Cost-Utility of Prostaglandin Analogues Compared to Beta Blockers as First-Line Medication for Treating Primary Open Angle Glaucoma in Ghana

Enock Takyi

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Department of Health Management and Health Economics

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Enock Takyi

Supervised by:

Professor Eline Aas

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Abstract

Background – Ghana ranks among the countries most affected by glaucoma in the world. Glaucoma is estimated to account for 20.6% of all cases of blindness in the country. In recent years, there has been a growing concern that anti-glaucoma medications listed on the National Health Insurance Scheme's (NHIS) medicines list are not adequate to manage the disease. This has led to calls from different stakeholders for prostaglandin analogues, particularly latanoprost, to be added to the NHIS medicines list. However, the cost-effectiveness of this medication is yet to be established.

Objective – To establish the cost-effectiveness of prostaglandin analogue as a first-line medication for treating primary open angle glaucoma (POAG) in Ghana.

Method – A Markov Model was constructed to assess the life-time cost-effectiveness of treating a cohort of one thousand 55-year-old POAG patients with prostaglandin analogues compared to beta blockers. Effectiveness data was taken from literature. Cost data was obtained mainly from Ghana's National Health Insurance Scheme (NHIS) medicines list for 2016 and the recently revised Ghana Diagnostic-related group (G-DRG) tariff lists. Costs of treatments not covered by the NHIS were estimated as the average of retail prices quoted by some leading pharmaceutical companies in Ghana. The effect of parameter uncertainty on cost-effectiveness was explored through one-way, two-way, and probabilistic sensitivity analyses.

Results – Compared to beta blockers, prostaglandin analogues resulted in an incremental cost-effectiveness ratio (ICER) of USD 11,600; based on an estimated incremental gain of 105 quality-adjusted life years (QALYs), at an additional cost of USD 1,222,400. The probability that prostaglandin analogue is cost-effective compared to beta blockers at a willingness to pay threshold of USD 4,100 per QALY was 0.27. The ICER was not sensitive to the age of the cohort, the cost of prostaglandin analogues, or the probability of developing asthma. However, the ICER was sensitive to the age of the cohort and the cost of prostaglandin analogues when varied simultaneously.

Conclusion – Given the existing evidence, prostaglandin analogue is not a cost-effective alternative to beta blockers as a first-line treatment for POAG in Ghana. The study, however, shows that further research to reduce decision uncertainty would be necessary if expected cost of research does not exceed USD 131 billion.

Keywords: Glaucoma, Ghana, prostaglandin analogue, beta blocker, ICER, Cost-effectiveness.

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Dedication

Dedicated to my future wife and kids.

List of Abbreviations

BMCs	Budget Management Centres
CBA	Cost-Benefit Analysis
CEA	Cost-Effectiveness Analysis
CEAC	Cost-Effectiveness Acceptability Curve
CEAF	Cost-Effectiveness Acceptability Frontier
CHAG	Christian Health Association of Ghana
COAG	Chronic Open Angle Glaucoma
CUA	Cost-Utility Analysis
DALYs	Disability-Adjusted Life-Years
dB	Decibels
DHMT	District Health Management Teams
EQ-5D	Euroqol Five-Dimensions Questionnaire
EVPI	Expected Value of Perfect Information
FBOs	Faith Based Organisations
GDP	Gross Domestic Product
G-DRG	Ghana Diagnostic-Related Group
GGHE	General Government Expenditure on Health
GHS	Ghana Health Service
HASS	Health Administration and Support Service
HRQoL	Health Related Quality of Life

ICD	Institutional Care Directorate
ICER	Incremental Cost-Effectiveness Ratio
IOP	Intraocular Pressure
MOH	Ministry of Health
NECU	National Eye Care Unit
NGOs	Non-Governmental Organizations
NHIA	National Health Insurance Authority
NHIS	National Health Insurance Scheme
NMB	Net Monetary Benefit
NSB	Net Social Benefit
PCMB	Private Clinics and Maternity Board
PHD	Public Health Directorate
POAG	Primary Open Angle Glaucoma
PPME	Policy, Planning, Monitoring and Evaluation
PSA	Probabilistic Sensitivity Analysis
PvtHE	Private Expenditure on Health
QALY	Quality-Adjusted Life Year
QALYs	Quality-Adjusted Life-Years
RCTs	Randomized Controlled Trials
RHMT	Regional Health Management Teams
RR	Relative Risk

SSDM	Stores, Supplies and Drugs Management
THE	Total Expenditure on Health
USD	United States Dollars
VOI	Value of Information
WHO	World Health Organization
WTP	Willingness to Pay

Table of Contents

1 INTRODUCTION

Ghana ranks among the countries most affected by glaucoma in the world (Potter, Debrah, Ashun, & Blanchet, 2013; World Glaucoma Association, 2010). Glaucoma is estimated to account for 20.6% of all cases of blindness in Ghana (Guzek, Anyomi, Fiadoyor, & Nyonator, 2005). Glaucoma, with the resulting blindness, is a burden not only to patients, but to the entire society. To patients, the burden takes the form of pain and loss of function. It is also a burden to society due to the use of resources needed for treatment and rehabilitation of patients and due to permanent disability, which adversely affect productivity. There are various types of glaucoma, but the commonest in Ghana is Primary Open Angle Glaucoma (POAG) (Ministry of Health (Ghana), 2010) In some literature, POAG is also referred to as Chronic Open Angle Glaucoma (COAG).

In recent years, there has been a growing concern that the anti-glaucoma medications listed on the country's National Health Insurance medicines list are not adequate to manage the disease. Many stakeholders, including the Glaucoma Association of Ghana, have suggested that the National Health Insurance Authority (NHIA) should review the anti-glaucoma medications on the NHIS medicines list to include more medications. In their study to establish the "efficacy of NHIS-listed anti-glaucoma medications in the management of primary open-angle glaucoma in Ghana", Koffuor, Ababio-Danso, Gyanfosu, and Amoateng (2012), observed that the NHIS-listed anti-glaucoma medications were not adequate in the management of POAG. The authors found that a class of anti-glaucoma medications called prostaglandin analogues, which was not listed by the NHIS, was more efficacious than the NHIS-listed medications. They, therefore, suggested that prostaglandin analogues, particularly latanoprost, be added to the NHIS list. A similar suggestion was made by the authors of the Ghana Eye Health System Assessment Report 2013 (Potter et al., 2013). However, the cost-effectiveness of this medication has not yet been established. The aim of this study, therefore, is to establish the cost-effectiveness of prostaglandin analogue as a first-line medication for the management of POAG in Ghana.

1.1 The Research Problem

As part of its mandate to regulate the health insurance schemes in Ghana, the National Health Insurance Authority has listed several anti-glaucoma medications to the health care needs of its registered clients. There are five main classes of anti-glaucoma medications: prostaglandin

analogues, beta blockers, carbonic anhydrase inhibitors, sympathomimetics and miotics (National Collaborating Centre for Acute Care (UK), 2009). The NHIS medicines list includes medications extracted from all the classes of anti-glaucoma medications except prostaglandin analogues, although prostaglandin analogues are proven to be more effective (Koffuor et al., 2012). This is probably because, generally, prostaglandin analogues cost more than medications from the other classes. Although, in the short term, prostaglandin analogues appear to be more costly in treating glaucoma patients, the picture may look different if the long term cost-effectiveness is taken into account. This study therefore seeks to establish the cost-effectiveness of prostaglandin analogues as a first-line anti-glaucoma medication in Ghana.

Currently, the main first-line anti-glaucoma medications used in Ghana are beta blockers and prostaglandin analogues (expert opinion). Thus, the study compares prostaglandin analogues to beta blockers.

Studies on glaucoma in Ghana are very scanty. Koffuor et al. (2012) established the efficacy of anti-glaucoma medications in Ghana, but did not account for their costs. Wittenborn and Rein (2011) also compared the Cost-effectiveness of glaucoma interventions in Barbados and Ghana. However, the authors did not establish the cost-effectiveness between different ant-glaucoma medications. Thus, studies that establish the cost-effectiveness of anti-glaucoma medications in Ghana are almost non-existent. It is this gap that the current study seeks to fill.

Health care needs are insatiable, but the resources to meet these needs are always limited. This is true even for the highly developed countries. It is, therefore, imperative to prioritize our health care needs to get the most out of our limited resources. Establishing the cost-effectiveness of prostaglandin analogues, thus, becomes important, especially, considering the resource constraints of Ghana.

The primary question that this study seeks to answer is: Is prostaglandin analogue a cost-effective first-line treatment for primary open angle glaucoma in Ghana?

1.2 Structure of the Thesis

In the next chapter, I try to place the study in context by giving a brief overview of Ghana's demographic and economic features. Besides, an overview of the health care system of Ghana is presented. I also present a brief background to glaucoma, specifically, its prevalence, nature, prognosis, and treatment options.

Chapter 3 presents the theoretical foundations of the study. First, decision-analytic modeling is briefly introduced. A specific reference is then made to economic evaluation, and the different types of economic evaluation are described. Value of Information (VOI) analysis is also introduced briefly. The chapter also discusses the main study perspectives in health economic evaluation; the perspective adopted in this study is then clearly stated.

In Chapter 4, I outline the methods and data used to in the study. The step-by-step procedures followed from data collection to the establishment of cost-effectiveness, including uncertainty analysis, are presented. Sources of data used in the study are clearly identified.

Results of the study are presented in Chapter 5, while Chapter 6 discusses the results, including limitations of the study.

2 BACKGROUND

2.1 Overview of the Country Ghana

Ghana is a country in West Africa. The country is bounded to the north by Burkina Faso, to the east by Togo, to the west by la Cote d'Ivoire, and to the south by Gulf of Guinea. Ghana covers a land area of 238,533 square kilometres (Ghana Statistical Service, 2012).

