economic evaluation will be referred to as a cost-effectiveness analysis in the remainder of this thesis, as the cost-utility analysis is considered to be a type of cost-effectiveness analysis, and the terms are commonly used interchangeably (Drummond et al., 2015).

4.3 Methods Utilized for the Preliminary Cost-Effectiveness Analysis

4.3.1 Study Population and Setting

The population considered in this study was a hypothetical cohort of patients with confirmed pediatric BL in Ghana, receiving either the treatment regimen that is current practice in Ghana, which does not include NHIS coverage, or treatment with an NHIS-funded treatment regimen. The cohorts include only individuals receiving treatment at the two pediatric cancer units located in Ghanaian public hospitals; the pediatric cancer unit at Korle-Bu Teaching Hospital (KBTH) and the pediatric cancer unit at Komfo Anokye Teaching Hospital (KATH). The number of children in the starting cohorts were calculated based on the expected total number of children to receive pediatric BL treatment at KBTH or KATH in a given year. Due to the restrictions of the model, the cohort was assumed to be the same age, calculated by the average age at start of treatment for pediatric BL patients at KBTH and KATH.

4.3.2 Intervention and Comparator

Intervention

The intervention being evaluated against the comparator in this preliminary economic evaluation is a pediatric BL treatment regimen with NHIS coverage. In order to be considered for NHIS coverage, a treatment program can only include drugs included on the Ghana National Essential Medicines List (NEML) (Boateng et al., 2020). The current treatment regimen used at KBTH, the only Ghanaian pediatric BL treatment regimen publicly available, utilizes the drug Cytarabine. Cytarabine is not listed on the NEML (Ministry of Health of Ghana, 2017; Offor et al., 2018). Because of this, the treatment regimen that would be brought into use should pediatric BL be included in NHIS coverage is not clear. Therefore, in order to determine an acceptable comparator for the purposes of this study, a literature search was performed for review articles and systematic review articles for pediatric BL treatments in areas where pediatric BL is endemic. A systematic review for chemotherapy treatments for BL performed by Rocca et al. (2021) was discovered through this literature search. This systematic review identified the Malawi 2012-2014 Protocol as the most promising treatment protocol for pediatric BL in countries with endemic BL (Rocca et al., 2021). Additionally, this treatment protocol includes only drugs which are listed on the National Essential Medicines List. Because the intervention was identified as the most promising treatment for endemic BL through a systematic review, and because the intervention only includes drugs listed on the National Essential Medicines List, the intervention for this study was chosen to be a hypothetical treatment regimen according to the Malawi 2012-2014 Protocol with NHIS coverage. The details of a treatment regimen following the Malawi 2012-2014 Protocol can be seen in table 4.1.

Table 4.1: *This table presents the Malawi 2012-2014 protocol for the treatment of pediatric Burkitt's Lymphoma. This table is adapted using information from Molyneux et al. (2017).*

Tumor Stage	Course of Treatment
Stages I & II	- Cyclophosphamide 40 mg/kg (max, 1.6 g) IV; days 1, 15, 28 - Cyclophosphamide 60 mg/kg (max, 2.4 g) IV; day 8 - Vincristine 1.5 mg/m2 (max, 2 mg) IV; days 1, 8, 15, 28 - Prednisone 60 mg/m2 by mouth; days 1-5 - Methotrexate 12.5 mg IT; day 1, 8, 15, 28
Stages III & IV	Same treatment as the protocol for Stages I & II, with the addition of the following: - Doxorubicin 60 mg/m2 IV; days 15, 28

Comparator

The comparator for this study is the regimen considered to be current treatment practice for pediatric BL in Ghana. As the treatment regimen used in KBTH is the only regimen publicly available, this treatment regimen is considered to be the comparator for this study. This intervention is referred to as "treatment with the Current Practice

in Ghana protocol" for the purposes of this study. The treatment regimen does not include NHIS coverage, so families must pay out-of-pocket for treatment-related expenses. The treatment regimen utilized is a protocol that uses low-intensity Cyclophosphamide monotherapy for Stage I and II disease and higher-intensity therapy with anthracyclines for Stage III and IV disease (Offor et al., 2018). The details of the treatment regimen for the Current Practice in Ghana protocol can be seen in Table 2.2.

4.3.3 Outcome measure

The primary effect measure in this study is the DALY. The YLL portion of the DALY was calculated by subtracting the age at death from the life expectancy in Ghana. Because all individuals are assumed to be the same age, this value is multiplied by the number of individuals in a death state. The YLD portion of the DALY was calculated by multiplying the number of individuals in a non-death state by the disability weight associated with the treatment received and the assumed treatment length. Treatment length was assumed to be 1 year in this study. A more in depth explanation of the methods used for DALY calculation can be seen in Appendix A.

The primary outcome measure used in this thesis is the ICER, expressed in terms of the incremental cost per DALY averted for the intervention compared to the comparator. The ICER was calculated using the costs and effects derived from the decision tree decision-analytic model. In addition to these deterministic outcomes from the base-case analysis, sensitivity analyses are presented in order to explore the effect of uncertainty in this study.

Determining Cost-effectiveness

The cost-effectiveness of NHIS-funded treatment with the Malawi 2012-2014 Protocol compared to treatment with the Current Practice in Ghana protocol will be determined according to the WHO-CHOICE methodology. This methodology for the determination of cost-effectiveness is commonly used in cost-effectiveness analyses in LMIC contexts. For example, all of the cost-effectiveness analyses of existing related research that were examined in section 2.6 of this thesis utilize this methodology. In studies utilizing WHO-CHOICE cost-effectiveness thresholds, interventions are said to be "cost-effective" if the incremental cost per DALY averted is less than or equal to three times the GDP per capita of the country of the intervention being evaluated. They are "very cost-effective" if the incremental cost per DALY averted is less than or equal to one times the GDP per capita of the country of the intervention being evaluated (Tan-Torres Edejer et al., 2003). The most recent estimate of the GDP per capita of Ghana from the World Bank is from 2019, where the GDP per capita was estimated to be $2202 (World Bank, 2019a). Therefore, this thesis considered NHIS-funded Treatment with the Malawi 2012-2014 Protocol to be cost-effective if the incremental cost per DALY averted is less than $6606, and very cost-effective if the incremental cost per DALY averted is less than $2202.

4.3.4 Calculation and Discounting of DALYs

DALYs in this study were calculated using the method presented in in Larson (2013). This methodology allowed for a seamless integration of DALY calculation into an Excel model utilizing discrete time (Larson, 2013). The model in this thesis constitutes such a model. This is in contrast to the established method to calculate DALYs using continuous time presented in Fox-Rushby and Hanson (2001), involving complex formulas that are difficult to integrate in models such as the one utilized in this study. This study also adapts the method presented by Larson for discounting future DALYs to their present values (Larson, 2013). This study did not utilize age-weighting when calculating DALYs. These methods for DALY calculation and discounting can be seen in more detail in Appendix A.

4.3.5 Time Horizon

The decision-analytic model simulated outcomes 1 year after initial treatment, with Event-free survival as the primary indication of treatment efficacy. This measure is considered a reasonable indicator of long-term survival in pediatric BL (Molyneux et al., 2012).

4.3.6 Study Perspective

This study adopted a healthcare payer perspective, with only costs incurred by the governmental payers of healthcare being factored into the model. Treatment with the Current Practice in Ghana regimen was therefore not calculated to have any per-patient treatment costs, as this treatment is not covered by the NHIS.

4.4 Model Parameters

In order to simulate the real-world situation as closely as possible, model parameters were populated with data from a Ghanaian context where possible. In situations where Ghanaian data was not available, data was taken from similar contexts. This section details the parameters used in the model and the methods used to derive those parameters, when applicable.

4.4.1 Assumptions and Starting Points

To implement this study, assumptions and starting points were derived from relevant literature sources. The sizes of the starting cohorts for both the intervention and the comparator, the starting age of the cohorts, and the life expectancy at birth were all able to be derived through Ghana-specific sources. All assumption and starting point parameters can be seen in Table 4.2.

The size of the cohorts for this study was calculated by adding the average number of pediatric BL patients per year at KBTH with the average number of pediatric BL patients per year at KATH. The data for KBTH was derived from a study by Offor et al. (2018), and the data for KATH was derived from a study by Paintsil et al. (2015).

Table 4.2: *This table shows the description, value, and source for the assumption and starting point parameters used to populate the decision-analytic model in this study.*

Parameter Description	Parameter Value	Parameter Source
Starting cohort size, intervention	70	Tan-Torres Edejer et al. (2003)
Starting cohort size, comparator	70	Tan-Torres Edejer et al. (2003)
Starting age	6.9 years	Offor et al. (2018), Paintsil et al. (2015)
Life expectancy at birth, Ghana	64.1 years	World Bank (2019b)
GDP per Capita, Ghana	$2,202	World Bank (2019a)

The study from Offor et al. (2018) observed 173 pediatric BL patients over a 6 year span, indicating an average of 28 patients per year. The study from Paintsil et al. (2015) observed 126 pediatric BL patients over a 3 year span, indicating an average of 42 pediatric BL patients per year. This led to this study assuming a cohort size of 70 patients per year. The addition of NHIS coverage in the intervention was assumed to not affect the cohort size.

The starting age of the cohort was derived from Offor et al. (2018), where the average age at diagnosis of pediatric BL patients at KBTH was shown to be 6.9 years old.

Life expectancy at birth for Ghana was used in the calculation of the YLL aspect of the DALY outcome. The value for life expectancy at birth used in this study is 64.1 years, as reported by the World Bank (World Bank, 2019b).

4.4.2 Discount Rates

The discount rate used in order to convert future values to present values for both costs and effects is 3%, seen in table 4.3. This rate was chosen in accordance with the WHO-CHOICE methodology for cost-effectiveness analysis (Tan-Torres Edejer et al., 2003). The sensitivity of the results to discount rate were in the deterministic sensitivity analyses.

Table 4.3: *This table shows the description, value, and source for the discount rate parameters used to populate the decision-analytic model in this study.*

Parameter Description	Parameter Value	Parameter Source
Discount rate, costs	0.03	Tan-Torres Edejer et al. (2003)
Discount rate, effeccts	0.03	Tan-Torres Edejer et al. (2003)

4.4.3 Chance Node Probabilities

Probabilities for the first-, second- and third-order chance nodes, described in Part 1 of this chapter, were populated using a combination of Ghana-specific sources and sources from similar settings. The values and sources used for all chance node probability parameters for the "Treatment with the Malawi 2012-2014 Protocol" treatment arm can be

seen in Table 4.4. The values and sources used for all chance node probability parameters for the "Current Practice in Ghana" treatment arm can be seen in table 4.5.

Table 4.4: *This table shows the description, value, and sources for the chance node probability parameters used to populate the "Treatment with the Malawi 2012-2014 Protocol" treatment arm of the decision-analytic model in this study.*

Parameter Description	**Parameter Value**	**Parameter Source**
Probability of being diagnosed with Stage I pediatric BL	0.0578	Offor et al. (2018)
Probability of being diagnosed with Stage II pediatric BL	0.0578	Offor et al. (2018)
Probability of being diagnosed with Stage III pediatric BL	0.4451	Offor et al. (2018)
Probability of being diagnosed with Stage IV pediatric BL	0.4393	Offor et al. (2018)
Probability of abandoning treatment	0.2554	Offor et al. (2018), Martijn et al. (2017)
Probability of completing treatment	0.7446	Offor et al. (2018), Martijn et al. (2017)
Probability of Event-free survival for Stage I pediatric BL	0.6875	Molyneux et al. (2017)
Probability of Survival with Events for Stage I pediatric BL	0.0625	Molyneux et al. (2017)
Probability of Death for Stage I pediatric BL	0.2500	Molyneux et al. (2017)
Probability of Event-free survival for Stage II pediatric BL	0.6875	Molyneux et al. (2017)
Probability of Survival with Events for Stage II pediatric BL	0.0625	Molyneux et al. (2017)
Probability of Death for Stage II pediatric BL	0.2500	Molyneux et al. (2017)
Probability of Event-free survival for Stage III pediatric BL	0.6667	Molyneux et al. (2017)
Probability of Survival with Events for Stage III pediatric BL	0.0476	Molyneux et al. (2017)
Probability of Death for Stage III pediatric BL	0.2857	Molyneux et al. (2017)
Probability of Event-free survival for Stage IV pediatric BL	0.6667	Molyneux et al. (2017)
Probability of Survival with Events for Stage IV pediatric BL	0.0476	Molyneux et al. (2017)
Probability of Death for Stage IV pediatric BL	0.2857	Molyneux et al. (2017)

First-order Chance Node

The first-order chance node in the decision-analytic model used for this study dictated the proportion of the cohort diagnosed with each stage of pediatric BL. These proportions were derived from a study from Offor et al. (2018), which examined patterns of pediatric BL patients at KBTH over a 6-year period. Because Offor et al. (2018) reported Stages I and II combined as "localized disease" and Stages III and IV combined as "advanced disease", this study assumes an equal distribution of patients in the combined stages rounded to the nearest individual. The proportions used for the first-order chance node were assumed to be equal in both the intervention and the comparator.