Figure 1: Map of Ghana

Source: http://www.ghanaweb.com/GhanaHomePage/geography/maps.php

The World Bank estimates Ghana's population at 27.41 million ("Ghana Home," n.d.). According to the 2010 population and housing census of Ghana, 51.2 percent of the country's

population is made up of females, while males constitute 48.8 percent (Ghana Statistical Service, 2012). Also, 50.9 percent of the population live in urban areas, while the remaining live in rural areas. Of the population aged 11 years and older, 74.1 percent is said to be literate.

According to the World Health Organization (WHO), the life expectancy of a Ghanaian at birth is 63 years (i.e. 64 years and 62 years for females and males respectively) ("GHO | By category | Life expectancy - Data by country," n.d.). Maternal mortality ratio in Ghana is 485 per 100,000 live births (Ghana Statistical Service, 2012), while infant mortality rate is 43 per 1000 live births ("Mortality rate, infant (per 1,000 live births) | Data," n.d.).

The 2010 census report also indicates that 54.2 percent of the population aged 5 years and older is economically active, while 45.8 percent (majority being students) is economically not active (Ghana Statistical Service, 2012). Ninety-five percent of the economically active population is employed while 5 percent is unemployed.

The World Bank classifies Ghana as a lower middle income country (World Health Organization, n.d.). The World Bank figures from 2015 estimated Ghana's gross domestic product (GDP) at USD 37.86 billion ("Ghana Home," n.d.). This translates into a GDP per capita of USD 1381.40. It is estimated that 24.2 percent of Ghana's population live below the poverty line, while an estimated 8.4 percent is considered to be extremely poor (Ghana Statistical Service, 2014).

2.2 Overview of the Health System in Ghana

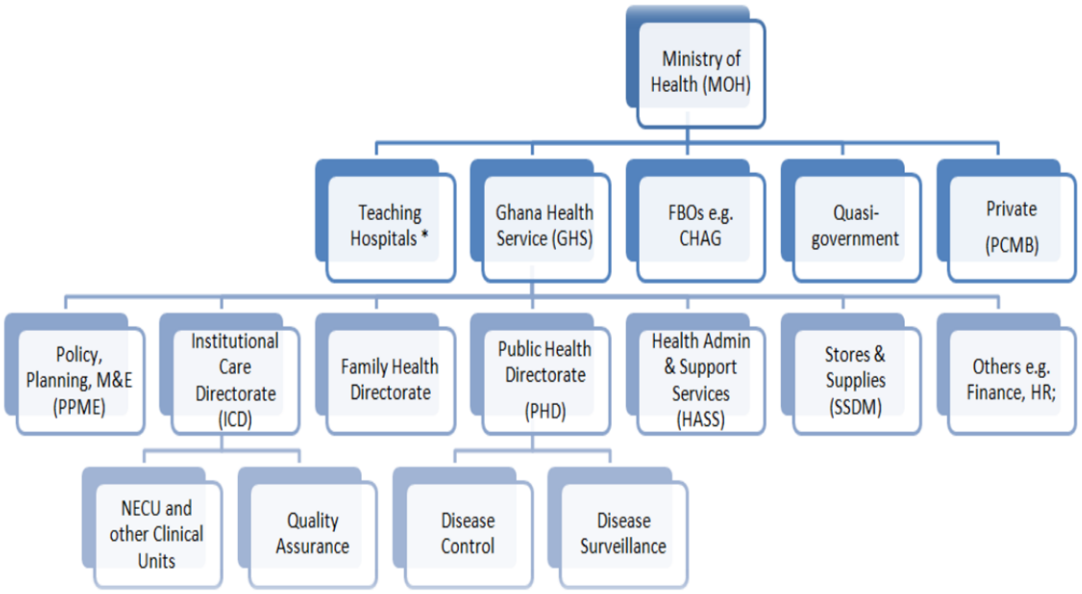
2.2.1 Organisation of services

In Ghana, the Ministry of Health is responsible for policy formulation, monitoring and evaluation, resource mobilization and regulation of the health services delivery ("Organisational Structure | Ghana Health Service," n.d.). Curative and public health services are provided by Ghana Health Service (GHS). GHS is "an independent public agency, under the decentralised management of Regional Health Management Teams (RHMT) in each of the 10 regions, and District Health Management Teams (DHMT) in every district" (Potter et al., 2013, p. 13). The greater part of planning and management of both preventative and curative services takes place at the district level (Mills, Ally, Goudge, Gyapong, & Mtei, 2012). There are Budget Management Centres (BMCs) or cost centres, at each of the administrative levels,

namely, national, regional and district, for administering funds from the government and development partners ("Organisational Structure | Ghana Health Service," n.d.).

Ghana Health Service is the major health care provider in Ghana, with about half of all health facilities and almost two-thirds of health personnel in the formal sector (Potter et al., 2013). About 8 percent of all health facilities are provided by nongovernmental, faith based organisations (FBOs), the largest being the Christian Health Association of Ghana (CHAG) (Potter et al., 2013). "These facilities can be seen as quasi-public as the majority of their staff salaries are provided through the Ministry of Health and service delivery is overseen by GHS" (p. 13). Besides, there are other quasi-government providers of health services (such as police or military clinics/hospitals), teaching hospitals, and private health care providers, whose activities are overseen by the Private Clinics and Maternity Board (PCMB) (Potter et al., 2013).

Figure 2: Organisations and Departments Involved in Delivering Health Care in Ghana



See list of abbreviations for full names of each of the Directorate
**Teaching Hospitals are separate to GHS and autonomous, with links to the Ministry of Education.*
Source: (Potter et al., 2013)

2.2.2 Health Care Financing

The most recent figures available (from 2014) indicate that Ghana spends 3.6% of its GDP (approximately USD 1.36 billion) on health care ("WHO | Ghana," n.d.). Sixty percent of

expenditure on health is from government sources, the remaining 40% coming from National Health Insurance, out of pocket payments and national and international donors (Potter et al., 2013). Government budgets are decentralised to facilities at the regional and district levels with the exception of funds spent on capital and human resources, which are held centrally (Potter et al., 2013).

Table 1: Ghana - National Expenditure on Health

Expenditure Ratio	**Ghana (2014)**
Total expenditure on health (THE) as % of GDP	3.6
External resources on health as % of THE	15.4
General government expenditure on health (GGHE) as % of THE	59.8
Private expenditure on health (PvtHE) as % of THE	40.2
GGHE as % of General government expenditure	6.8
Social security funds as % of GGHE	32.5
Private insurance as % of PvtHE	2.0
Out of pocket expenditure as % of PvtHE	66.8
Total expenditure on health per capita at exchange rate	58*
Total expenditure on health per capita at Purchasing Power Parity (NCU per USD)	145*

**Absolute amount*
Source: ("WHO | Ghana," n.d.) (http://www.who.int/countries/gha/en/)

Ghana adopted a social health insurance system in 2003. The National Health Insurance Scheme was established by the National Health Insurance Act, 2003 (Act 650) (Government of Ghana,

2003). The act also established the National Health Insurance Authority (NHIA), which regulates all health insurance schemes in the country and implements the NHIS (National Health Insurance Authority (Ghana), 2011).

As a social insurance system, citizens contribute premium annually to a mutual fund, from which their health care services are paid in case they fall sick. Formal sector employees are exempt from paying the premium, because 2.5% of their social security contribution is deducted from their salaries to support the scheme. Besides, indigents, people above 70 years, children under 18 years, pensioners, and pregnant women are exempt from payment of the premium, but have to register to obtain the scheme's benefits. (Witter & Garshong, 2009). The mutual funds are managed at the district level. However, the central government supports the district schemes from National Health Insurance Fund - a fund generated from 2.5% Health Insurance Levy on selected goods and services, and 2.5% of social security contributions of all Ghanaian workers. Other sources are funds from investment returns from the National Health Insurance Council, parliament, and donors, such as the World Bank, International Labour Organization, and Danish International Development Agency (Amarteyfio & Yankah, 2012).

The National Health Insurance Act, 2003 (Act 650), as amended by the National Health Insurance Act, 2012 (Act 852), makes it mandatory for all residents in Ghana to belong to a health insurance scheme in line with NHIS objective of achieving universal health coverage. Although this universality has not yet been achieved, the scheme currently covers about two thirds of the country's population (Potter et al., 2013). Recent studies suggest that the educated and the rich are more likely to enroll in the NHIS than the uneducated, poor ("Achieving a Shared Goal | Oxfam International," n.d.; Brugiavini & Pace, 2016; Potter et al., 2013).

The insured population access health services, covered by the NHIS tariff, for free at NHIA-accredited facilities. Health facilities are then reimbursed via monthly billing, according to regularly updated tariff lists (Potter et al., 2013). However, health services not covered by the NHIS are paid for out of pocket. For the uninsured, all health care expenses are paid out of pocket.

The National Health Insurance Authority has the mandate to decide which medications or medical procedures to be reimbursed. The authority has therefore come out with a list of services and medicines that are reimbursed under the National Health Insurance Scheme. No service or medicine is reimbursed outside of this list.

2.2.3 Eye Health Status in Ghana

There has not been any national population-based study to directly assess the prevalence of blindness in Ghana (Potter et al., 2013). The World Health Organization (WHO) estimates that 1% of the Ghanaian population is blind (Ghana Health Service, 2011; Potter et al., 2013). This implies that about 274,000 out of the estimated 27,410,000 people living in Ghana are blind. Another 3% (822,300 people) is estimated to be visually impaired (Potter et al., 2013).