Table 4.5: *This table shows the description, value, and sources for the chance node probability parameters used to populate the "Current Practice" treatment arm of the decision-analytic model in this study.*

Parameter Description	**Parameter Value**	**Parameter Source**
Probability of being diagnosed with Stage I pediatric BL	0.0578	Offor et al. (2018)
Probability of being diagnosed with Stage II pediatric BL	0.0578	Offor et al. (2018)
Probability of being diagnosed with Stage III pediatric BL	0.4451	Offor et al. (2018)
Probability of being diagnosed with Stage IV pediatric BL	0.4393	Offor et al. (2018)
Probability of abandoning treatment	0.6821	Offor et al. (2018)
Probability of completing treatment	0.3179	Offor et al. (2018)
Probability of Event-free survival for Stage I pediatric BL	0.4211	Traoré et al. (2011)
Probability of Survival with Events for Stage I pediatric BL	0.2632	Traoré et al. (2011)
Probability of Death for Stage I pediatric BL	0.3158	Traoré et al. (2011)
Probability of Event-free survival for Stage II pediatric BL	0.4783	Traoré et al. (2011)
Probability of Survival with Events for Stage II pediatric BL	0.2174	Traoré et al. (2011)
Probability of Death for Stage II pediatric BL	0.3043	Traoré et al. (2011)
Probability of Event-free survival for Stage III pediatric BL	0.6667	Molyneux et al. (2017)
Probability of Survival with Events for Stage III pediatric BL	0.0476	Molyneux et al. (2017)
Probability of Death for Stage III pediatric BL	0.2857	Molyneux et al. (2017)
Probability of Event-free survival for Stage IV pediatric BL	0.6667	Molyneux et al. (2017)
Probability of Survival with Events for Stage IV pediatric BL	0.0476	Molyneux et al. (2017)
Probability of Death for Stage IV pediatric BL	0.2857	Molyneux et al. (2017)

Second-order Chance Nodes

The second-order chance nodes in the decision-analytic model used for this study dictated the proportion of the cohort that completed treatment and the proportion that abandoned treatment. This proportion is assumed to be equal across all stages for a given treatment. Health insurance coverage has been identified as a way to increase adherence and reduce treatment abandonment of pediatric cancer treatment in Ghana (Boateng et al., 2020). In other LMIC contexts, insurance coverage has been shown to increase treatment completion and decrease treatment abandonment (Martijn et al., 2017). This study, therefore, used different abandonment rates for the intervention, which includes NHIS coverage, and the comparator, which does not include NHIS coverage.

Treatment Completion and Abandonment without NHIS Coverage

The proportion of pediatric BL patients completing treatment with the Current Practice in Ghana protocol with no NHIS coverage was derived from a study by Offor et al. (2018), which examined patterns of pediatric BL patients at KBTH over a 6-year period. This study indicated that 118 of the 173 pediatric BL patients seen over that period were lost to follow-up. For the purposes of this thesis, "lost to follow-up" was assumed to be equivalent to treatment abandonment as it is defined in the decision-analytic model. Therefore, the probability of abandonment for treatment with the Current Practice in Ghana protocol used in this study was 68.2% (118/173) , and the probability of treatment completion used was 31.8% (55/173).

Treatment Completion and Abandonment with NHIS Coverage

Martijn et al. (2017) attempted to determine the influence of health insurance coverage status on pediatric Non-Hodgkin's Lymphoma treatment in Kenya. The study found that treatment abandonment was the most frequent outcome amongst uninsured patients, with 44% of uninsured patients abandoning treatment. Amongst those with health insurance, 5% abandoned treatment (Martijn et al., 2017). As this study was performed in a country in SSA where BL is endemic, and because BL is a type of Non-Hodgkin's Lymphoma, this study was used in estimating the effect of NHIS coverage on treatment abandonment in pediatric BL in Ghana.

Of the 67% of pediatric BL patients who were lost to follow-up in Offer et al, 75% were said to abandon treatment due to financial constraint (Offor et al., 2018). This implies that 51% of the total cohort of patients abandoned treatment due to financial constraint in Offor et al. (2018). This portion of patients was considered to be the group of patients for whom NHIS coverage would affect likelihood of treatment abandonment. In order to estimate the effect of NHIS coverage on pediatric BL treatment abandonment, an effect proportional to the effect seen in Martijn et al. (2017) was assumed with regard to the 51% of patients who abandoned due to financial constraint in Offor et al. (2018). Following this assumption, 5.1% of pediatric BL patients with health insurance coverage would abandon due to financial constraints. After adding the new portion of the cohort who abandon due to financial constraint with the portion of the cohort who abandon due

to non-financial reasons, the result is 22.5% of the cohort abandoning treatment when their treatment is covered by the NHIS. Therefore, the probability of abandonment for NHIS-funded treatment with the Malawi 2012-2014 Protocol was 22.5% , and the probability of treatment completion used was 77.5%. A more detailed explanation of the mathematics behind the method used to derive this parameter can be found in Appendix B.

Third-order Chance Nodes

The third-order chance nodes in the decision-analytic model used for this study dictated the proportion of the cohort that went into the end states "Event-Free Survival", "Survival with Events", and "Death". In other words, the third-order chance nodes were meant to capture the efficacy of the treatment. As there does not exist data for the effectiveness of pediatric BL treatment in a Ghanaian context, effectiveness data was adapted from other SSA contexts. All effectiveness data was taken from individual studies as opposed to the performing network-meta analyses, due to the lack of robust Randomized Control Trial data in the literature, as well as to ensure that parameter uncertainty was not underestimated via the uncertainty values associated with these parameters used in the PSA.

Treatment with the Malawi 2012-2014 Protocol

In order to populate the third-order chance nodes for the "Treatment with the Malawi 2012-2014 Protocol" treatment arm, effect data was implemented from a single study; a study performed in Malawi by Molyneux et al. (2017). The probability parameters derived for the "Treatment with the Malawi 2012-2014 Protocol" treatment arm are presented by disease stage in the following paragraphs. These parameters can also be seen in table 4.4.

After the 1-year horizon, those who completed treatment for Stage I pediatric BL with the Malawi 2012-2014 Protocol had a 68.8% chance to be in the "Event Free Survival" state, a 6.2% chance to be in the "Survival with Events" state, and a 25.0% chance to be in the "Dead" state (Molyneux et al., 2017).

Those who completed treatment for Stage II pediatric BL with the Malawi 2012-2014 Protocol had a 68.8% chance to be in the "Event Free Survival" state, a 6.2% chance to be in the "Survival with Events" state, and a 25.0% chance to be in the "Dead" state (Molyneux et al., 2017).

Those who completed treatment for Stage III pediatric BL with the Malawi 2012-2014 Protocol had a 66.7% chance to be in the "Event Free Survival" state, a 4.8% chance to be in the "Survival with Events" state, and a 29.0% chance to be in the "Dead" state (Molyneux et al., 2017).

Those who completed treatment for Stage IV pediatric BL with the Malawi 2012-2014 Protocol had a 66.7% chance to be in the "Event Free Survival" state, a 4.8% chance to be in the "Survival with Events" state, and a 29.0% chance to be in the "Dead" state (Molyneux et al., 2017).

Treatment with Current Practice Protocol in Ghana

The Current Practice in Ghana protocol does not follow a "named" protocol, such as the Malawi 2012-2014 protocol or the "CHOP" protocol. Therefore, in order to populate the third-order chance nodes for the "current practice in Ghana" treatment arm, treatment with the Current Practice in Ghana protocol for each stage of BL was categorized based on the categories of treatment intensity presented in the study by Gopal and Gross (2018), as discussed in section 2.4. The most relevant clinical study performed in a SSA context for the effectiveness of a pediatric BL treatment of the same intensity classification was then identified via review articles or manual literature searches. The parameters for the third-order chance nodes were then populated with data from the sources identified via this method. The treatment strategies used for each disease stage with the Current Practice in Ghana protocol can be seen in table 2.2.

Treatment for Stages I and II pediatric BL is identical under treatment with the Current Practice in Ghana protocol. The treatment uses Cyclophosphomade monotherapy, and is classified as "Low-Intensity" treatment according to Gopal and Gross (2018). The literature search identified the study of the effectiveness of Cyclophosphamide Monotherapy in children With Burkitt Lymphoma from the French–African Pediatric Oncology Group over several countries as the most relevant clinical study performed in a SSA context (Traoré et al., 2011).

While treatment for Stages III and IV pediatric BL is not identical between the stages, they are classified in the same category of treatment according to Gopal and Gross. Stage III and IV treatment with the Current practice protocol is classified as "Anthracycline-based treatment" (Gopal & Gross, 2018). The literature search identified a study by Molyneux et al in Malawi utilizing the Malawi 2012-2014 protocol as the most relevant clinical study performed in a SSA context (Molyneux et al., 2017).

The probability parameters derived for the "Current Practice" treatment arm using the above methods are presented by disease stage in the following paragraphs. These parameters can also be seen in table 4.5.

After the 1 year horizon, those who completed treatment for Stage I pediatric BL with the Current Practice in Ghana Protocol had a 42.1% chance to be in the "Event Free Survival" state, a 26.3% chance to be in the "Survival with Events" state, and a 31.6% chance to be in the "Dead" state (Traoré et al., 2011).

Those who completed treatment for Stage II pediatric BL with the Current Practice in Ghana Protocol had a 47.8% chance to be in the "Event Free Survival" state, a 21.7% chance to be in the "Survival with Events" state, and a 30.4% chance to be in the "Dead" state (Traoré et al., 2011).

Those who completed treatment for Stage III pediatric BL with the Current Practice in Ghana Protocol had a 66.7% chance to be in the "Event Free Survival" state, a 4.8% chance to be in the "Survival with Events" state, and a 29.0% chance to be in the "Dead" state (Molyneux et al., 2017).

Those who completed treatment for Stage IV pediatric BL with the Current Practice in Ghana Protocol had a 66.7% chance to be in the "Event Free Survival" state, a 4.8%

chance to be in the "Survival with Events" state, and a 29.0% chance to be in the "Dead" state (Molyneux et al., 2017).

4.4.4 Disability Weights

In order to calculate the YLD portion of the DALY outcomes for the given interventions, disability weights were assigned to the model's end node states. The disability weights used in this thesis were derived from the most recent Global Burden of Disease (GBD) Study. This study provides disability weights for diagnosis and primary treatment of cancer, as well as disability weights for metastatic cancer. For Stage I and Stage II pediatric BL, this study used the disability weight of 0.288, which is the disability weight used in the GBD study for diagnosis and primary treatment of cancer. For Stage III and Stage IV pediatric BL, this study used the disability weight of 0.451 which is the disability weight used in the GBD study for metastatic cancer (Salomon et al., 2015). These disability weights can also be seen in Table 4.6.

Table 4.6: *This table shows the description, value, and source for the assumption and disability weight parameters used to populate the decision-analytic model in this study.*

Parameter Description	**Parameter Value**	**Parameter Source**
Disability Weight for patients having received treatment for Stage I BL	0.288	Salomon et al. (2015)
Disability Weight for patients having received treatment for Stage II BL	0.288	Salomon et al. (2015)
Disability Weight for patients having received treatment for Stage III BL	0.451	Salomon et al. (2015)
Disability Weight for patients having received treatment for Stage IV BL	0.451	Salomon et al. (2015)

4.4.5 Costs

As this study was conducted from a healthcare payer perspective, only costs incurred by the governmental payers of healthcare were considered. Two types of costs were considered in this study: fixed costs and variable costs. The values and sources used for all cost parameters for the "Treatment with the Malawi 2012-2014 Protocol" treatment arm can be seen in Table 4.7. The values and sources used for all cost parameters for the "Current Practice" treatment arm can be seen in Table 4.8. All monetary sources of costs in this study present the cost data in US dollars. This currency was therefore used throughout the study.