Cataract is the leading cause of blindness in Ghana, accounting for about 45 - 50% of the burden of blindness, followed by glaucoma which contributes around 20% of the burden. Other eye conditions that contribute to the burden of blindness in Ghana are trachoma, onchocerciasis, childhood blindness, refractive errors and low vision. The incidence of blindness in Ghana is very high. It is estimated that 24,000 people become blind each year from cataract alone (Potter et al., 2013)

Over 75% of the causes of blindness in Ghana are avoidable ("800,000 Ghanaians have eye problems - GEF," n.d.). However, there are several challenges why many people still go blind, even due to avoidable causes. Such challenges include late presentation to health facilities, inadequate eye care personnel and resources, and uneven distribution of the available personnel and resources across the country ("800,000 Ghanaians have eye problems - GEF," n.d.; Potter et al., 2013)

2.2.4 Strategies and Policies Relating to Eye Health

The National Eye Care Unit (NECU) of the Ghana Health Service operates within the framework of the National Eye Health Programme, whose aim is taken from the global initiative VISION 2020 THE RIGHT TO SIGHT, which targets the elimination of avoidable blindness by the year 2020 (Potter et al., 2013). The Government of Ghana signed the global declaration of support to VISION 2020 in 2000, to commit the country to working towards achieving the aim. To this end, the NECU has undertaken a number of programmes, including the National Eye Health Programme 5-year strategic plan (2004-2008), entitled "Imagine Ghana Free of Avoidable Blindness", and an updated strategic plan 2009-2014 entitled "A Shared Vision" to reflect partnership working between NECU and the international non-governmental organizations (NGOs) involved in eye care in Ghana (Potter et al., 2013).

2.2.5 Challenges of the Health Sector

The health sector of Ghana is faced with many challenges. Notable among them include inadequate human and material resources. Besides, the available resources, including human resource, are poorly distributed geographically, leading to inefficiency and poor responsiveness (Mills et al., 2012; Potter et al., 2013). Also, there have been reports of inefficiency in NHIS reimbursements at facility level, which makes planning for health care difficult (Potter et al., 2013).

2.3 Prevalence and Incidence of Glaucoma

Glaucoma is the second leading cause of preventable blindness in the world (Ministry of Health (Ghana), 2010). A recent estimate of the number of people affected by glaucoma worldwide suggested that, by 2020 there will be approximately 80 million people living with the disease, of which 11 million will be bilaterally blind (Quigley & Broman, 2006). Blindness from glaucoma is irreversible, making it the most common cause of irreversible blindness (Gyasi, Francis, Chen, Harrison, & Kodjo, 2014). In Ghana, it is estimated that 700,000 people are affected by glaucoma; out of this, 60,000 people are already blind ("About 700,000 people in Ghana suffer glaucoma," n.d.). Studies on incidence of glaucoma in Ghana, and Africa in general, are hard to find. A search for studies on incidence of glaucoma and Africa retrieved only one study (Cook, 2009). This study estimated the annual incidence of glaucoma in Africa at 0.04% (i.e 400 new cases for every 1 million population). Thus, considering Ghana's population of 27.41 million, the annual incidence of glaucoma can be estimated to be 10,964 per year.

2.4 Nature and Prognosis of Glaucoma

"Glaucoma is a group of disorders, principally optic neuropathy resulting from cupping and atrophy of the optic nerve head leading to visual loss and blindness" (Khandekar et al., 2008, as cited in Koffuor et al., 2012, p. 50). Glaucoma is often associated with increased intraocular pressure (IOP) in the eye (Ministry of Health (Ghana), 2010). The higher the IOP, the greater the risk of visual loss (Ministry of Health (Ghana), 2010). IOP is measured in millimetres of mercury (mmHg). In anti-glaucoma therapy, an IOP between 19 mmHg and 22 mmHg is

considered to be the safest for patients, although there is no single IOP level that is safe for every patient (Koffuor et al., 2012; Rathore & Nema, 2009).

Diagnostically, visual field loss is the most specific sign of glaucoma (Koffuor et al., 2012; Thylefors & Négrel, 1994). The visual field is the portion of an individual's surroundings that can be seen at any given point in time (Ophthalmology, 2009). Visual field is measured in decibels (dB) (Carroll & Johnson, 2013; Shafranov, 2011). Lower dB values represent lower retinal sensitivity, while higher dB values represent higher retinal sensitivity (Shafranov, 2011).

Blindness from glaucoma is irreversible. Treatment for glaucoma is, therefore, meant to reduce the risk of progression (Heijl et al., 2002). IOP is an important modifiable risk factor for glaucoma (Ting, Li Yim, & Ng, 2014). It has been proven that lowering IOP reduces progression of visual field loss in glaucoma (Heijl et al., 2002; Ting et al., 2014).

2.5 Treatment Alternatives for Glaucoma

The main alternative interventions for treating glaucoma are medications, laser therapy, and surgery (Ting et al., 2014). The aim of glaucoma treatment, often, is to achieve a pressure reduction of at least 30% from the initial IOP (Rathore & Nema, 2009). There are five main classes of anti-glaucoma medications: prostaglandin analogues, beta blockers, carbonic anhydrase inhibitors, sympathomimetics and miotics (National Collaborating Centre for Acute Care (UK), 2009).

3 THEORETICAL FRAMEWORK

3.1 Decision-Analytic Modeling

Treatment choices are often made in the face of uncertainty about effectiveness, safety and economic implications (Xie et al., 2009). There is always a chance that the wrong decision has been made (Briggs, Claxton, & Sculpher, 2006; Hoomans, Fenwick, Palmer, & Claxton, 2009). Wrong decisions will lead to costs in terms of health benefits forgone and resources forgone (Briggs et al., 2006). According to (Siebert, 2003), evaluating the introduction of a new intervention involves answering two conceptually separate research questions. First, given the available information, should the new technology be adopted? Second, should more evidence be obtained to confirm or change this decision in the future? In this study, I attempt to answer these questions with specific reference to prostaglandin analogue as a first-line treatment for POAG in Ghana.

To answer the first question, we use decision analysis (Siebert, Rochau, & Claxton, 2013). Decision-analytic modeling is a systematic approach to decision making under uncertainty that is used widely in economic evaluation of pharmaceuticals and other health care technologies (Siebert et al., 2013). Decision models enable us to compare the expected costs and consequences of alternative strategies after considering the probabilities, and clinical outcomes of all relevant events, as well as complications (Siebert, 2003). This can be either medical decision analysis, meant to inform clinical guideline development, or economic evaluation, which investigates the expected cost-effectiveness of an intervention, thereby helping to guide reimbursement decisions given existing evidence (Sculpher & Claxton, 2005; Siebert, 2003). Economic evaluation is the focus of this study.

It must be pointed out, however, that economic evaluation does not show whether sufficient evidence exists or not. Hence, to answer the question as to whether more information should be obtained, Value-of-Information (VOI) analysis is used (Siebert et al., 2013). VOI analysis helps to set priorities for future research. “It intends to answer the question about the value of collecting additional information to reduce the uncertainty when making medical decisions” (Siebert et al., 2013, p. 577).

3.2 Economic Evaluation

Economic evaluation is increasingly used to inform the decisions of various health care systems about which health care interventions to fund from available resources (Briggs et al., 2006). According to Drummond, Sculpher, Torrance, O'Brien, & Stoddart (2005), economic evaluation is "the comparative analysis of alternative courses of action in terms of both their costs and consequences" (p. 9). Resources are limited; hence it is not possible to provide all beneficial health services to the entire population. This makes priority setting unavoidable. The basic tasks of economic evaluation are, therefore, "to identify, measure, value, and compare the costs and consequences of the alternatives being considered" (Drummond et al., 2005, p. 9). Thus, economic evaluation is a decision support tool to guide decisions about health care interventions.

3.2.1 Types of Economic Evaluation

(Drummond et al., 2005) identified three main types of economic evaluation, namely, Cost-Effectiveness Analysis (CEA), Cost-Utility Analysis (CUA), and Cost-Benefit Analysis (CBA). These types of economic evaluation are similar in terms of cost, in that they all identify similar costs and express costs in monetary terms; however, they express consequences in different terms (Drummond et al., 2005).

Cost-Effectiveness Analysis (CEA)

CEA measures health outcomes in terms of natural units such as life years saved, number of episode-free days, number of incidents averted or number of cancers detected. CEA is, therefore, applicable when comparing alternative programmes in which costs are related to a single, common effect that may differ in magnitude (Drummond et al., 2005).

Results in CEA are presented as an incremental cost-effectiveness ratio (ICER), i.e. ratio of incremental costs to incremental effects for an alternative health program compared with another (Johnston, Buxton, Jones, & Fitzpatrick, 1999).

Cost-effectiveness analysis is most suitable where a decision-maker, with a fixed budget, is considering a limited range of options within a given field (Drummond et al., 2005). In order to maximize the health gains for a given budget, the alternative programmes are ranked in terms of their ICERs, from the lowest to the highest; the programmes are then implemented, beginning

with the alternative with the lowest ICER until the budget is exhausted (Drummond et al., 2005).

The result of CEA (the ICER) does not tell us whether an intervention is worthwhile, considering the social opportunity costs that come with its implementation (Drummond et al., 2005). Therefore, to make a decision using CEA, an external criterion of value – a societal willingness to pay (WTP) threshold – is employed (Drummond et al., 2005; Olsen, 2009). The threshold, which is often arbitrary, is the highest amount of money that society is willing to pay for a unit of health gain (Drummond et al., 2005).

Cost-Utility Analysis (CUA)

CUA measures outcomes of health care programmes in terms of utilities – "the preferences individuals or society may have for any particular set of health outcomes" (Drummond et al., 2005, p. 14). CUA is a useful technique because "it allows for health-related quality of life adjustments to a given set of treatment outcomes, while simultaneously providing a generic outcome measure for comparison of costs and outcomes in different programmes" (Drummond et al., 2005, p. 14). The generic outcome, usually expressed as quality-adjusted life-years (QALYs), is arrived at in each case by adjusting the length of time affected through the health outcome by the utility value, on a scale of 0 (death) to 1 (perfect health), of the resulting level of health status (Drummond et al., 2005). Health care interventions are meant to improve life both in quality and quantity dimensions (Olsen, 2009). The advantage of QALY as a measure of health output is that it can simultaneously capture both quality and quantity of health changes, and integrate these into a single measure (Drummond et al., 2005). As QALY integrates different types of health effects into a single preference based measure, it allows for comparison between interventions with different types of health effects (Brazier, 2007).

Health outcomes in CUA may also be measured in terms of disability-adjusted life-years (DALYs), which is basically a measure of overall disease burden. The main difference between QALY and DALY is that health-related quality of life weights used in QALY calculations represent levels of quality of life enjoyed by individuals in respective health states, while disability weights used in DALY calculations represent levels of loss of functioning caused by diseases. Hence, while the former is measured on a scale in which 1 represents full health and 0 represents death, the latter is measured on a scale in which 0 represents no disability and 1 represents death. This implies that QALYs represent a gain which should be maximised, while

DALYs represent a loss which should be minimised. In this sense, a DALY can be seen as an inverse of QALY (Robberstad, 2009).

As in CEA, the results of CUA are presented as an incremental cost-effectiveness ratio (ICER), expressed in terms of the cost per quality-adjusted life-year gained by implementing one intervention instead of another (Drummond et al., 2005). CUA shares a lot of similarities with CEA. As already mentioned, the results of both CEA and CUA are presented as the ratio of incremental costs to incremental effects, although each technique measures effects differently. Besides, both techniques are well suited when operating within a given budget. Also, the result from both CEA and CUA cannot tell us whether an intervention is worthwhile; they require a societal WTP threshold in order to decide whether or not the intervention in question should be implemented (Drummond et al., 2005).

Due to the similarities between CEA and CUA, some authors do not distinguish between the two (Drummond et al., 2005). This study adopts CUA.

Cost-Benefit Analysis (CBA)

CBA measures both costs and effects of health interventions in monetary terms. As already mentioned, both CEA and CUA are well suited when considering how best to allocate an existing budget; they do not tell us whether it is worthwhile to expand the budget given the social opportunity costs of all the resources consumed (Drummond et al., 2005). CBA goes beyond considering the specific effects themselves to attach monetary values to the effects of interventions. As Drummond et al., (2005) pointed out, this allows for comparison across programs not only in the health sector, but also in other sectors of the economy.

The primary goal of CBA is to identify whether a programme's benefits exceed its costs (Drummond et al., 2005). Hence, CBA weighs the benefits of each alternative intervention against its costs (Drummond & Jefferson, 1996). A positive net social benefit (NSB) indicates that the program is worthwhile. When operating within a fixed budget, the programme (or combination of programmes) that maximizes NSB is selected for implementation.

The use of CBA in health economic evaluation has been highly criticized, mainly because it places monetary value on human life (Drummond et al., 2005).

3.2.2 Value-of-Information (VOI) Analysis

Once a decision has been reached based on the currently available evidence, VOI can be used to evaluate whether we should gather additional evidence or not. Due to uncertainties surrounding decisions based on existing information, there is always a possibility that a wrong decision would be made. "If our decision based on current information turns out to be 'wrong', there will be cost in terms of health benefits and resources forgone" (Briggs et al., 2006). The expected cost of uncertainty is determined jointly by the probability that a decision based on current information will be wrong and the consequence of wrong decision. Thus, with estimates of probability of error and the opportunity costs of error, the expected cost of uncertainty or the opportunity loss surrounding the decisions can be calculated. Since perfect information can eliminate the possibility of making a wrong decision, the expected cost of uncertainty can be interpreted as the expected value of perfect information (EVPI).

3.2.3 Expected Value of Perfect Information (EVPI)

EVPI estimates the value of simultaneously eliminating all the uncertainty of all uncertain parameters related to the decision (Groot Koerkamp et al., 2007). In other words, the EVPI is the difference between the expected net-benefit of decision made with perfect information and decision made with current information (Briggs et al., 2006). In practice, any additional research to decrease uncertainty will never resolve all uncertainties. However, the EVPI places an upper bound on the value of additional evidence, and it provides a measure of the maximum return to further research (Briggs et al., 2006; Claxton, 2008). In other words, EVPI estimates the highest benefit we can expect from further research aimed at obtaining additional evidence. In this sense the EVPI also represents the maximum amount that a health care system should be willing to pay for additional evidence to inform this decision. The EVPI, therefore, puts a cap on the cost of conducting further research (Briggs et al., 2006). Hence, if the EVPI exceeds the expected costs of further research, then it is potentially cost-effective to conduct additional research on the technology; otherwise, further research is not worthwhile (Briggs et al., 2006; Claxton, Neumann, Araki, & Weinstein, 2001).

3.2.4 Population EVPI

To decide whether to invest in additional research, the size of the population that is expected to benefit from the new intervention and the relevant time horizon must be considered. "This

requires some assessment of the effective lifetime of the technology, the period over which the information will be used (T), and estimates of the incidence over this period (I_t)" (Briggs et al., 2006, p. 176). The EVPI associated with future patients is discounted at the rate r to provide the total EVPI for the population of current and future patients. Population EVPI is the product of the individual EVPI and the total number of people who are expected to benefit from the intervention over the intervention's expected lifetime. The population EVPI is the upper limit for the expected return on investment of research (Briggs et al., 2006; Siebert et al., 2013). This implies that further research is potentially cost-effective if the population EVPI exceeds the expected cost of additional research.

3.3 Perspectives in Health Economic Evaluation

In any economic evaluation, it is essential to specify the study perspective; for it defines the basis of analysis and determines which costs are relevant to include (Centre for Health Service Research (Singapore), 2012; Drummond et al., 2005). According to Centre for Health Service Research (Singapore) (2012), there are three main perspectives in health economic evaluation, namely the health care provider's perspective, the patient's perspective, and the societal perspective.

From the perspective of the health care provider, the relevant costs to be included in economic evaluation include costs of medication, equipment, hospitalization, physician visits, and other costs involved in health service delivery (Centre for Health Service Research (Singapore), 2012; Drummond et al., 2005).

From the perspective of the patient, relevant costs include those costs the patient incurred for receiving health service (Centre for Health Service Research (Singapore), 2012). These may include travelling expenses to and from hospital, co-payments, and home expenses due to adoption of the health care intervention in question (Drummond et al., 2005).

The societal perspective accounts for all costs incurred by society in delivering health service. These include the costs incurred by the patient and the health care provider, but also include two other cost components, namely costs of resources consumed in other sectors due to adoption of the health care intervention and loss of productivity due to the employee taking a sick leave (Centre for Health Service Research (Singapore), 2012; Drummond et al., 2005). The societal perspective represents the most comprehensive approach; it has the benefit of

quantifying costs and effects associated with all relevant stakeholders in the society (Centre for Health Service Research (Singapore), 2012; Walter & Zehetmayr, 2006).

This study, however, adopts the health care provider's perspective. This is because the study is meant to inform the NHIS of Ghana, whose responsibility is limited to the costs incurred by the health care provider in providing services to NHIS card holders.

4 METHODS AND DATA

4.1 Markov Model

A Markov model was developed to ascertain the cost-effectiveness of treating a cohort of one thousand 55-year-old glaucoma patients until 80 years or death. The cohort entered the model at 55 years because the mean age of POAG patients in Ghana was estimated to be 55 years (expert opinion). A Markov model is a mathematical method for quantifying the costs and health consequences of disease as patient progresses through various disease stages over time. It is therefore useful when dealing with a chronic condition like glaucoma. "Glaucoma is a progressive disease where a patient's sight can deteriorate and never recover" (National Collaborating Centre for Acute Care (UK), 2009, p. 239). The model is, therefore, a Markov model where patients cannot go back to previous health states.

4.1.1 Staging of Glaucoma

The Hodapp, Parrish and Anderson classification, as adapted by the National Collaborating Centre for Acute Care (UK) (2009) was used to define the POAG stages. The Hodapp, Parrish and Anderson classification classifies glaucoma based on severity of visual field defect. This staging system was adopted because it allows for costs and utility values associated with different severity levels of POAG already present in the literature (National Collaborating Centre for Acute Care (UK), 2009).

Compared to the original staging system, the National Collaborating Centre for Acute Care (UK) (2009) collapsed the last two stages (severe POAG and blindness) on the grounds that there was an overlap of their definitions and a lack of data of progression in the absence of treatment from severe POAG to blindness (National Collaborating Centre for Acute Care (UK), 2009).