Fixed Costs

Fixed costs in this study were defined as the costs associated with the operation of the pediatric oncology units at KBTH and KATH over the 1-year time horizon of the study. These costs were assumed not to vary with the size of the cohort. These costs were assumed to be the same across both interventions. The factors included in the calculation of the fixed costs were: medical personnel costs, nonmedical personnel costs,

Table 4.7: *This table shows the description, value, and sources for the cost parameters used to populate the "NHIS-funded treatment with the Malawi 2012-2014 regimen" treatment arm of the decision-analytic model in this study.*

Parameter Description	**Parameter Value**	**Parameter Source**
Fixed Costs (Overhead Costs)	$689,853	Renner et al (2018)
Cost of Stage I pediatric BL treatment, given treatment abandonment	$1,719	Boateng et al. (2020), Molyneux et al. (2017)
Cost of Stage II pediatric BL treatment, given treatment abandonment	$1,719	Boateng et al. (2020), Molyneux et al. (2017)
Cost of Stage III pediatric BL treatment, given treatment abandonment	$1,759	Boateng et al. (2020), Molyneux et al. (2017)
Cost of Stage IV pediatric BL treatment, given treatment abandonment	$1,759	Boateng et al. (2020), Molyneux et al. (2017)
Cost of Stage I pediatric BL treatment, given treatment completion	$2,828	Boateng et al. (2020), Molyneux et al. (2017)
Cost of Stage II pediatric BL treatment, given treatment completion	$2,828	Boateng et al. (2020), Molyneux et al. (2017)
Cost of Stage III pediatric BL treatment, given treatment completion	$2,869	Boateng et al. (2020), Molyneux et al. (2017)
Cost of Stage IV pediatric BL treatment, given treatment completion	$2,869	Boateng et al. (2020), Molyneux et al. (2017)

Table 4.8: *This table shows the description, value, and sources for the cost parameters used to populate the "treatment with the Current Practice in Ghana protocol" treatment arm of the decision-analytic model in this study. In empty boxes in the parameter source column, no source was used as the assumed cost to the governmental payer is $0.*

Parameter Description	**Parameter Value**	**Parameter Source**
Fixed Costs (Overhead Costs)	$689,853	Renner et al (2018)
Cost of Stage I pediatric BL treatment, given treatment abandonment	$0	Assumption
Cost of Stage II pediatric BL treatment, given treatment abandonment	$0	Assumption
Cost of Stage III pediatric BL treatment, given treatment abandonment	$0	Assumption
Cost of Stage IV pediatric BL treatment, given treatment abandonment	$0	Assumption
Cost of Stage I pediatric BL treatment, given treatment completion	$0	Assumption
Cost of Stage II pediatric BL treatment, given treatment completion	$0	Assumption
Cost of Stage III pediatric BL treatment, given treatment completion	$0	Assumption
Cost of Stage IV pediatric BL treatment, given treatment completion	$0	Assumption

and administration and utilities costs. The main source of these costs for this study is a study by Renner et al. (2018), where the total costs of operating the pediatric cancer unit at KBTH are estimated.

The method for deriving the fixed cost data for pediatric BL treatment in Ghana from the cost of all pediatric cancer treatment were conceptually based on the calculation of fixed costs in the cost-effectiveness analysis of pediatric BL in Uganda in Denburg et al. (2019), where fixed costs were estimated based on the proportion of total resources in each of their fixed cost factors being used on pediatric BL (Denburg et al., 2019). Fixed costs for pediatric BL treatment in Ghana were estimated with a similar methodology for this study, where total fixed costs were obtained from study in Renner et al. (2018), and the proportion of those patients receiving pediatric BL treatment was derived from the studies in Offor et al. (2018), and Paintsil et al. (2015). Although the costs given in Renner et al. (2018) were the costs for all pediatric cancer in a year at KBTH, the costs for pediatric BL at KBTH were assumed to scale proportionally. As cost data for KATH was not available, these costs were assumed to be the same as the costs for KBTH, and were also assumed to scale proportionally to the costs in Renner et al. (2018). The fixed costs of treating pediatric BL in Ghana derived using this methodology was $689,853. The methodology and mathematics used in deriving the fixed costs can be seen in more detail in Appendix C.

Variable Costs

Variable costs in this study were defined as costs over the study time horizon that varied based on the number of patients treated, including direct costs of care and hoteling costs. As pediatric BL treatment varies by disease stage, the variable costs also varied according to stage.

As a consequence of this study taking a healthcare payer perspective and pediatric BL treatment currently not being included for reimbursement under Ghana's NHIS, the comparator, treatment with the Current Practice in Ghana protocol, was assumed to have $0 in variable costs.

The variable costs for the the intervention, treatment with the Malawi 2012-2014 Protocol, were broken down into the following categories: Pathology and laboratory costs, pharmacy costs, radiation costs, imaging costs, cost of blood services, and cost of hoteling patients. For all of these categories except for pharmacy costs, cost data was derived from Renner et al. (2018) following the same proportionality assumption as was used to derive the fixed costs. For pharmacy costs, the drugs expected to be used in a full course of the Malawi 2012-2014 protocol per person was derived. The total amount of drugs required was then compared to the current Ghanaian market price of the drugs as provided in Boateng et al. (2020). These pharmacy costs were added to the pathology and laboratory costs, radiation costs, imaging costs, cost of blood services, and hoteling costs to derive the cost per person of completing treatment for the intervention group. In treatment abandonment, the hoteling costs portion of variable costs per person were reduced by 50%. The methodology and mathematics used in deriving the variable costs can be seen in more detail in Appendix D.

4.5 Accounting for Uncertainty

4.5.1 One-Way Sensitivity Analyses

The structural uncertainty of the model was assessed through one-way deterministic sensitivity analyses. Such analyses were used in order to identify the individual parameters that have the most impact on the outcome within the model's current structure, as well as observe the impact on the outcome when key parameters were adjusted to extreme values.

One-Way Sensitivity Analysis of all Parameters

The first one-way sensitivity analysis performed in this study was performed on all parameters in the model in order to identify the individual parameters that had the most impact on the model's outcomes. To perform this analysis, all parameters in the model were adjusted individually to a minimum and maximum value, and the resulting change in ICER was recorded for each parameter. The ten parameters that had the largest impact on the outcomes were identified as having the most impact through this method. For all parameters values for which a minimum and maximum value was not presented in the literature, 85% and 115% of the base case values were used for the minimum and maximum values in the sensitivity analysis.

One-way Sensitivity Analyses of Individual Key Parameters

Further one-way sensitivity analyses were performed on key parameters identified within the most impacting parameters through the one-way sensitivity analysis on all parameters. The key parameters selected for examination in additional sensitivity analyses were parameters that had a notably higher impact than others, as well as parameters that are commonly examined individually in decision-analytic model-based cost-effectiveness analyses. The parameters identified as key parameters to be examined individually were: the discount rate of outcomes, probability of treatment abandonment for treatment with the Malawi 2012-2014 Protocol with NHIS reimbursement, fixed cost of treatment in treatment with the Malawi 2012-2014 Protocol with NHIS reimbursement, and fixed costs of treatment in treatment with Current Practice.

The discount rate of outcomes was varied from 0% to 6% in order to examine results when the somewhat controversial practice of discounting of health outcomes is not implemented, as well as when health outcomes are discounted more heavily than is recommended by WHO-CHOICE.

The probability of treatment abandonment for treatment with the Malawi 2012-2014 Protocol with NHIS reimbursement was varied from 0 to 0.65, in order to capture scenarios where the effect of NHIS reimbursement on abandonment is higher than predicted by the methodology used in this thesis, as well as scenarios where the effect of NHIS reimbursement on abandonment is negligible.

The fixed costs of treatment in treatment with Current Practice was varied from $0 to $800,000 in order to capture scenarios where there are no fixed costs incurred by the

governmental payers in Ghana, and scenarios where the actual fixed costs for treatment with the Current Practice in Ghana protocol are closer to the assumed max value of $793,331 seen in Appendix E.

The fixed costs of treatment in treatment with the Malawi 2012-2014 Protocol with NHIS reimbursement was varied from $600,000 to $1,000,000 in order to capture scenarios where fixed costs are higher for an NHIS funded treatment than assumed in the base-case analysis. This parameter was not varied to the same extreme low values as the fixed costs of treatment in treatment with Current Practice, as it would not be academically valid, from a governmental healthcare payer perspective, to assume a very-low fixed cost for NHIS funded treatment while keeping the fixed cost for non-NHIS funded treatment the same as in the base-case analysis.

4.5.2 Probabilistic Sensitivity Analysis

Uncertainty in the parameters used in the model was assessed through probabilistic sensitivity analysis. The parameters seen in tables 4.2-4.8 were assigned a relevant parameter distribution and appropriate uncertainty values were extracted from the literature or assumed. A Monte-Carlo simulation was then performed with 10,000 iterations, wherein each of these iterations randomly samples each of the parameters according to the assigned distribution and uncertainty. The resulting incremental results and ICERs were then recorded in order to analyse the effect of parameter uncertainty on the outcome.

Selection of Parameter Distributions

For binomial probability parameters, the beta distribution was assigned, as the beta distribution is constrained between 0 and 1 and the nature of the binomial data used to populate these parameters make the beta distribution the ideal candidate (Hunink et al., 2014). For multinomial probability parameters, the dirichlet distribution was assigned, due to it being the multivariate generalization of the beta distribution (Briggs et al., 2006). In this study, the Alpha statistic of the beta and dirichlet distributions were populated with the number observed in the given state, and the Beta statistic was populated with the total number of individuals observed minus the number observed in the given state. The distributions, alpha and beta values of each probability parameter can be seen in Appendix E.

For the disability weight parameters, the normal distribution was assumed. This distribution can be assumed for any type of parameter for use in PSA so long as they fit the requirements of the normal distribution (Briggs et al., 2006). This was done due to how the outputs were reported, as well as the nature of how the source study for the disability weights, the Global Burden of Disease 2013 study, was carried out. The study involved over 60,000 participants, and presents disability weights with a 95% confidence interval based on these individuals' preferences to the given health states. However, the study did not specify how many participants were asked about each individual health state. As the number of participants was unknown, but large, a normal distribution was determined to be the most suitable distribution for these parameters. The standard

deviation of the parameters was derived by converting the value of the 1.96 standard deviations from the mean associated with a 95% confidence interval into the value of 1 standard deviation from the mean. In scenarios where one side of the confidence interval had a longer distance from the mean than the other side of the confidence interval, the side that implied a higher confidence interval was used to calculate the standard deviation (Salomon et al., 2015). The ranges used in the PSA for the disability parameters can be seen in Appendix E.

For all cost parameters, a uniform distribution was assumed. When randomly sampling parameters from a uniform distribution, any parameter value is equally likely over a given range. For the cost parameters used in this thesis, the lower bound of this range was chosen to be 85% of the original value, and the upper bound was chosen to be 115% of the original value. The upper and lower bounds used in the cost parameters can be seen in Appendix E.

This distribution was selected in lieu of the commonly used gamma distribution because the gamma distribution is associated with a long right tail, implying sampling from individual-level cost data (Briggs et al., 2006). Because the cost parameters in this thesis were not derived from individual-level data, the more flexible uniform distribution was chosen to be the best fitting distribution for these parameters.

Chapter 5

Results

This chapter presents an overview of the outcomes resulting from this study. These outcomes were derived using the methods described in the Chapter 4.

5.1 Base-case Cost-Effectiveness Analysis

The decision-analytic model simulated the health outcomes of two cohorts of 70 pediatric Burkitt's Lymphoma patients, with one cohort receiving an NHIS-funded treatment with the Malawi 2012-2014 protocol and one cohort receiving treatment with the Current Practice in Ghana protocol. After the one year time horizon of the model, the number of individuals at each end-node for both cohorts was captured. Note that, even though cohort is measured in number of individuals, the results are presented in the unrounded proportion of the original 70 individuals, including decimals, in each cohort.

In the cohort of 70 individuals receiving the NHIS-funded treatment with the Malawi 2012-2014 protocol, 34.87 individuals were at an "Event-Free Survival" end-node, 2.57 individuals were at a "survival with events" end-node, and 32.55 individuals were at either a "Treatment Abandonment" end-node or a "Death" end-node, which were both considered death-states in this model. This corresponds to a simulated 1-year EFS of 50%, and a 1-Year overall survival of 53%

In the cohort receiving treatment with the Current Practice in Ghana protocol, 14.28 individuals were at an "Event-Free Survival" end-node, 1.56 individuals were at a "survival with events" end-node, and 54.17 individuals were at either a "Treatment Abandonment" end-node or a "Death" end-node. This corresponds to a simulated 1-year EFS of %20, and a 1-Year overall survival of 23%.

Using the information regarding the number of individuals at each end-node in the model, the total cost of treatment and DALYs per patient associated with both treatment strategies, as well as the incremental costs, incremental effects, and the ICER, were derived. The results from the base-case cost-effectiveness analysis can be seen in their entirety in table 5.1, with both discounted and undiscounted outcomes. NHIS-funded treatment with the Malawi 2012-2014 Protocol was more costly and resulted in fewer DALYs, with a cost of $11,836 per patient and 12.84 DALYs per patient, when discounting costs and effects. The treatment with the Current Practice in Ghana pro-

tocol resulted in lower costs and more DALYs per patient, with a cost of $9,568 per patient and 20.38 DALYs per patient, when discounting costs and effects. This led to NHIS-funded treatment with the Malawi 2012-2014 Protocol having an incremental cost of $2,268 and incremental effect of 7.54 DALYs averted. Based on this, the ICER in the base-case cost-effectiveness analysis was $301 per DALY averted. Based on the results of the base-case cost-effectiveness analysis, NHIS-funded treatment with the Malawi 2012-2014 Protocol is very cost-effective according to the WHO-CHOICE methodology for determining cost-effectiveness.

Table 5.1: *The discounted and undiscounted incremental costs and effects of the base-case cost-effectiveness analysis, as well as the discounted and undiscounted ICER.*

Discounted Results

Strategy	**Cost per patient**	**DALY per patient**
Current Practice	$9,568	20.38
NHIS-funded treatment with Malawi 2012-2014 protocol	$11,836	12.84

ICER: $301 per DALY averted

Undiscounted Results

Strategy	**Cost per patient**	**DALY per patient**
Current Practice	$9,855	43.56
NHIS-funded treatment with Malawi 2012-2014 protocol	$12,191	26.79

ICER: $139 per DALY averted

5.2 Sensitivity Analyses

5.2.1 One-Way Sensitivity Analyses

One-Way Sensitivity Analysis of all Model Parameters

In the one-way sensitivity analysis of all model parameters, the effect of change in individual parameters on the ICER was examined in order to identify the parameters that had the largest impact on the cost-effectiveness of pediatric BL treatment in Ghana. The ten parameters that were identified to have the most impact on the ICER when varied, as well as the ICER values resulting from the minimum analysed value (Pmin) and the maximum analysed value (Pmax), can be seen in the Tornado Diagram presented in figure 5.1. The model parameters identified as the ten parameters with the most impact on the ICER in order of most to least impacting were: fixed cost of treatment in treatment with the Malawi 2012-2014 Protocol with NHIS reimbursement, fixed costs of treatment in treatment with the Current Practice in Ghana protocol, probability of treatment abandonment in treatment with the Current Practice in Ghana protocol, probability of Event-Free Survival for Stage III BL treatment with the Malawi 2012-2014 Protocol with NHIS reimbursement, probability of Event-Free Survival for Stage IV BL treatment with the Malawi 2012-2014 Protocol with NHIS reimbursement, discount rate

of outcomes, probability of treatment abandonment in treatment with the Malawi 2012-2014 Protocol with NHIS reimbursement, variable cost of Stage III/IV treatment with NHIS reimbursement with treatment completion, variable cost of Stage III/IV treatment with NHIS reimbursement with treatment abandonment, and probability of death for Stage III BL treatment with the Malawi 2012-2014 Protocol with NHIS reimbursement.

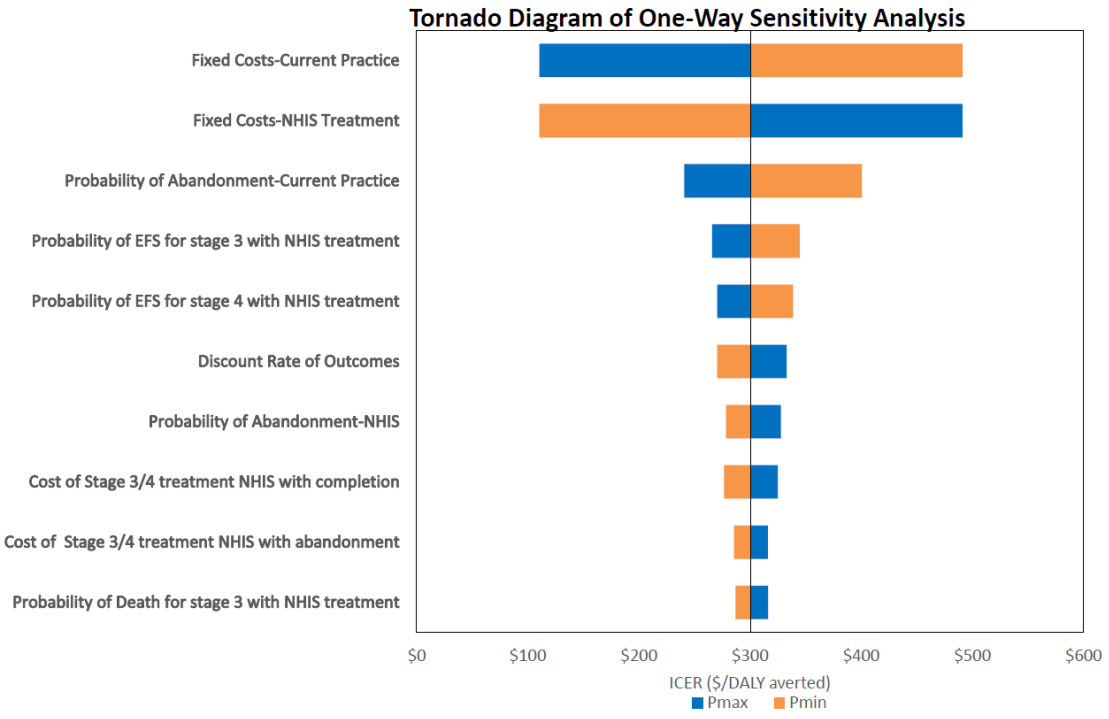

Figure 5.1: *This Tornado Diagram shows the results of the one-way sensitivity analysis of all model parameters. The ten parameters that were determined to have the most impact on the the ICER were identified, and are presented in this figure. The ICER values shown in the blue bars represent the ICER when the given parameter was adjusted to the maximum analysed value (Pmax), and the ICER values shown in the blue bars represent the ICER when the given parameter was adjusted to the minimum analysed value (Pmin).*

One-way Sensitivity Analyses of Individual, Key Parameters

In the one-way sensitivity analyses of individual key parameters, parameters of interest were varied in order to observe sensitivity of the ICER to change in that variable.

In figure 5.2, the sensitivity of the ICER to discount rate is shown. The ICER increased with discount rate, with an ICER of $135/DALY averted when the discount rate was 0, and an ICER of $551/DALY averted when the discount rate was 6%. NHIS-funded treatment with the Malawi 2012-2014 protocol was found to be very cost-effective in all examined scenarios.

In figure 5.3, the sensitivity of the ICER to probability of treatment abandonment of NHIS-funded treatment with the Malawi 2012-2014 Protocol is shown. As can be seen in the figure, the ICER is not particularly sensitive to changes in treatment abandonment at probabilities between 0 and 0.5, with the ICER increased from $201 per DALY averted to $693 per DALY averted over this range. However, as the probabil-

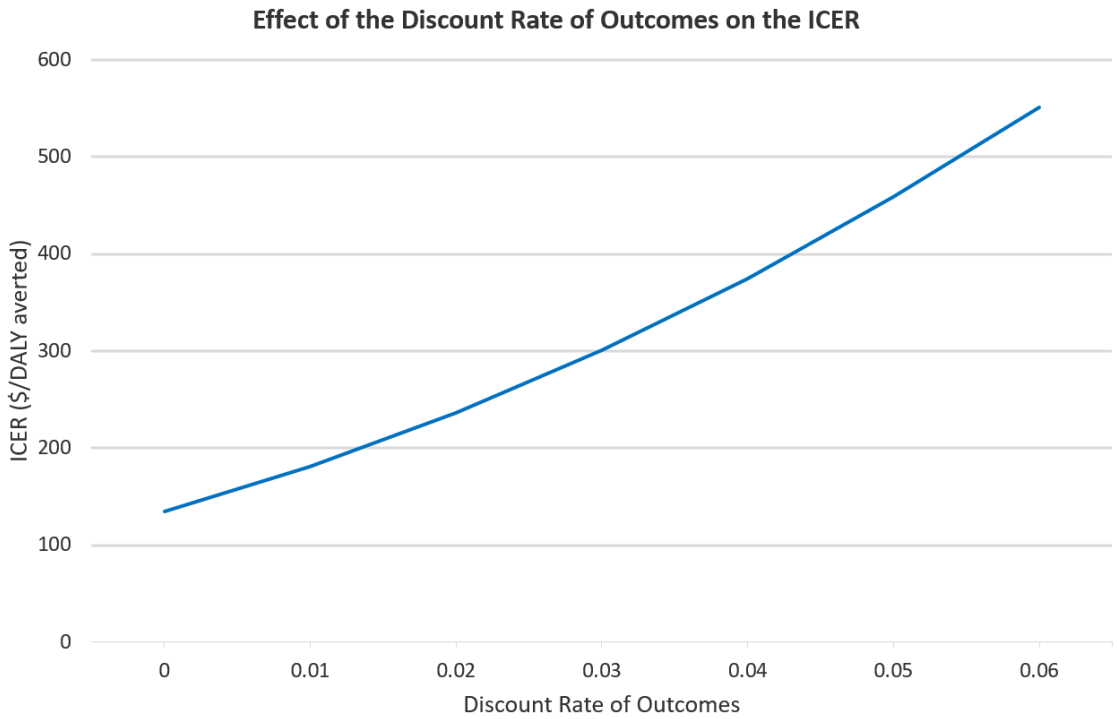

Figure 5.2: *This figure shows the effect of varying the Discount Rate of Outcomes on the Incremental Cost-Effectiveness Ratio of NHIS-funded Treatment with the Malawi 2012-2014 Protocol compared to treatment with the Current Practice in Ghana protocol.*

ity of treatment abandonment of NHIS-funded treatment with the Malawi 2012-2014 protocol nears the probability of treatment abandonment of treatment with Current Practice in Ghana protocol, the ICER increases sharply. Between abandonment probabilities of 0.5 and 0.65, the ICER increasing from $693 per DALY averted to $8373 per DALY averted. NHIS-funded treatment with the Malawi 2012-2014 protocol was found to be very cost-effective in scenarios with a proportion of treatment abandonment up to 0.61. In scenarios with a proportion of treatment abandonment between 0.62 and 0.64, NHIS-funded treatment with the Malawi 2012-2014 protocol was found to be cost-effective. NHIS-funded treatment with the Malawi 2012-2014 protocol was not found to be cost-effective with proportions of treatment abandonment at and above 0.65.

In figure 5.4, the sensitivity of the ICER to the fixed costs of treatment with the "Current Practice in Ghana protocol" parameter is shown. The figure shows a direct negative relationship between fixed costs associated with treatment with the Current Practice in Ghana protocol and the ICER, with the ICER being the highest at a fixed cost of $0 per year and the lowest at a fixed cost of $800,000 per year. Notably, even with no fixed costs for treatment with the Current Practice in Ghana protocol, NHIS funded treatment with the Malawi 2012-2014 protocol was still found to be very cost effective, having an ICER of $1570 per DALY averted.

In figure 5.5, the sensitivity of the ICER to the fixed costs of NHIS-funded treatment with the Malawi 2012-2014 Protocol parameter is shown. The figure shows a direct positive relationship between fixed costs associated with treatment with the Current Practice in Ghana protocol and the ICER, with the ICER being the lowest at a fixed cost of $600,000 per year and the highest at a fixed cost of $1,000,000 per year. NHIS-

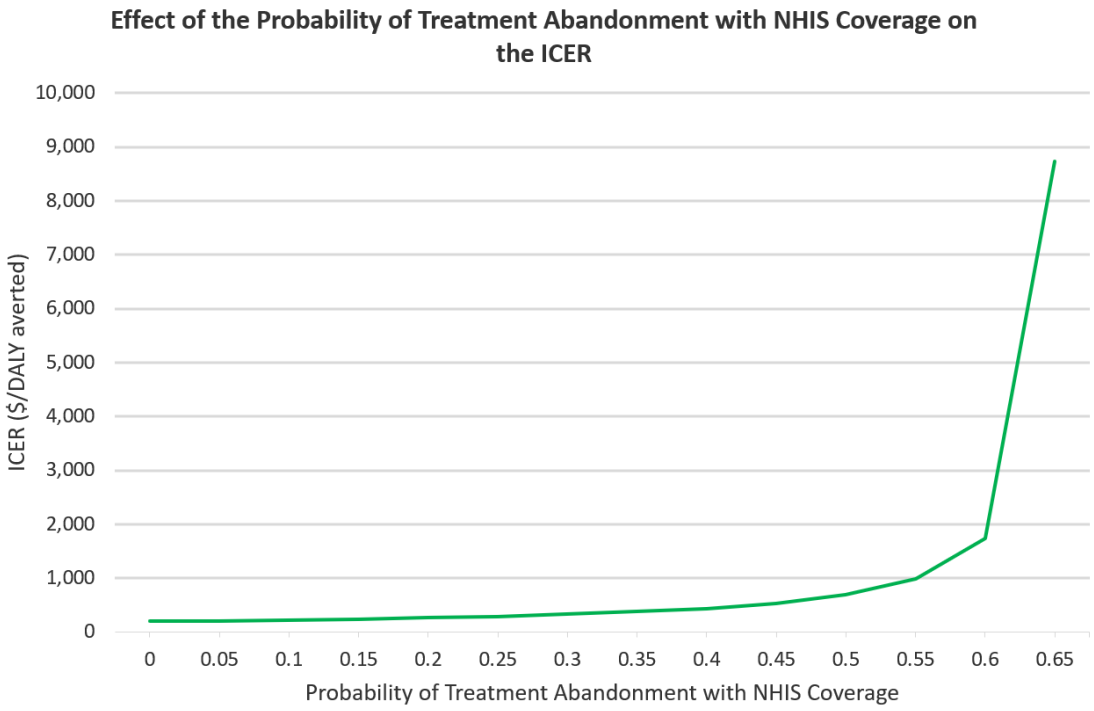

Figure 5.3: *This figure shows the effect of varying the probability of treatment abandonment for NHIS-funded Treatment with the Malawi 2012-2014 Protocol on the Incremental Cost-Effectiveness Ratio of NHIS-funded Treatment with the Malawi 2012-2014 Protocol compared to treatment with the Current Practice in Ghana protocol.*