Table 2: Staging Classification for POAG

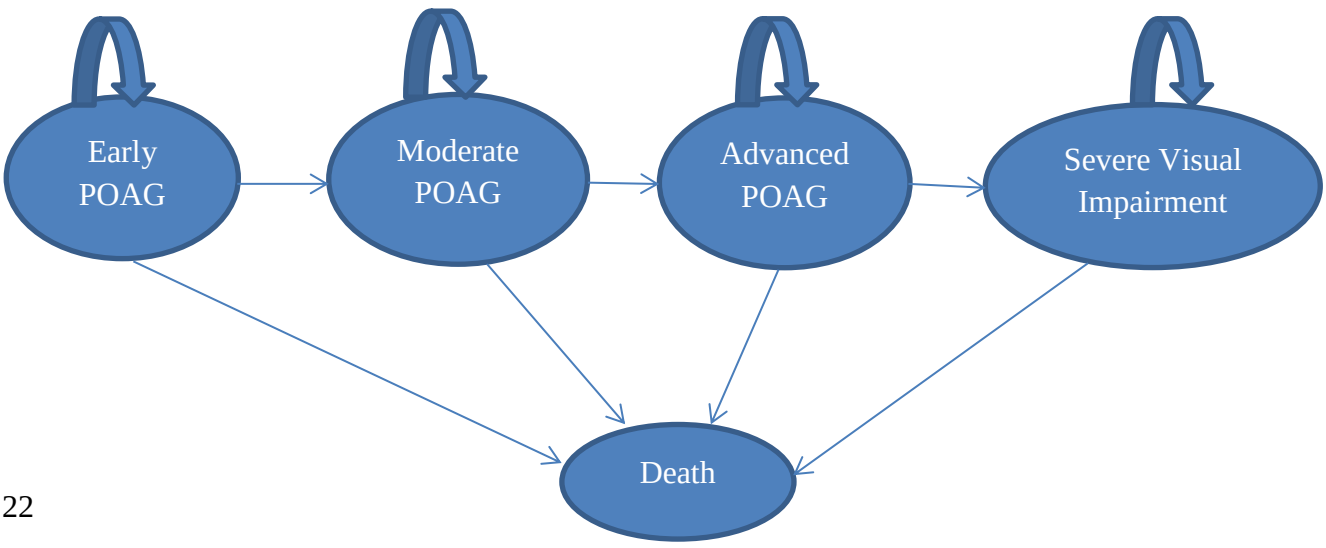
POAG Stage	Defect Score Interval (in decibels)
No POAG	No visual field defect
Early	-0.01 to -6.00 dB
Moderate	-6.01 to -12.00 dB
Advanced	-12.01 to -20.00 dB
Severe Mental Impairment	-20.01dB or worse

Source: (National Collaborating Centre for Acute Care (UK), 2009)

4.1.2 The Model Structure

I assumed that, under each intervention, all patients in the cohort entered the model at early POAG stage. During each cycle, a patient may either remain in the early POAG stage, progress to moderate POAG stage, or die. Similarly, a patient at moderate POAG stage may remain in the stage, progress to advanced POAG stage or die. A patient who begins a cycle at the advanced POAG stage may also progress to severe visual impairment, remain in the advanced POAG stage, or die. Finally, a patient with severe visual impairment may remain in that stage or die during a cycle. The structure of the Markov model is presented in Figure 3.

Figure 3: Structure of the Markov Model



4.1.3 Cycle Length

The cycle length was set at 2 months as this was thought to be the minimum time after which a change in treatment could occur (expert opinion). All the probabilities, costs and health utilities were, therefore, converted to reflect the two-month values.

The conversion of yearly probabilities to two-month probabilities involved two steps. First, the annual probability was converted to two-month rate as follows:

$$r = - [\ln (1-p)] / t \qquad (I)$$

where r = rate, p = probability, t = time period of interest

The two-month rate was then converted to two-month probability by rearranging *(I):*

$$p = 1 - \exp^{(-rt)} \qquad (II)$$

4.2 Treatment Strategies

Patients diagnosed with POAG could be treated either with a beta-blocker or a prostaglandin analogue. For each strategy, the expected health care costs and expected QALYs were calculated by estimating the costs and QALYs for each POAG stage and then multiplying them by the proportion of patients who would be in that stage as determined by the strategy taken.

4.2.1 Treatment Effect and Transition Probabilities

The main treatment effect considered was a change in risk of progression to the next POAG stages. However, the most commonly reported treatment outcome in literature is the change in intraocular pressure (IOP).

Conversion of a change in IOP to a change in probability of progression involved two steps. First the change in IOP (i.e. mean reduction in IOP) associated with each intervention was multiplied by the percentage reduction in progression per 1 mmHg reduction in IOP to obtain the effectiveness of the intervention. This was done as follows:

$$Eff_i = \Delta IOP_i * \Delta P \qquad (III)$$

Where:

Eff_i = *Effectiveness of intervention i*

ΔIOP_i = *change in IOP associated with intervention i*

ΔP = *percentage change in progression associated with 1 mmHg change in IOP*

i=beta blockers, prostaglandin analogues

Subsequently, the baseline probability of progression without treatment was adjusted by the effectiveness of the respective treatment to obtain the probability of progression after treatment as follows:

$$TP_i = BP_u * (1 - Eff_i) \qquad (IV)$$

Where:

TP_i = *Transition probability associated with intervention i*

BP_u = *Baseline transition probability in untreated patients*

The relative risk between prostaglandin analogues and beta blockers was obtained by dividing the transition probability associated with prostaglandin analogues by that of beta blockers.

The probabilities calculated above were used only in early POAG. Once a patient progressed from early POAG, the baseline probability in treated patients for the respective stage was used

(Table 3). The transition probabilities for nonspecific treatments were used, because after progression any new treatment could be introduced.

Transition probabilities were assumed to be constant throughout the model.

4.3 Probability of Adverse Events

Some treatments for glaucoma could cause adverse events. "Nevertheless not all of them result in important increased costs or reduced quality of life (National Collaborating Centre for Acute Care (UK), 2009, p. 241). Asthma (associated with beta blockers) was the only complication considered in the model, because, as far as medical treatment is concerned, asthma is the only known complication with a considerable impact on costs and quality of life (National Collaborating Centre for Acute Care (UK), 2009).

4.4 Life Expectancy

Life expectancy in patients with POAG was assumed to be the same as the general population in Ghana. Similarly, life expectancy in POAG patients who develop asthma due to the use of beta blockers was assumed to be the same as that of the general population in Ghana.

4.5 Quality of life

Health gain was measured in terms of quality-adjusted life-years (QALYs) gained. Health utilities for the health states used in the model were obtained from literature.

With the exception of asthma, all adverse events were assumed to be negligible in terms of quality of life since, according to National Collaborating Centre for Acute Care (UK), (2009), they could be promptly treated. The reduction in quality of life due to asthma was estimated from quality of life measures in treated asthma patients as presented in literature.

For each strategy, the expected health benefits were calculated by estimating the health effects for each POAG stage and then multiplying them by the proportion of patients who would be in that stage as determined by the strategy taken. The expected health benefit per the cohort in each cycle was calculated as follows:

$$\textit{Expected Health Benefit} = \Sigma\ (Q_i \times P_i) \qquad (V)$$

Where:

Q_i = *health utility of stage i*

P_i = *proportion of patients in the stage i*

i=early POAG, moderate POAG, advanced POAG, severe visual impairment

The proportion of patients in each POAG stage depends on the magnitude of the progression reduction of the treatment and on the proportion of patients still alive per the mortality rate for the general population of Ghana.

4.6 Costs

All costs used in the model were estimated using a bottom-up approach. Follow-up costs were not considered in the model. Where the primary interest is incremental cost, as is the case when comparing the introduction of a new intervention against an existing intervention, costs that remain approximately the same for each alternative being considered can be ignored (Drummond, Torrance, O'Brien, & Stoddart, 1997; Gold, Siegel, Russel, & Weinstein, 1996; Johns, Baltussen, & Hutubessy, 2003). This is because such costs will not affect the choice between the given alternatives (Drummond et al., 1997; Johns et al., 2003). All glaucoma patients in Ghana are followed up every two months, except a few patients whose IOP levels are exceptionally too high, or who develop intolerance to treatment before their next appointment date (expert opinion). Besides, follow-up procedures are the same for all glaucoma patients in Ghana, irrespective of their level of the disease. Hence, I assumed that follow-up cost is the same for both the intervention group and the comparator group. Since my primary interest is incremental cost, therefore, I decided not to include the follow-up cost.

Costs were categorized based on the health states used in the model. Hence the cost categories include early POAG costs, moderate POAG costs, advanced POAG costs, severe visual impairment costs, and costs of adverse events.

Early POAG costs are costs incurred in treating a patient diagnosed with early POAG. They are costs that arise before progression from early POAG stage. As already mentioned, the model primarily compares the first-line anti-glaucoma medications used in Ghana (i.e. beta blockers and prostaglandin analogues). Hence, early POAG costs are those costs directly associated with either beta blockers or prostaglandin analogues as a mono therapy.

When mono-therapy fails to significantly lower IOP, combination therapy is sought for (Koffuor et al., 2012). I assumed that all patients who progressed beyond early POAG were given combination therapies. Koffuor et al. (2012) observed that, in Ghana, a POAG patient could be given up to four-medication combination therapies, depending on the severity of the disease and patients' tolerance to medication. However, the number of patients on four-medication combination therapy, as reported in their study, was almost insignificant. Therefore, I assumed that patients at moderate and advanced POAG stages are put on two-medication and three-medication combination therapies respectively. Besides, at both moderate and advanced POAG stages, a patient can undergo surgery (trabeculectomy). Although some patients undergo laser trabeculoplasty, the practice is not common in Ghana (expert opinion). This option was, therefore, ignored.

It was assumed (based on expert opinion) that 10% of patients with severe visual impairment are given timolol; the remaining are not given further treatment.

All adverse events, except asthma, were assumed to be negligible in terms of costs. The cost of treating asthma was estimated based on the Standard Treatment Guidelines of Ghana (Ministry of Health (Ghana), 2010). I assumed that no additional follow-up cost was associated with the change in treatment due to asthma.