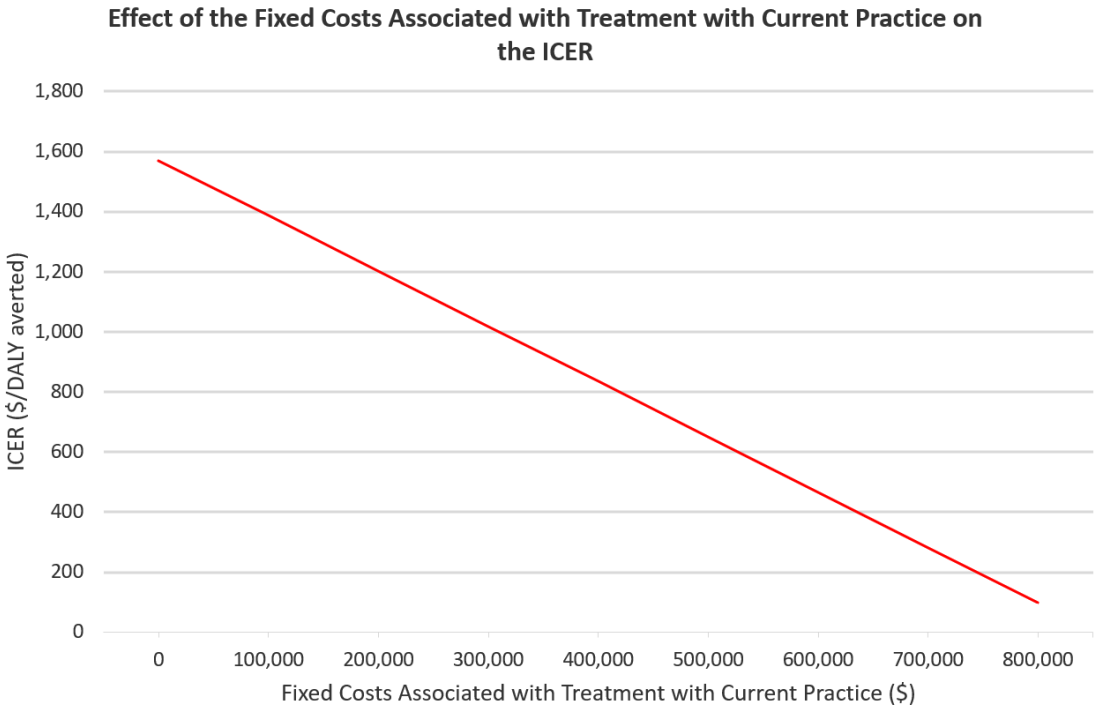

Figure 5.4: *This figure shows the effect of fixed costs for Treatment with Current Practice on the Incremental Cost-Effectiveness Ratio of NHIS-funded Treatment with the Malawi 2012-2014 Protocol compared to the Current Practice in Ghana protocol.*

funded treatment with the Malawi 2012-2014 protocol was found to be very cost-effective in all examined scenarios.

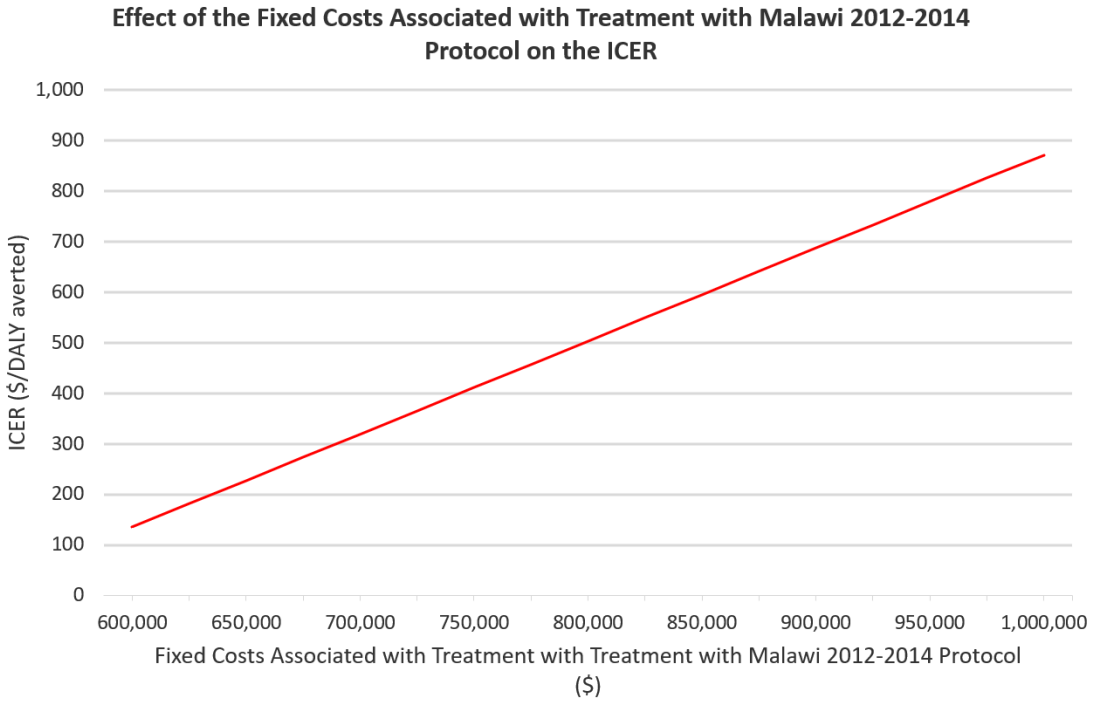

Figure 5.5: *This figure shows the effect of fixed costs for NHIS-funded treatment with the Malawi 2012-2014 Protocol on the Incremental Cost-Effectiveness Ratio of NHIS-funded Treatment with the Malawi 2012-2014 Protocol compared to the Current Practice in Ghana protocol. Note the break in scale along the X axis.*

5.2.2 Probabilistic Sensitivity Analysis

The PSA included 10,000 Monte Carlo simulations of outcomes of the decision-analytic model. The results of these simulations are summarized in tables 5.2 and 5.3, which present the summary statistics of these simulations.

As can be seen in table 5.2, all summary statistics for costs were higher for NHIS-funded treatment with the Malawi 2012-2014 protocol than treatment with the Current Practice in Ghana protocol. The variance in costs for the two treatment strategies was similar, with treatment with the Current Practice in Ghana protocol in Ghana having a standard deviation of $832 per patient, and NHIS-funded treatment with the Malawi 2012-2014 protocol having a standard deviation of $845 per patient.

As can be seen in table 5.3, the mean number of DALYs incurred after the 1-year study horizon was higher for treatment with the Current Practice in Ghana protocol in Ghana when compared to NHIS-funded treatment with the Malawi 2012-2014 protocol. The variance in DALYs incurred throughout the study horizon was not the same across the two treatments, with treatment with the Current Practice in Ghana protocol in Ghana having a standard deviation of 0.65 DALYs incurred per patient, and NHIS-funded treatment with the Malawi 2012-2014 protocol having a standard deviation of 2.27 DALYs incurred per patient. This difference in variance in the number of DALYs incurred can also be seen in the size of the difference between min and max values and

the difference between 2.5th percentile and 97.5th percentile values, with this difference being larger for the NHIS-funded treatment with the Malawi 2012-2014 protocol in all scenarios.

Table 5.2: *Summary statistics for the cost per individual ($) for both treatment strategies in the 10,000 Monte Carlo simulations of the PSA.*

	Current Practice	**Intervention**
Mean	9,551	11,842
Min	8,135	10,025
Max	11,003	13,651
St.dev.	832	845
2.5th percentile	8,199	10,446
97.5th percentile	10,932	13,233

Table 5.3: *Summary statistics for the DALYs incurred per individual for both treatment strategies in the 10,000 Monte Carlo simulations of the PSA.*

	Current Practice	**Intervention**
Mean	20.37	12.86
Min	18.18	5.52
Max	22.69	23.16
St.dev.	0.65	2.27
2.5th percentile	19.08	8.64
97.5th percentile	21.63	17.45

The incremental outcomes of all 10,000 simulations are plotted in figure 5.6, with incremental effects on the X axis and incremental costs on the Y axis. The black line that can also be seen in the figure represents an ICER of $2,202/DALY averted, which is the WHO-CHOICE threshold for NHIS-funded treatment with the Malawi 2012-2014 Protocol to be considered very cost-effective. 99.65% of the PSA simulations fell below this threshold.

Cost-Effectiveness Acceptability Curve

Figure 5.7 shows the Cost-Effectiveness Acceptability Curve (CEAC) generated from the results of the PSA simulations. This figure shows the likelihood of a treatment being recommended at a given willingness-to-pay per DALY-averted threshold, given the results of the PSA. At Willingness to Pay (WTP) thresholds of up to $300 per DALY averted, treatment with the Current Practice in Ghana protocol was more likely to be the preferred treatment. At WTP thresholds of $310 and above, NHIS-funded treatment with the Malawi 2012-2014 Protocol was more likely to be the preferred treatment.

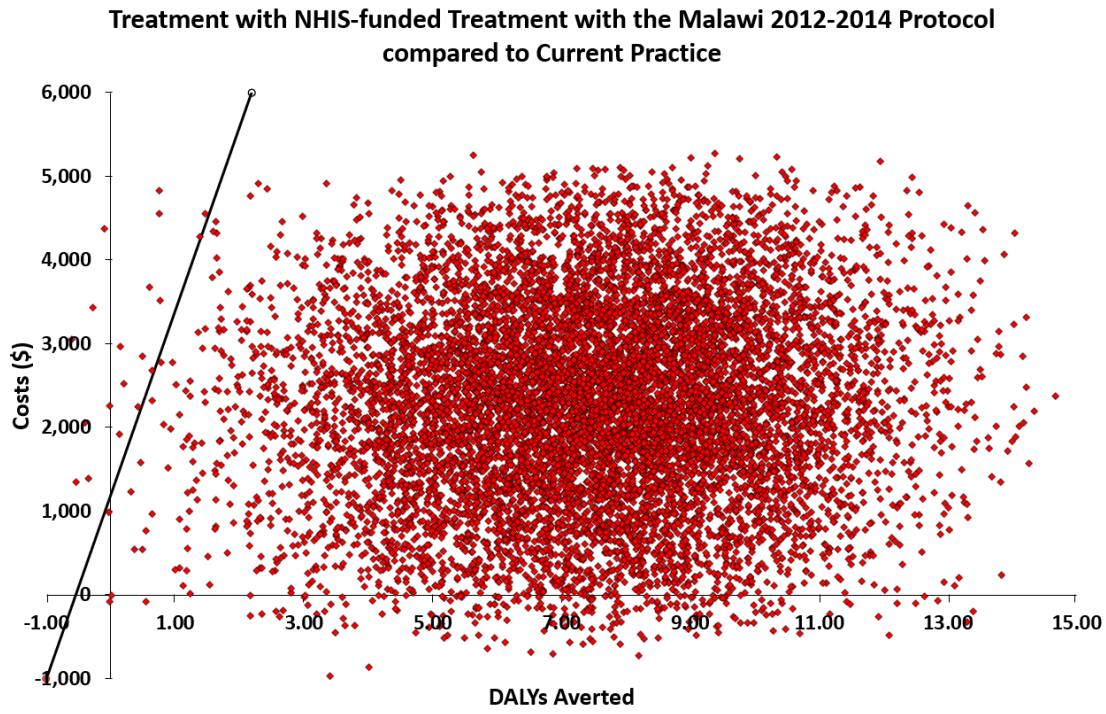

Figure 5.6: *This figure shows the incremental cost and effect results for the 10000 Monte Carlo simulation for the PSA of NHIS-funded treatment with the Malawi 2012-2014 Protocol compared to treatment with the Current Practice in Ghana protocol. Each of the red diamonds represent the outcome of one simulation. The black line shows the decision threshold for a very cost-effective intervention according to WHO-CHOICE methodology.*

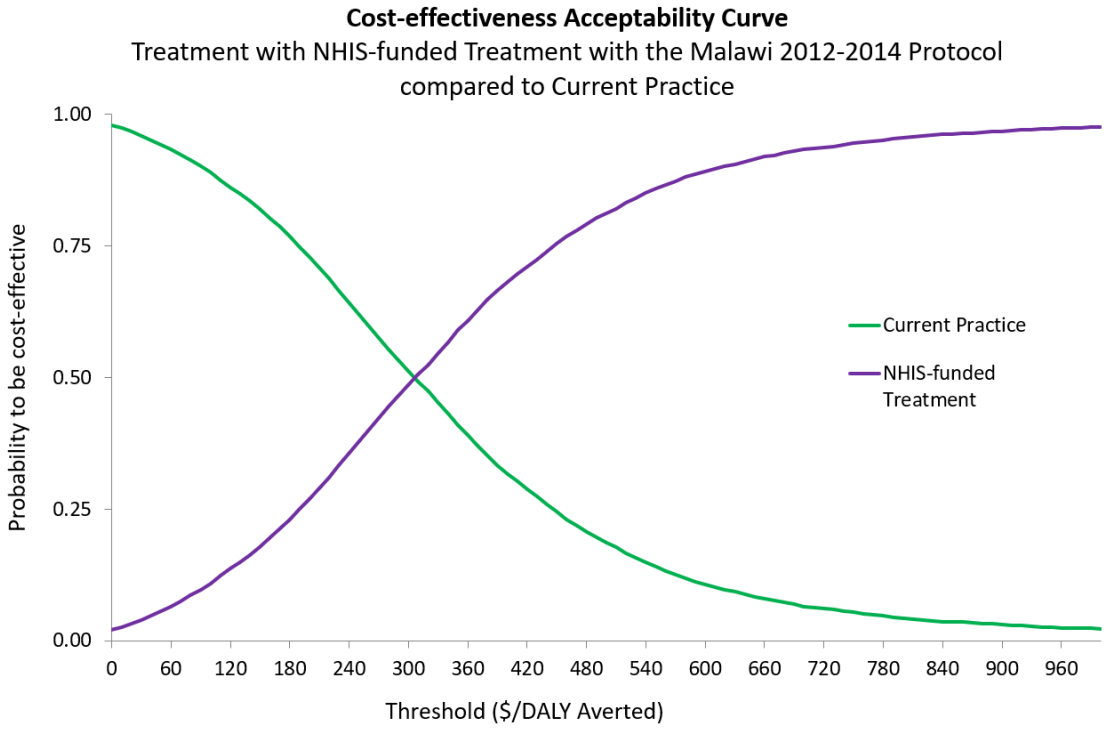

Figure 5.7: *This figure shows the Cost-Effectiveness Acceptability Curve for the PSA results. The lines represent the probability of the given treatment to be preferred at a given willingness-to-pay per DALY averted.*

Chapter 6

Discussion

This chapter reflects upon the completion of the objectives of this thesis, including the methods used to complete them and the results derived from their completion. Further, this chapter examines how the methods used and results derived from the completion of the objectives can be interpreted in order to make conclusions regarding the research aims of this thesis, as well as the implications of this study regarding the decision problem facing the Ministry of Health of the Republic of Ghana. Reflections on the strengths and limitations of this study, as well as areas requiring future research is also be examined.

6.1 Primary Findings

The objectives of this thesis were to pilot a decision-analytic model to simulate the clinical progression and outcomes of pediatric Burkitt's Lymphoma, and to populate this decision-analytic model with appropriate parameter data in order to perform a preliminary assessment the cost-effectiveness of treatment with an NHIS-funded treatment for pediatric Burkitt's compared to treatment with the current practice in Ghana. A decision tree decision-analytic model that uses disease staging, treatment abandonment, and treatment efficacy to predict clinical outcomes of pediatric BL was created utilizing the methods described in Part 1 of Chapter 4. This model was populated with parameter data as described in Part 2 of Chapter 4 in order to carry out a preliminary cost-effectiveness analysis. This preliminary cost-effectiveness analysis included deterministic and probabilistic sensitivity analyses.

These objectives were carried out in order to evaluate the cost-effectiveness of NHIS-funded treatment compared to treatment with the current practice in Ghana. Through the methods described in section 4.3.2, treatment with Malawi 2012-2014 protocol specifically was used to model an NHIS-funded treatment in Ghana. For the cohort that received NHIS-funded treatment with the Malawi 2012-2014 protocol, the simulated 1-year EFS and 1-Year overall survival was 50% and 53% respectively. For the cohort that received treatment with the Current Practice in Ghana protocol, the simulated 1-year EFS and 1-Year overall survival was 20% and 23% respectively.

The base-case deterministic results showed NHIS-funded treatment with the Malawi 2012-2014 protocol to be the treatment regimen resulting in higher costs and fewer

DALYs incurred through the study horizon, as can be seen in table 5.1. The resulting ICER for the base-case deterministic results was $301 per DALY averted, as can also be seen in table 5.1. According to these results, NHIS-funded treatment with the Malawi 2012-2014 protocol is very cost-effective compared to treatment with the Current Practice in Ghana protocol, according to the WHO-CHOICE criteria for cost-effectiveness. Notably, the ICER threshold for considering pediatric BL to be very cost-effective under the WHO-CHOICE definition is $2202 per DALY averted, which is more than seven times larger than the deterministic ICER in this study. This finding indicates that, while funding treatment for BL adds a large up-front cost, significant gains are possible to be achieved.

The one-way sensitivity analyses in this study were performed in order to examine the structural uncertainty of the model. In the one-way sensitivity analysis of all model parameters, the ten parameters whose variation most effected the ICER were identified. These parameters can be seen in figure 5.1. Through this analysis, it was shown that the yearly fixed costs of treatment for both types of treatment were the two parameters that had the highest impact on the ICER, having more than twice the impact on the ICER as the next most impactful parameter. This is internally consistent within the study framework, as the fixed costs represented the majority of costs in this study. This is also consistent with other studies, which note that fixed costs, which primarily consist of personnel costs, make up the largest proportion of costs in pediatric cancer treatment (Denburg et al., 2019; Renner et al., 2018). Treatment costs for advanced-stage treatment were also identified among the ten most impactful parameters, but the impact of these cost variables was seven times less than the impact of the fixed cost variables.

The one-way sensitivity analyses of all model parameters also identified treatment abandonment for both interventions as among the ten most impactful parameters. This is consistent with literature that points to treatment abandonment as an important factor in pediatric BL outcomes (Gopal & Gross, 2018; Offor et al., 2018; Renner et al., 2018).

The other parameters that were determined to have the most impact on the ICER were parameters measuring treatment efficacy for advanced-stage treatment for both treatment arms. This is consistent with the literature because the majority of pediatric BL patients in Ghana are diagnosed with advanced-stage disease (Offor et al., 2018). It stands to reason, therefore, that the efficacy of treatment for these stages specifically would be among the parameters with the highest impact on the ICER. The discount rate of outcomes was also among the most influential parameters.

When considering a decision problem of an intervention for potential governmental financing, there are additional factors that should be taken into account that cannot be captured solely by numerical data. For example, it could be of extra consideration that this disease impacts children, as 39.3% of Ghana's population was under the age of 15 as of the 2010 census, compared to the global average of 26% (Ghana Health Service, 2015). Adding pediatric BL to the NHIS for coverage may also have an impact on the life span of the population, leading to a lower proportion of the population being under

15 years old.

In the one-way sensitivity analyses of key parameters, four key parameters were more closely examined to explore the impact of more extreme values on the ICER. The key parameters examined were the discount rate of outcomes, the probability of treatment abandonment for NHIS-funded treatment with the Malawi 2012-2014 Protocol, fixed costs associated with treatment with Current Practice in Ghana protocol, and fixed costs associated with NHIS-funded treatment with the Malawi 2012-2014 Protocol. These results are visualized in figures 5.2-5.5. Discount rate of outcomes and fixed costs associated with NHIS-funded treatment to the Malawi 2012-2014 Protocol showed straightforward positive relationship to the ICER, with none of the extreme values exceeding the $2202 threshold at which they would no longer be cost-effective. Likewise, fixed costs associated with treatment with the Current Practice in Ghana protocol showed a straightforward negative relationship to the ICER.

Notably, while the probability of treatment abandonment with NHIS coverage had a positive relationship to the ICER, the effect of change in the parameter on the ICER was much more impactful at values nearer the probability of treatment abandonment in treatment with Current Practice in Ghana protocol. At all abandonment probabilities at or below 0.61, the ICER was still below the very cost-effective threshold. This is notable because this parameter was derived with an assumption based on data from a non-Ghanaian context. While overestimation was possible in deriving this parameter using the methods in this study, this sensitivity analysis implies that the deterministic results would still indicate NHIS-funded treatment as very cost effective in scenarios where treatment abandonment was only reduced by as little as 7%.

The probabilistic sensitivity analysis in this study was performed in order to examine parameter uncertainty on the model, and how parameter uncertainty affected the ICER. 10,000 Monte Carlo simulations were performed The plot of the ICERs resulting from the 10,000 Monte Carlo simulations can be seen in figure 5.6. 99.85% of the Monte Carlo simulations resulted in an ICER less than $2202 per DALY averted. This result shows that, despite the uncertainty present within the parameters in this thesis, NHIS-funded treatment with the Malawi 2012-2014 protocol is very likely to be considered very cost-effective for the treatment of pediatric BL in Ghana.

6.2 Model Validity

Internal validity in this thesis was primarily ensured through internal checks within the coding of the model in the Microsoft Excel 2013 software. This included recursive coding with visual cues indicating whether or not the proportionality of the chance nodes was correct or if the total number of the cohort was consistent throughout the model. Internal validity was also checked in the one-way sensitivity analysis of key parameters, where results of the change key parameters were observed to ensure they produced expected results.

Face validity was not able to be assessed for the model used in this thesis, as it was not possible to consult with an impartial expert for this study. However, the fact that

the model was developed under the guidance of the expert supervisors of this thesis and that the results produced by the model are similar to the observed real world data do provide positive indications of face validity.

Cross validity was not possible to be assessed for the model used in this thesis, as there are no other existing decision-analytic models for pediatric BL. Predictive validity was not able to be assessed because it measures the ability of a model to predict outcomes before they are measured. This would necessitate the comparison of a clinical study of pediatric BL in Ghana with the results of this model.

Predicative validity can be measured by comparing the predictions of the model to real world event data. The paucity of existing data makes measuring predicative validity challenging. There are few studies that measure outcomes in the same manner as this study while being in a relevant context. The 22% overall survival simulated for treatment with the Current Practice in Ghana protocol is close to the 20% overall survival reported in Offor et al. (2018). However, it should be noted that this statistic censors abandonment data, and does not provide information regarding the length of time since treatment for these individuals. The 50% event-free survival and 53% overall survival simulated for the NHIS-funded treatment with the Malawi 2012-2014 regimen are similar to outcomes commonly reported in clinical studies using treatments of a similar intensity, such as the 55% 2-year overall survival seen in a study of a similar intensity in Uganda (Denburg et al., 2019). Compared to the study in this thesis, this study presents survival over a longer time frame, and it had a 99% treatment completion rate. In addition, the simulated results for the NHIS-funded treatment in the study in this thesis also are in line with what are considered to be expected survival rates seen in SSA contexts (Denburg et al., 2019). These results indicate a degree of predicative validity.

6.3 Study Strengths

This study incorporates the first decision-analytic model for the simulation of clinical outcomes of pediatric BL. Although the cost-effectiveness analysis performed using the model is considered a preliminary cost-effectiveness analysis, the model was able to produce results that indicate a good degree of predictive validity. Because this study was performed in order to inform the Ministry of Health in Ghana's decision regarding the NHIS financing of BL treatment, the relative ease and inexpensiveness of performing a model-based cost-effectiveness evaluation should be considered as a strength of this study.

Despite the paucity of relevant data for pediatric BL in Ghana, most parameters used in the model were able to be taken from Ghanaian contexts. In situations where Ghanaian data was not available, data from other LMIC SSA contexts was able to be used. The PSA performed in this study allowed conclusions to be drawn regarding the likelihood of NHIS-funded treatment being cost-effective despite the uncertainty inherent in the parameter data. That this study was able to populate the model with the most relevant data possible should be considered a study strength.

This one-way sensitivity analyses performed in this thesis provided insight into which parameters have the most impact on the cost-effectiveness of pediatric BL treatment in Ghana, as well as the degree of the impact of these parameters. This is a novel addition to the academic understanding of pediatric BL in Ghana, and can also be applicable to other SSA contexts.