For each strategy, the expected cost per the cohort in each cycle was calculated as follows:

$$Expected\ cost = \Sigma\ (C_i\ x\ P_i) \qquad (VI)$$

Where:

C_i = *cost of stage i*

P_i = *proportion of patients in the stage i*

i=early POAG, moderate POAG, advanced POAG, severe visual impairment

4.7 Analyses

The cost-effectiveness analysis was conducted using Microsoft Excel 2016. All future costs and QALYs were discounted at the rate of 3 percent per annum in line with Global Burden of Disease (World Health Organization, 2003), using equation (VII).

$$PV = \frac{FV}{(1+r)^n} \qquad (VII)$$

Where:

PV = Present value

FV = Future value

r = Discount rate

n = Number of periods under consideration

Costs and health outcomes were corrected for continuity. The basic assumption behind Markov model is that the transition of patients occurs between cycles, and that the number of patients in each health state is constant for the duration of a cycle. In other words, the flow of patients occurs only at the beginning or the end of each cycle. This assumption can result in overestimation or underestimation of health outcomes and costs since, in reality, patients move between the different health states continuously rather than at discrete points in time (Briggs &

Sculpher, 1998). Half-cycle correction is a method used in health economic evaluation to improve these accuracies. Rather than the basic assumption that patients move between health states at the beginning or the end of a cycle, a half-cycle correction operates on the assumption that patients, on average, move between the health states halfway through the cycle (Briggs & Sculpher, 1998).

In this study, half-cycle correction was adopted to help improve the inaccuracies that might have occurred in the measures of costs and health outcomes. For each intervention, half-cycle correction was performed by dividing the costs and health outcomes of the first and the last cycles by two. Thus, in each intervention, the total cost and the total health effect was each calculated as follows:

$$A = 1/2 + 1 + 1 + 1 + \ldots + 1 + 1 + 1 + 1/2 \qquad (VIII)$$

Where A = total cost, total health effect.

The overall lifetime expected health benefit of each intervention is given by the sum of health benefits calculated for all the cycles. Since each cycle represented 2 months, the overall lifetime expected health benefit was divided by 6 to get the overall lifetime QALYs. The incremental QALY (ΔE) associated with prostaglandin analogues was calculated as the difference between the expected QALY gained with prostaglandin analogues and the expected QALY gained with the comparator (beta blockers).

Similarly, the overall lifetime expected cost of each intervention is given by the sum of costs calculated for all the cycles. The incremental cost (ΔC) associated with prostaglandin analogues was calculated as the difference between the expected cost with prostaglandin analogues and the expected cost with beta blockers.

4.7.1 Incremental Cost-Effectiveness Ratio (ICER)

The result of cost-utility analysis was expressed as incremental cost-effectiveness ratio (ICER), i.e. the ratio of incremental costs (ΔC) to incremental effects (ΔE) brought about by

prostaglandin analogues compared to beta blockers. Thus, the numerator of the ICER is the difference in cost between patients in the intervention group and those in the comparator group, while the denominator is the difference in health outcomes (QALYs) between patients in the intervention group and those in the comparator group. The ICER is defined by equation IX.

$$ICER = \Delta C/\Delta E \qquad (IX)$$

where*:*

ΔC = *incremental cost*

ΔE = *incremental effect*

To determine whether, or not, prostaglandin analogues is cost-effective, the resulting ICER is compared to the society's willingness-to-pay threshold (λ). Prostaglandin analogue is cost-effective only if the ICER is less than the willingness-to-pay threshold (i.e. $\Delta C/\Delta E < \lambda$).

4.7.2 Threshold Value for Ghana

Ghana has no explicit willingness-to-pay threshold per QALY gained. The willingness-to-pay threshold was, therefore, estimated from the country's gross domestic product (GDP) as suggested by the World Health Organization (World Health Organization, 2003). According to the WHO, interventions that cost less than three times per capita GDP per disability-adjusted life-year (DALY) averted are cost-effective, and interventions that cost less than per capita GDP per DALY averted are highly cost-effective.

Using this approach, however, presented a challenge: while the WHO guidelines are based on DALYs averted, the current study measures health effect in terms of QALYs gained. "Although QALYs and DALYs stem from the same broad conceptual framework, they are not interchangeable, as they are partly based on different assumptions and different methodologies" (Sassi, 2006).

Sassi (2006) pointed out some of the factors that account for differences between a QALY gained and a DALY averted. First, the health-related quality of life weights used in QALY and the disability weights used in DALY are derived in different ways, using different techniques. Besides, DALY incorporates an age-weighting function assigning different weights to life years lived at different ages; QALY does not incorporate any age-weighting function. Also, discounting procedures are different in QALYs and DALYs.

According to Sassi, (2006), however, the difference between QALYs gained and DALYs averted is more significant when a health intervention is aimed at preventing or treating a life-threatening disease. "The standard life expectancy assumption leads to a consistently larger estimate of DALYs saved, and the difference is greater where actual life expectancy is shorter" (Sassi, 2006, p. 408). The author also pointed out that the impact of discount rate variations used in the two measures is minimal. Thus "when a health intervention is aimed at preventing or treating a non-fatal disease, the relationship between QALYs gained and DALYs saved depends on age of onset and duration of the disease, as well as the quality of life and disability weights" (p. 402).

Morton (2007) also asserted that the use of age-weighting function is currently considered discretionary among users of the DALY approach. Morton argues further that once the age-weighting function and differences between the loss in quality of life determined by a respective disease in QALY calculation and disability-weights in DALY calculations are set aside, the two frameworks do not differ considerably.

Since glaucoma is a non-fatal disease, the WHO criterion for determining the cost-effectiveness of interventions was adopted based on the following assumptions:

- No age-weighting function is used in calculating DALYs for the glaucoma stages used in the model
- The loss of quality of life determined by each stage of glaucoma in QALY calculations is exactly equivalent to the level of disability estimated in DALY calculations.

4.7.3 Sensitivity Analyses

Sensitivity analyses were performed to assess the robustness of the model results against the imprecision in the model parameters. Almost all parameters used in the model were estimates;

there is uncertainty surrounding their true values. The purpose of sensitivity analyses was to capture this uncertainty in the model. One-way, two-way, and probabilistic sensitivity analyses were performed.

One-way sensitivity analysis was performed on probability of developing asthma, age of the cohort, and cost of latanoprost. I found that costs and QALYs in the comparator could be significantly influenced by asthma. For this reason, I conducted a one-way sensitivity analysis on the probability of developing asthma. In the base-case model, the annual probability of developing asthma in patients using beta blockers was set to be 3.3%. However, in the sensitivity analysis the probability was varied between 0 and 6%.

Longevity is influenced largely by age. The age at which the cohort entered the model would, therefore, determine how long the patients would live to benefit from the intervention. If the cohort dies out too quickly, the full effect of the intervention may not be realized. One-way sensitivity analysis was, therefore, performed on the age of the cohort to determine how varying the age of the cohort would affect the results. In the base-case analysis, the age of the cohort was set at 55 years. However, in the sensitivity analysis, the age of the cohort was varied between 30 years and 75 years.

I also performed one-way sensitivity analysis on the cost of prostaglandin analogues (i.e. latanoprost). This was because the disparity between the cost of generic latanoprost and branded latanoprost (Xalatan) was very wide. In the base-case model, the cost per bottle of prostaglandin analogues was estimated at USD 25.77 (reflecting the mean cost of generic latanoprost and Xalatan). In the sensitivity analysis, however, the cost was varied from USD 13.00 (corresponding to the cost per bottle of generic latanoprost) to USD 39.00 (corresponding to the cost per bottle of Xalatan).

A two-way sensitivity analysis was also performed to ascertain the combining effect of the age of the cohort and the cost of prostaglandin analogues on the results.

In the probabilistic sensitivity analysis (PSA), probability distributions were assigned to each model parameter where there was some degree of parameter variability. The main results were then re-calculated 1000 times; each time all the model parameters were set simultaneously, selecting from the respective parameter distribution at random. The decision uncertainty was

represented by plotting a cost-effectiveness plane, a cost-effectiveness acceptability curve (CEAC), and a cost-effectiveness acceptability frontier (CEAF).

The cost-effectiveness plane shows the spread of pairs of incremental costs (ΔC) and incremental effectiveness (ΔE) values from running 1,000 Monte Carlo simulations. Incremental effectiveness was presented on the x-axis against incremental cost on the y-axis, such that the slope of the line joining any point on the plane to the origin is equal to the incremental cost-effectiveness ratio (ICER). In the Monte Carlo simulations, the differences in costs (ΔC) and effectiveness (ΔE) between the two interventions were used as base-case point estimates.

A cost-effectiveness plane has four quadrants: northeast (NE), southeast (SE), southwest (SW), and northwest (NW) (Briggs et al., 2006). A new intervention is said to dominate its comparator (more effective and less costly) if it is located in the SE quadrant. Conversely, a new intervention is said to be dominated by its comparator (less effective and more costly) if it is located on the NW quadrant. A new intervention is more effective and more costly if it is located in the NE quadrant, while a new intervention that is located in the SW quadrant is less effective and less costly.

As already stated, the decision rule for accepting the intervention (prostaglandin analogues) as cost-effective is that its ICER should be less than the willingness-to-pay threshold ($\Delta C/\Delta E < \lambda$). This inequality can be rearranged to give an alternative inequality based on net monetary benefit (NMB) (Briggs et al., 2006):

$$\lambda * \Delta E - \Delta C > 0$$

where $\lambda * \Delta E - \Delta C$ = *net monetary benefit*

The decision rule above implies that an intervention is cost-effective only if it yields a positive net monetary benefit. This decision rule is equivalent to the decision rule based on ICER. However, when applied to Monte Carlo simulation data, the NMB helps to calculate the probability that a new intervention is cost-effective (Briggs et al., 2006).