The one-way sensitivity analyses performed in this thesis provide novel insight to the impact of treatment abandonment on the cost-effectiveness of treatment for pediatric BL in Ghana. The impact of this parameter in particular is noteworthy because it has been identified as an important area for further research in Ghana (Renner et al., 2018). While the face validity of the calculation of the effect of NHIS coverage on abandonment is not clear, this model provides a framework upon which to investigate the relationship between treatment abandonment and clinical outcomes.

6.4 Study Limitations and Assumptions

As in all decision-analytic models, assumptions about reality were made in order to create a model that can produce results with available data. These assumptions, along with inherent limitations of the study, should be taken into consideration when interpreting the results.

One limitation for this study was the lack of Ghana-specific effectiveness data for the examined treatments. Because of this lack of data, effectiveness data was based on clinical studies in other LMIC SSA contexts. While the PSA examined the uncertainty of the parameter data, it does not assess the face validity of the use of single clinical studies outside of Ghana as a proxy for treatment effectiveness in Ghana. Heterogeneity inherent in the country healthcare contexts or in the individual trials may be present, and cannot be reflected in this study. This should be considered when interpreting the results of this study.

This study assumed that the overhead costs for treating pediatric BL at KBTH is proportional to the overhead costs for treating all childhood cancer in KBTH. This study also assumed the overhead costs for treating childhood cancer at KATH were the same as the costs for treating childhood cancer at KBTH, and that the costs of treating pediatric BL at KATH followed the same proportionality as in KBTH. This assumption was necessitated by a lack of relevant data. The face validity of this assumption was unable to be assessed in this study. This should be taken into consideration when interpreting the results of this study, because the one-way sensitivity analysis of all model parameters identified the overhead costs for both treatments as having the largest impact on the ICER.

This study assumed that the non-pharmacy related variable costs of treatment of treating pediatric BL with NHIS-funded treatment with the Malawi 2012-2014 Protocol at KBTH was proportional to the non-pharmacy related variable costs of treatment of treating all pediatric cancer at KBTH. This study also assumed that the non-pharmacy related variable costs of treatment of treating all pediatric cancers at at KATH was the same as the non-pharmacy related variable costs of treating all pediatric cancers

at KBTH. This study then used the same proportionality assumption for pediatric BL treatment compared to the treatment of all pediatric cancers for KATH that was made in the case of KBTH. The face validity of this assumption was unable to be assessed in this study.

In order to populate the parameter for the proportion of patients abandoning treatment with NHIS-funded treatment, an assumption was made regarding the effect of NHIS coverage on abandonment rate. This study assumed a proportional effect of NHIS coverage on abandonment rate to the implied effect seen in Martijn et al. (2017). While the uncertainty associated with the parameter data was able to be examined in the PSA, the face validity of this assumption was unable to be assessed in this study.

DALYs averted was chosen as the outcome of this study because of a lack of the local preference data required for other outcome measures, as well as due to the existing norm of using DALYs averted in cost-effectiveness analyses in LMIC contexts. With this being said, it should be noted that the Global Burden of Disease study, upon which the disability weights for the DALYs are based, was performed with European participants from primarily High-Income Countries. Therefore, the disability weights used in this study may not necessarily reflect the preferences of Ghanaians. While this should be taken into consideration when interpreting the results of this study, it should also be noted that the disability weight parameters were not identified as one of the ten most impactful parameters by the one-way sensitivity analysis of all parameters.

The EFS and survival with event end-node states were included to account for differences in long-term outcomes. These long-term differences were not able to be accounted for due to the short time horizon of this study. This short time horizon was necessitated by a lack of time-dependent long-term outcome data.

The length of time represented by the decision tree model was 1 year. Based on the literature, this is an overestimation of time of treatment. This was done in order to be able to simulate outcomes given the fact that clinical data is usually presented with no earlier than 1-year outcomes. If individual-level survival data existed, more accurate calculations of treatment length would have been able to be made. This likely led to an overestimation of DALY's through the overestimation of YLL and YLD for all who were considered to have died in the model. Although the face validity of this treatment length assumption was not able to be validated in this study, other studies in similar contexts have made this same assumption. The same treatment length assumption was also made in the cost-effectiveness analysis of treating BL in Uganda seen in Denburg et al. (2019), as well as the cost-effectiveness of the treatment of childhood cancer at KBTH seen in Renner et al. (2018).

This study was performed with a healthcare payer perspective. This was primarily done because the study was performed in order to inform a governmental healthcare payer. In addition, ideal data needed to perform an analysis with a broader perspective, such as a societal perspective, was not present, and additional assumptions would have needed to be made in order to populate the additional parameters that would have been required for such an analysis. However, due to the societal burden pediatric BL poses in Ghana, a societal perspective would have been informative.

In this study, all patients in the starting cohorts were assumed to have confirmed pediatric BL. This was done due to a lack of data regarding sensitivity and specificity of the diagnostic testing, as well as little high-quality data regarding the incidence rates of pediatric BL in the population in Ghana.

The use of the WHO-CHOICE thresholds for the determination of cost-effectiveness is academically contested. Theoretically, a cost-effectiveness threshold should be a value that represents the opportunity cost of healthcare investment. However, the WHO-CHOICE thresholds are not created with this principle (Woods et al., 2016). Nonetheless, the WHO-CHOICE thresholds were still chosen to be used in this study in order to maintain comparability with related studies, as well as due to a lack of Ghana-specific opportunity-cost-based thresholds.

6.5 Further Research

The results of this research imply that NHIS-funded treatment for pediatric BL in Ghana is likely to be very cost-effective. These conclusions were drawn based on a preliminary cost-effectiveness analysis. This analysis involved assumptions of unassessed face validity. The validity of these assumptions should be researched further in order to provide context to the results of this study.

The effect of NHIS-coverage on treatment abandonment in this study was derived from a study in a context outside of Ghana. Research into the effect of NHIS treatment on abandonment rates is a topic that has been identified by Ghanaian healthcare providers as important to inform further decision making (Renner et al., 2018). Further research into this relationship should be undertaken in order to help inform decisions not only regarding pediatric BL in Ghana, but also other types of reimbursement decisions regarding childhood cancer in Ghana.

In order to more accurately capture the societal burden of pediatric BL in Ghana, more data is needed regarding the location-specific prevalence and impact of the disease. Information on potential individuals who do not seek treatment due to distance challenges should also be examined. As this study only examines the governmental payer perspective of this decision problem, only government-operated hospitals are considered. Data on potential treatment in private hospitals could also contribute to the understanding of pediatric BL in Ghana. Considering the resources required to undertake such studies, a Value of Information analysis could be used to inform which types of data should be prioritized for further research.

The model piloted in this thesis simulates the clinical outcomes of pediatric BL in Ghana by separating the impact of treatment abandonment and treatment efficacy on the outcomes. Treatment abandonment in pediatric BL is a problem in many SSA contexts (Molyneux et al., 2012). This model, if populated with appropriate parameters, should be used for research into the cost-effectiveness of pediatric BL treatment in other SSA contexts.

Chapter 7

Conclusion

Through this study, a decision tree decision-analytic model for the simulation of pediatric Burkitt's Lymphoma outcomes was created. This model was able to isolate the impacts of treatment abandonment and treatment efficacy on pediatric BL outcomes, and was able to produce simulated outcomes that are similar to observed Ghanaian pediatric BL outcomes. It identified fixed costs, treatment abandonment, advanced-stage treatment efficacy and advanced-stage treatment costs as the parameters with the largest impact on the cost-effectiveness of pediatric Burkitt's Lymphoma treatment in Ghana. Because the model is being provided as a public-goods deliverable to the Ministry of Health of Ghana, it will also able to serve as a tool to inform further pediatric BL research.

The results from the preliminary cost-effectiveness analysis performed in this study found treatment with an NHIS-Funded treatment for pediatric BL to be very cost effective compared to treatment with the current practice protocol, with an Incremental Cost-Effectiveness Ratio of $301 per DALY averted. This conclusion was found to be robust even when considering the uncertainty of the parameters used in the model, 99.65% of the iterations in the probabilistic sensitivity analysis producing a very cost-effective result. Although the addition of pediatric BL to NHIS coverage will pose an up-front expense, the results in this study indicate that this could be a very cost-effective use of resources. The better outcomes that could be achieved through NHIS coverage of pediatric BL treatment could help reduce the burden that pediatric BL poses on both the health system of Ghana, and Ghanaian society as a whole.

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Appendices

Appendix A

Method for Calculating DALYs

$$B = \frac{1}{(1 + oDR) \cdot t} \tag{A.1}$$

$$YLL \ or \ YLD = A \cdot P \cdot N \tag{A.2}$$

$$YLL \ or \ YLD = A \cdot P \cdot B \cdot N \tag{A.3}$$

In this thesis, DALYs were calculated using a methodology adapted from Larson (2013). In order to calculate the YLL and YLD aspects of the DALY, a number of variables were defined and calculated. The variables created or adapted for this purpose are presented in the following paragraph.

The variable t is the time in years, with 0 representing present time. The variable A is the DALY weight of the year lost, with 1 being the DALY weight used when calculating YLL. The variable P is the proportion of a year lost. That is to say, if an individual dies at 20.5 years of age, the proportion of a life year lost is 0.5 for that year. The variable B is the discrete time discount factor, seen in equation A.1, where oDR is the discount rate of outcomes. The variable N is the number of individuals in the state being evaluated at a given time t. With these variables, both undiscounted and discounted YLL or YLD can be calculated. The formula for calculating undiscounted YLL or YLD can be seen in equation A.2. The equation for calculating discounted YLL or YLD can be seen in equation A.3.

An example of how these equations were utilized in the decision-analytic model described in this thesis can be seen in table A.1. This example shows the calculation of the YLD aspect of the DALY for the Current Practice in Ghana treatment arm. This methodology was used to calculate discounted and undiscounted YLL and YLD in both treatment arms. Because the original formulas in Larson (2013) calculate outcomes at the start of the cycle, and the decision tree model calculates outcomes at the end of the cycle, the outcomes for the first cycle have been changed to 0.

Table A.1: *This table shows an example of the methodology used to calculate DALYs in this thesis. The example shown in this table shows the calculation of the discounted and undiscounted YLL for the Current Practice in Ghana treatment arm. The N variable in this calculation is 54.17.*

Year of life	t	DALY weight of year lost, A	Proportion of year lost, P	Discrete time discount factor, B=1/(1+oDR)t	Undiscounted YLL or YLD value, Undiscounted=A*P*N	Discounted YLL or YLD value, Discounted=A*P*B*N
7,9	1	1	1	0,9708737864	0	0
8,9	2	1	1	0,9425959091	54,16670407	51,05731367
9,9	3	1	1	0,9151416594	54,16670407	49,57020744
10,9	4	1	1	0,8884870479	54,16670407	48,12641499
11,9	5	1	1	0,8626087844	54,16670407	46,72467475
12,9	6	1	1	0,8374842567	54,16670407	45,36376189
13,9	7	1	1	0,8130915113	54,16670407	44,04248727
14,9	8	1	1	0,7894092343	54,16670407	42,75969638
15,9	9	1	1	0,7664167323	54,16670407	41,51426833
16,9	10	1	1	0,7440939149	54,16670407	40,30511489
17,9	11	1	1	0,7224212766	54,16670407	39,1311795
18,9	12	1	1	0,7013798802	54,16670407	37,99143641
19,9	13	1	1	0,68095134	54,16670407	36,88488972
20,9	14	1	1	0,6611178058	54,16670407	35,81057254
21,9	15	1	1	0,6418619474	54,16670407	34,76754616
22,9	16	1	1	0,6231669392	54,16670407	33,75489918
23,9	17	1	1	0,6050164458	54,16670407	32,77174678
24,9	18	1	1	0,5873946076	54,16670407	31,81722988
25,9	19	1	1	0,5702860268	54,16670407	30,89051445
26,9	20	1	1	0,5536757542	54,16670407	29,99079073
27,9	21	1	1	0,5375492759	54,16670407	29,11727255
28,9	22	1	1	0,5218925009	54,16670407	28,26919665
29,9	23	1	1	0,5066917484	54,16670407	27,44582199
30,9	24	1	1	0,4919337363	54,16670407	26,64642912
31,9	25	1	1	0,4776055693	54,16670407	25,87031953
32,9	26	1	1	0,4636947274	54,16670407	25,11681508
33,9	27	1	1	0,4501890558	54,16670407	24,38525736
34,9	28	1	1	0,4370767532	54,16670407	23,67500714
35,9	29	1	1	0,4243463623	54,16670407	22,98544383
36,9	30	1	1	0,4119867595	54,16670407	22,31596488
37,9	31	1	1	0,3999871452	54,16670407	21,66598532
38,9	32	1	1	0,3883370341	54,16670407	21,03493721
39,9	33	1	1	0,3770262467	54,16670407	20,42226913
40,9	34	1	1	0,3660448997	54,16670407	19,82744576
41,9	35	1	1	0,3553833978	54,16670407	19,24994734
42,9	36	1	1	0,3450324251	54,16670407	18,68926926
43,9	37	1	1	0,3349829369	54,16670407	18,14492161
44,9	38	1	1	0,3252261524	54,16670407	17,61642875
45,9	39	1	1	0,315753546	54,16670407	17,10332888
46,9	40	1	1	0,3065568408	54,16670407	16,60517367
47,9	41	1	1	0,2976280008	54,16670407	16,12152784
48,9	42	1	1	0,288959224	54,16670407	15,65196878
49,9	43	1	1	0,280542936	54,16670407	15,19608619
50,9	44	1	1	0,2723717825	54,16670407	14,75348174
51,9	45	1	1	0,2644386238	54,16670407	14,32376868
52,9	46	1	1	0,2567365279	54,16670407	13,90657153
53,9	47	1	1	0,249258765	54,16670407	13,50152576
54,9	48	1	1	0,2419988009	54,16670407	13,10827744
55,9	49	1	1	0,2349502922	54,16670407	12,72648295
56,9	50	1	1	0,2281070798	54,16670407	12,35580869
57,9	51	1	1	0,2214631843	54,16670407	11,99593076
58,9	52	1	1	0,2150128003	54,16670407	11,64653472
59,9	53	1	1	0,2087502915	54,16670407	11,30731526
60,9	54	1	1	0,2026701859	54,16670407	10,97797598
61,9	55	1	1	0,1967671708	54,16670407	10,65822911
62,9	56	1	1	0,1910360882	54,16670407	10,34779525
63,9	57	1	1	0,1854719303	54,16670407	10,04640316
64,9	58	1	0,17	0,1800698352	9,208339692	1,658144211
					Sum of undiscounted YLL or YLD: 3042,543767	Sum of discounted YLL or YLD: 1419,745808

Appendix B

Deriving the "Treatment Abandonment for NHIS-funded treatment with the Malawi 2012-2014 protocol" parameter

In Offor et al. (2018), 118 of the 173 patients seen at KBTH abandoned treatment. Of these individuals, 89 (75%) abandoned due to financial constraint, while 29 (25%) abandoned due to non-financial reasons. The effect of NHIS coverage on treatment abandonment was assumed to only impact these individuals who abandoned due to financial constraint. In order to estimate the abandonment rate of an NHIS-funded treatment, an effect proportional to the effect seen in Martijn et al. (2017) was assumed for the patients who abandoned treatment due to financial constraints. The proportion who abandoned due to non-financial reasons was assumed not to change

89 of the 173 (51% of cohort) abandoned treatment due to financial reasons in Offor et al. (2018). In Martijn et al. (2017), the effect of insurance coverage was calculated to reduce treatment abandonment from 44% to 5%. If we assume proportionality, it implies that 5.8% of individuals in a hypothetical cohort with NHIS coverage in Ghana would abandon due to financial constraint. This corresponds to 10 individuals. If we assume the 29 individuals who abandoned for non-financial reasons stays the same, then a hypothetical cohort receiving NHIS funded BL treatment would see 10 individuals abandoning due to financial constraint and 29 individuals due to non-financial reasons, or 39 individuals in total.

39/173 individuals abandoning treatment corresponds to a 22.5% abandonment rate. This was the method utilized to derive the parameter for the proportion of individuals abandoning NHIS-funded treatment with the Malawi 2012-2014 protocol.

Appendix C

Deriving the "Fixed costs" parameters

Table C.1: *This table presents the methodology and mathematics used to derive the annual fixed cost of treatment for both the intervention and the comparator. The proportion of pediatric cancer patients who are pediatric BL at KBTH and KATH are derived from Offor et al. (2018) and Paintsil et al. (2015) respectively. Fixed costs for the treatment of all childhood cancers is derived from Renner et al. (2018).*

Fixed cost category	Total annual operating cost ($)	Proportion of pediatric BL patients, KBTH	Proportion of pediatric BL patients, KATH	Total Cost ($)
Medical Personnel	574,960	0.307	0.408	411,096.40
Nonmedical Personnel	193,653	0.307	0.408	138,461.89
Utilities	196,217	0.307	0.408	140,461.16
Total Annual Fixed Costs				**689,853.45**

Appendix D

Deriving the "Variable costs for NHIS-funded treatment with the Malawi 2012-2014 Protocol" parameters

Table D.1: *This table presents the methodology used to estimate the pharmacy costs of an NHIS-funded treatment with the Malawi 2012-2014 Protocol, separated by disease stage. To calculate the total required dosage of each drug, it is assumed that each patient goes through the full treatment protocol, and that the average patient has a body surface area of 1 square meter. The drug and required dosage information are sourced from Molyneux et al. (2017). The number of drug units required is derived by taking the total dosage required and dividing that dosage by the size of the drug units sold in Ghanaian pharmacies as stated in Boateng et al. (2020), rounded up to the nearest whole number. The cost per dose is sourced from Boateng et al., 2020, where the costs are provided in US dollars ($).*

Stage I and II

Drug:	Total dosage required (mg)	Number of drug units	Cost per dose ($)	Total cost ($)
Cyclophosphamide	3960	8	2.94	23.52
Vincristine	6	6	2.94	17.64
Prednisalone	300	60	0.02	1.20
Methotrexate	50	2	2.94	5.88
Total Cost				**48.24**

Stage III and IV

Drug:	Total dosage required (mg)	Number of drug units	Cost per dose ($)	Total cost ($)
Cyclophosphamide	3960	8	2.94	23.52
Vincristine	6	6	2.94	17.64
Prednisalone	300	60	0.02	1.20
Methotrexate	50	2	2.94	5.88
Doxorubicin	120	3	13.73	41.19
Total Cost				**89.43**

Table D.2: *This table presents the methodology used to derive the total variable costs per person for NHIS-funded treatment with the Malawi 2012-2014 protocol. The pharmacy costs are derived from the process in table D.1. The other cost categories are derived from Renner et al. (2018).*

Stage I and II

Cost category	Cost per person ($)
Pathology and labs	267.73
Pharmacy	48.24
Radiation	88.99
Imaging	186.08
Blood	15.83
Hotelling	2221.39
Total Cost Per Person	**2828.26**

Stage III and IV

Cost category	Cost per person ($)
Pathology and labs	267.73
Pharmacy	89.43
Radiation	88.99
Imaging	186.08
Blood	15.83
Hotelling	2221.39
Total Cost Per Person	**2869.45**

Appendix E

Parameter Distributions and Uncertainty Values

Table E.1: *This table shows the assigned parameter distribution and uncertainty data for the chance node probability parameters for the "treatment with the Current Practice in Ghana protocol" treatment arm in this study*

Parameter Description	**Parameter Value**	**Assigned Parameter Distribution**	**Alpha**	**Beta**
Probability of being diagnosed with Stage I pediatric BL	0.0578	Dirichlet	10	163
Probability of being diagnosed with Stage II pediatric BL	0.0578	Dirichlet	10	163
Probability of being diagnosed with Stage III pediatric BL	0.4451	Dirichlet	77	96
Probability of being diagnosed with Stage IV pediatric BL	0.4393	Dirichlet	76	97
Probability of abandoning treatment	0.6821	Beta	118	55
Probability of completing treatment	0.3179	Beta	55	118
Probability of Event-free survival for Stage I pediatric BL	0.4211	Dirichlet	8	11
Probability of Survival with Events for Stage I pediatric BL	0.2632	Dirichlet	5	14
Probability of Death for Stage I pediatric BL	0.3158	Dirichlet	6	13
Probability of Event-free survival for Stage II pediatric BL	0.4783	Dirichlet	11	12
Probability of Survival with Events for Stage II pediatric BL	0.2174	Dirichlet	5	18
Probability of Death for Stage II pediatric BL	0.3043	Dirichlet	7	16
Probability of Event-free survival for Stage III pediatric BL	0.6667	Dirichlet	14	7
Probability of Survival with Events for Stage III pediatric BL	0.0476	Dirichlet	1	20
Probability of Death for Stage III pediatric BL	0.2857	Dirichlet	6	15
Probability of Event-free survival for Stage IV pediatric BL	0.6667	Dirichlet	14	7
Probability of Survival with Events for Stage IV pediatric BL	0.0476	Dirichlet	1	20
Probability of Death for Stage IV pediatric BL	0.2857	Dirichlet	6	15

Table E.2: *This table shows the assigned parameter distribution and uncertainty data for the chance node probability parameters for the "NHIS-funded treatment with the Malawi 2012-2014 Protocol" treatment arm in this study*

Parameter Description	**Parameter Value**	**Assigned Parameter Distribution**	**Alpha**	**Beta**
Probability of being diagnosed with Stage I pediatric BL	0.0578	Dirichlet	10	163
Probability of being diagnosed with Stage II pediatric BL	0.0578	Dirichlet	10	163
Probability of being diagnosed with Stage III pediatric BL	0.4451	Dirichlet	77	96
Probability of being diagnosed with Stage IV pediatric BL	0.4393	Dirichlet	76	97
Probability of abandoning treatment	0.2554	Beta	4.34	12.66
Probability of completing treatment	0.7446	Beta	12.66	4.34
Probability of Event-free survival for Stage I pediatric BL	0.6875	Dirichlet	5.5	2.5
Probability of Survival with Events for Stage I pediatric BL	0.0625	Dirichlet	0.5	7.5
Probability of Death for Stage I pediatric BL	0.2500	Dirichlet	2.0	6.0
Probability of Event-free survival for Stage II pediatric BL	0.6875	Dirichlet	5.5	2.5
Probability of Survival with Events for Stage II pediatric BL	0.0625	Dirichlet	0.5	7.5
Probability of Death for Stage II pediatric BL	0.2500	Dirichlet	2.0	6.0
Probability of Event-free survival for Stage III pediatric BL	0.6667	Dirichlet	14	7
Probability of Survival with Events for Stage III pediatric BL	0.0476	Dirichlet	1	20
Probability of Death for Stage III pediatric BL	0.2857	Dirichlet	6	15
Probability of Event-free survival for Stage IV pediatric BL	0.6667	Dirichlet	14	7
Probability of Survival with Events for Stage IV pediatric BL	0.0476	Dirichlet	1	20
Probability of Death for Stage IV pediatric BL	0.2857	Dirichlet	6	15

Table E.3: *This table shows the assigned parameter distribution and uncertainty data for the disability weight parameters used in this study*

Parameter Description	Parameter Value	Assigned Parameter Distribution	Standard Deviation
Disability Weight for patients having received treatment for Stage I BL	0.288	Normal	0.066
Disability Weight for patients having received treatment for Stage II BL	0.288	Normal	0.066
Disability Weight for patients having received treatment for Stage III BL	0.451	Normal	0.088
Disability Weight for patients having received treatment for Stage IV BL	0.451	Normal	0.088

Table E.4: *This table shows the assigned parameter distribution and uncertainty data for the cost parameters for the "treatment with the Current Practice in Ghana protocol" treatment arm in this study*

Parameter Description	Parameter Value	Assigned Parameter Distribution	Minimum Value	Maximum Value
Overhead costs	$689,853	Uniform	586,375.43	793,331.47

Table E.5: *This table shows the assigned parameter distribution and uncertainty data for the cost parameters for the "NHIS-funded treatment with the Malawi 2012-2014 Protocol" treatment arm in this study*

Parameter Description	**Parameter Value**	**Assigned Parameter Distribution**	**Minimum Value**	**Maximum Value**
Overhead costs	$689,853	Uniform	586,375.43	793,331.47
Cost of Stage I pediatric BL treatment, given treatment abandonment (Intervention)	$1,719	Uniform	1460.78	1976.36
Cost of Stage II pediatric BL treatment, given treatment abandonment (Intervention)	$1,719	Uniform	1460.78	1976.36
Cost of Stage III pediatric BL treatment, given treatment abandonment (Intervention)	$1,759	Uniform	1494.95	2022.57
Cost of Stage IV pediatric BL treatment, given treatment abandonment (Intervention)	$1,759	Uniform	1494.95	2022.57
Cost of Stage I pediatric BL treatment, given treatment completion (Intervention)	$2,828	Uniform	2404.02	3252.50
Cost of Stage II pediatric BL treatment, given treatment completion (Intervention)	$2,828	Uniform	2404.02	3252.50
Cost of Stage III pediatric BL treatment, given treatment completion (Intervention)	$2,869	Uniform	2439.03	3299.87
Cost of Stage IV pediatric BL treatment, given treatment completion	$2,869	Uniform	2439.03	3299.87