In the Monte Carlo simulation, the NMB was calculated and simulated 1000 times. The probability that prostaglandin analogue is cost-effective was then estimated by counting the number of simulations in which NMB for prostaglandin analogue was greater than the NMB for beta blockers and divided by 1000. Conversely, the probability that beta blocker is cost-effective was estimated by counting the number of simulations in which NMB for beta blockers was greater than that for prostaglandin analogues and divided by 1000. NMB for each intervention was estimated over a willingness-to-pay threshold range of USD 0 to USD 60,100 per QALY. The results were then presented as a cost-effectiveness acceptability curve (CEAC). The CEAC indicates the probability that prostaglandin analogue is cost-effective compared to beta blockers given a range of willingness-to-pay threshold values. Probability that an intervention is cost-effective was plotted on the y-axis against willingness-to-pay threshold values on the x-axis.

A cost-effectiveness acceptability frontier (CEAF) was also presented from the Monte Carlo simulations. The CEAF indicates the probability that the alternative with the highest net-benefit will be cost-effective. Hence the decision uncertainty (or error probability) is 1 minus the value of the frontier. The CEAF was plotted from the same results used to plot the CEAC, except that probabilities below 0.5 were dropped.

4.7.4 Expected Value of Perfect Information (EVPI)

Considering the uncertainty surrounding the results, it became imperative to establish whether it was worthy, or not, to gather more evidence. The EVPI was estimated directly from the results of the PSA. As already stated, the EVPI is the difference between the expected net benefit with perfect information and that of current information. The EVPI was estimated using the following steps. First, the average overall NMBs from the 1000 simulations for each intervention was calculated. With current information, the optimal decision is the intervention with the maximum expected net benefit. Afterwards, the maximum of the net benefits between the two interventions for each simulation were chosen, summed up and averaged to get the expected net benefit of a decision with perfect information. The EVPI was then estimated as the difference between the expected net benefit with perfect information and the expected net benefit with current information. The EVPI thus estimated was for a single individual.

To decide whether to invest in additional research or not, the size of the population that is expected to benefit from the new intervention and the relevant time horizon of the new

intervention must be taken into account (Briggs et al., 2006). The incidence of glaucoma in Ghana was estimated at 10,964 per annum. It was assumed that 175,000 people currently living with glaucoma in Ghana (i.e. 25% of the estimated prevalence of 700000) would also be eligible for the new intervention. It was further assumed that prostaglandin analogues would be useful for 10 years. Population EVPI was calculated as the product of the individual EVPI and the total number of people who are expected to benefit from the intervention (equation X). Incidence associated with future years was discounted at the rate of 3%.

$$Population\ EVPI = EVPI.\sum_{t=1,2,\ldots,T} I_t/(1+r)^t \qquad (X)$$

Where:

T= expected lifetime of the new intervention

I_t = estimated incidence of the disease over the period

r = discount rate

Population EVPI estimates were calculated over a cost-effectiveness threshold range of USD 0 to USD 60,100 per QALY. As a decision rule, further research is potentially cost-effective if population EVPI exceeds the expected cost of additional research at any given threshold.

4.8 Key Assumptions

- No shift in treatment before the first progression
- No need for medication after surgery
- Death rate for POAG patients same as death rate for general population in Ghana
- Death rate for asthma patients same as death rate for general population in Ghana
- Patients cannot jump over any of the stages
- After first progression, all patients either use adjunctive medication or undergo surgery

- In the absence of treatment, the change in IOP is equal to 0.
- The severity of the condition is similar in both eyes of a patient.
- In the base case, the average age of patients at the beginning of the model is 55 years, as this was assumed to be the mean age of POAG patients in Ghana.
- Patients are reviewed every two months.
- Post-surgery complications are negligible.

4.9 Sources of Data

4.9.1 Baseline Probability of Progression

A search was conducted for studies reporting the probability for progression from one POAG stage to the next. Specifically, the search was to identify studies that reported the probability of progression from Early to Moderate POAG in treated and untreated patients, from Moderate to Advanced POAG in treated and untreated patients, and from Advanced POAG to Severe Visual Impairment in treated and untreated patients. Only studies using a definite staging system were included. The search yielded two relevant results. Using randomized controlled trials (RCTs), Burr et al. (2007) estimated the progression rates of mild, moderate and severe POAG stages based on visual field mean defect. These stages correspond to the National Collaborating Centre for Acute Care (UK) (2009) definitions of early, moderate and advanced POAG, being employed in this study. The National Collaborating Centre for Acute Care (UK) (2009) adopted Burr's progression rates, and projected the progression rate for severe visual impairment, which was missing in the study. The annual progression probabilities, as presented by the National Collaborating Centre for Acute Care (UK) (2009), were employed in this study, because they cover all the relevant POAG stages. The annual probabilities were converted to two-month probabilities using equations I and II. These are shown in Table 3.

Table 3: Probability of progression in POAG patients

Transition	Annual Probability in Untreated Patients	Two-Months Probability in Untreated Patients	Annual Probability in Treated Patients	Two-Months Probability in Treated Patients
Early to Moderate POAG	0.25	0.048	0.20	0.037
Moderate to Advanced POAG	0.11	0.019	0.07	0.012
Advanced POAG to Severe Visual Impairment	0.10	0.018	0.06	0.01

Source: (National Collaborating Centre for Acute Care (UK), 2009)

4.9.2 Effects of Treatment Interventions on Intraocular Pressure (IOP)

Data on reduction in IOP from baseline due to each treatment was derived from the National Collaborating Centre for Acute Care (2009). This was done because the data presented by the National Collaborating Centre for Acute Care was based on rigorous search for systematic reviews of clinical effectiveness of treatments in POAG patients. The data used in the model is summarised in Table 4.

Table 4: Mean Reduction in IOP from Baseline per Intervention

Intervention	Mean Reduction
Beta Blockers	2.88 mmHg*
Prostaglandin Analogues	4.2 mmHg

**mmHg (millimetres of mercury) is the unit of measure for intraocular pressure*
Source: (National Collaborating Centre for Acute Care (UK), 2009)

4.9.3 IOP Reduction and Progression

A search was conducted to find a measure of the link between IOP reduction and reduced progression of POAG. Studies included were those reporting the relative risk (RR) of each mmHg reduction in IOP for progression from one POAG stage to the next, defined by deterioration in visual field or optic nerve appearance or both. Two relevant studies found were Leske et al. (2007) and Leske et al. (2003). Leske et al. (2007)) was found to be more current and was, therefore, used in the model. The study reported that a 1 mmHg reduction in IOP is associated with 8% decrease in progression from one POAG stage to the next.

4.9.4 Overall Effectiveness of Interventions

The overall effectiveness of each intervention was calculated by multiplying the mean reduction in IOP associated with the intervention by the percentage reduction in progression per mmHg of IOP reduction (equation III). The overall effectiveness of each intervention is presented in Table 5.

Table 5: Overall Effectiveness of Interventions

Intervention	Change in IOP (mmHg)	Progression Reduction per mmHg reduction in IOP	Overall Annual Progression Reduction
Beta Blockers	2.88	0.08	0.23
Prostaglandin Analogues	4.2	0.08	0.34

4.9.5 Probability of Progression after Treatment

Under each intervention, probability of progression after treatment was estimated by adjusting the baseline probability of progression without treatment by the overall effectiveness of the intervention (equation IV). A ratio between the two-week probability of progression associated with prostaglandin analogues and that of beta blockers yielded a relative risk of 0.843. The probabilities are shown in Table 6.

Table 6: Probability of Progression after Treatment

Intervention	Annual Probability in Untreated Patients	Overall Annual Progression Reduction	Annual Probability of Progression	Two-Months Probability of Progression	Relative Risk (95% Confidence Interval)
Beta Blockers	0.25	0.23	0.193	0.0351	-
Prostaglandin Analogues	0.25	0.34	0.165	0.0296	0.843* (0.57, 1.24)

** 0.0296/0.0351*

4.9.6 Probability of Developing Asthma

Probability of developing asthma after use of beta blockers was estimated from a prospective cohort study (Kirwan, Nightingale, Bunce, & Wormald, 2002). The authors compared the difference in respiratory disease in 2,645 patients treated with beta blockers to a control group of 9,094 patients who were not exposed to beta blockers. After 12 months, it was observed that patients who were treated with beta blockers were 3.3% more likely to develop reversible airways obstruction than those who were not exposed. This translates into a two-month probability of 0.6%. The study, however, showed that the risk of respiratory problems was no longer significant after the first year of exposure. Hence the probability of developing asthma was used in the model only within the first year.

4.9.7 Life Expectancy

Life expectancy was estimated for the cohort by calculating the mean of the figures for men and women reported in the 2013 World Health Organization (WHO) statistics ("GHO | By category | Life expectancy - Data by country," n.d., "GHO | By category | Life tables by country - Ghana," n.d.). The WHO, in 2013, estimated that the life expectancy of a Ghanaian at birth was 63 years (i.e. 64 years and 62 years for females and males respectively) ("GHO | By category | Life expectancy - Data by country," n.d.). The cohort in this study entered the model at the age of 55 years. However, the WHO estimations indicate that the probability of death increases as people advance in age. In other words, the WHO projected different probabilities of death for different age categories. These age-based probabilities of death were adopted in this study. The 2013 life table for Ghana as shown by WHO ("GHO | By category | Life tables by country - Ghana," n.d.) is presented in Appendix 1. Since the cycle length of the model was two months, the probabilities of death were converted from one year to two months.

4.9.8 Quality of life

A search was conducted for studies reporting health utilities for patients at the various stages of POAG. The search yielded three results: van Gestel et al. (2010), Béchetoille et al. (2008), and National Collaborating Centre for Acute Care (UK) (2009). van Gestel et al. (2010) could not be used because the authors did not employ the staging classification being used in this study. Similarly, Béchetoille et al. (2008) could not be used, because the authors did not report the overall health related quality of life (HRQoL) for the stages; rather HRQoL was reported

per different health domains. The HRQoL reported in National Collaborating Centre for Acute Care (UK) (2009), which followed the same staging classification as adopted in this study, were therefore used. The National Collaborating Centre for Acute Care (UK) estimated the health utilities from Rein, Wirth, Johnson, & Lee (2007), who applied utilities for visual acuity to each category of visual field loss using data obtained from Brown, Brown, Sharma, and Landy (2003). The original data was based on EQ-5D.

A search for quality of life measures in treated asthma patients retrieved two studies: Schermer et al. (2002) and Chen et al. (2007), which respectively reported the health utility in treated asthma patients as 0.84 and 0.86. Both studies used EQ-5D. However, I opted for Chen et al. (2007), since it is more current. I therefore assumed that treated asthma symptoms reduce quality of life by 0.14 over one year.

Table 7 shows the health utilities associated with each POAG stage, as well as disutility associated with treated asthma.

Table 7: Health Utilities by POAG Stage/Adverse Event

Stage	Lower Limit	Upper Limit	Central Value	Source
Early POAG	0.974	0.990	0.989	National Collaborating Centre for Acute Care (UK) (2009)
Moderate POAG	0.900	0.974	0.944	National Collaborating Centre for Acute Care (UK) (2009)
Advanced POAG	0.712	0.900	0.819	National Collaborating Centre for Acute Care (UK) (2009)
Severe Visual Impairment	0.331	0.712	0.503	National Collaborating Centre for Acute Care (UK) (2009)
Asthma (a)	0.09	0.27	0.14	Estimated from Chen et al. (2007)

(a) Disutility due to asthma

NB: The upper and lower limits were used for the lognormal distribution in PSA

4.9.9 Costs

All costs were presented in United States Dollars (USD), based on Bank of Ghana exchange rates for 30th June, 2016 (USD 1.00 ≈ GHC 3.9240). Costs of all medicines were obtained from Ghana's NHIS medicines list for 2016 ("Medicines List," n.d.), except the cost of latanoprost which was not covered by the NHIS. Cost of latanoprost was taken as an average of the retail prices quoted by some leading pharmaceutical companies in Ghana. Two versions of latanoprost are used in Ghana, namely branded latanaprost (Xalatan) and generic latanoprost. The costs of these two versions were averaged. The cost of glaucoma surgery (trabeculectomy) was also obtained from the recently revised Ghana Diagnostic-related group (G-DRG) tariff lists (National Health Insurance Scheme (Ghana), 2016a, 2016b). The D-GRG offers different tariffs for services provided at Public Primary Care Hospitals and those provided at CHAG Primary Care Hospitals. The cost of glaucoma surgery was, therefore, taken as the average of the tariffs for Public Primary Care Hospitals and CHAG Primary Care Hospitals respectively. The unit costs of resources used in the model are presented in Table 8.

Table 8: Unit Costs of Resources

Resource	Unit of Pricing	Price (USD)	Source
Acetazolamide Tablet, 250 mg	Tablet	0.06	("Medicines List," n.d.)
Pilocarpine Eye Drops	Bottle	3.38(a)	("Medicines List," n.d.)
Timolol Maleate Eye Drops, 0.5%	Bottle	1.88	("Medicines List," n.d.)
Latanoprost	Bottle	25.77(b)	Expert opinion
Trabeculectomy	1 Procedure	34.53	National Health Insurance Scheme (Ghana) (2016a) National Health Insurance Scheme (Ghana) (2016b)
Budesonide DPI, 200 micrograms	Inhaler(d)	18.82	("Medicines List," n.d.)
Salbutamol Inhaler, 100 micrograms	Inhaler(d)	4.59	("Medicines List," n.d.)
Fluticasone MDI	Inhaler(d)	18.72(c)	("Medicines List," n.d.)
Beclometasone dipropionate Inhaler, 100 micrograms	Inhaler(d)	16.31	("Medicines List," n.d.)

(a) Average cost for Pilocarpine Eye Drops 2% and Pilocarpine Eye Drops 4% (see appendix 2) (b) Average cost of generic latanoprost and branded latanoprost (Xalatan) (c) Average cost for Fluticasone MDI 125 microgram and Fluticasone MDI 250 microgram (see appendix 2) (d) All inhalers are for the treatment of asthma

All anti-glaucoma medications used in Ghana are topical medications except Acetazolamide. Where a topical medication is concerned, a POAG patient would need 2 bottles for the two-month cycle whether used as mono-therapy or in combination with other medications (expert opinion). With Acetazolamide, a patient is given 2 tablets a day, making 120 tablets for the two-month cycle.

Where surgery becomes necessary, the procedure is first performed in one eye; two months later, the procedure is performed in the other eye. In between the two procedures, the patient is given 1 bottle of either latanoprost or timolol for the second eye.

Cost of Early POAG

Ideally, all POAG patients begin with mono-therapy (European Glaucoma Society, 2014; Koffuor et al., 2012; National Collaborating Centre for Acute Care (UK), 2009). I assumed that all patients at early POAG stage were given mono-therapy. Koffuor et al. (2012) found that the common mono-therapies for POAG treatment in Ghana are timolol (beta blocker) and latanoprost (prostaglandin analogue). This was confirmed by expert opinion. Hence, the costs of mono-therapy used in the model were based on timolol and latanoprost. According to expert opinion, a patient on mono-therapy would need 2 bottles of either timolol or latanoprost in the two-month cycle. Table 9 shows the treatment costs for early POAG patients.

Table 9: Cost of Early POAG per Cycle

Treatment Option	Resources Used	Cost (USD)	Standard Error	Source
Beta blockers	2 bottles of timolol	3.77	-	Koffuor et al. (2012); Expert Opinion
Prostaglandin analogues	2 bottles of latanoprost	51.54	25.55(a)	Koffuor et al. (2012); Expert Opinion

(a) Estimated from generic latanoprost and Xalatan

Cost of Moderate POAG

A patient who fails to respond to mono-therapy would either be given a combination therapy or undergo surgery. Where medication is concerned, I assumed that all patients at moderate POAG stage were put on two-medication combination therapy. In a two-medication combination therapy, a patient could be given Timolol-Pilocarpine, Timolol-Acetazolamide, Timolol-Latanoprost, or Pilocarpine-Acetazolamide (Koffuor et al., 2012). Table 10 shows the costs involved in treating patients with moderate POAG.

Table 10: Cost of Moderate POAG per Cycle

Medication Combination	**Cost (USD)**	**Source**
Timolol-Pilocarpine (Two bottles each)	10.52	Kuffour et al., 2012; Expert Opinion
Timolol-Acetazolamide (Two bottles of Timolol, 120 tablets of Acetazolamide)	11.41	Koffuor et al. (2012); Expert Opinion
Timolol-Latanoprost (Two bottles each)	55.31	Koffuor et al. (2012); Expert Opinion
Pilocarpine-Acetazolamide (Two of Pilocarpine, 120 tablets of Acetazolamide)	14.40	Koffuor et al. (2012); Expert Opinion
Trabeculectomy (2 surgical procedures plus 1 bottle of timolol or latanoprost)	82.90	Expert Opinion
Mean Cost per Cycle	34.91	-
Standard Error	14.64	-

Cost of Advanced POAG

I assumed that a patient at advanced POAG stage would either undergo surgery or be put on three-medication combination therapy. Typical three-medication therapies in Ghana as reported by Kuffour et al. (2012) include Timolol-Pilocarpine-Acetazolamide and Timolol-Acetazolamide-Latanoprost. These medication combinations were confirmed when expert opinion was sought. Table 11 shows the cost of treating patients with advanced POAG.

Table 11: Cost of Advanced POAG per Cycle

Medication Combination	Cost (USD)	Source
Timolol-Pilocarpine-Acetazolamide (Two bottles each of Timolol and Pilocarpine + 120 tablets of Acetazolamide)	18.17	Koffuor et al. (2012); Expert Opinion
Timolol-Acetazolamide-Latanoprost (Two bottles each of Timolol and Latanoprost + 120 tablets of Acetazolamide)	62.95	Koffuor et al. (2012); Expert Opinion
Trabeculectomy (2 surgical procedures plus 1 bottle of timolol or latanoprost)	82.90	Expert Opinion
Mean Cost per Cycle	54.67	-
Standard Error	19.14	-

Cost of Severe Visual Impairment

Generally, patients with severe visual impairment are not given further treatment (Expert opinion). However, a small percentage of this patient group is sometimes given some medication, usually timolol, to ease the pains in the affected eye. When asked what percentage

of patients with severe visual impairment would need further treatment, experts estimated between 5% and 15%. Based on these estimates, I assumed that 10% (the average of 5% and 15%) of patients with severe visual impairment would need further treatment. I further assumed that such patients would be given 2 bottles of timolol in each cycle. This yields USD 3.77 per respective patient per cycle.

Costs of Treating Asthma

The cost of treating asthma was estimated with beta-agonist and corticosteroids. The Standard Treatment Guidelines of Ghana (Ministry of Health (Ghana), 2010) recommend that chronic asthma should be treated with Salbutamol 100 microgram Inhaler (beta-agonist) plus one of the following corticosteroids: Budesonide DPI 200 microgram inhaler, Fluticasone MDI 125 or 250 microgram inhaler, and Beclometasone 100 microgram inhaler. With all the inhalers, except Fluticasone MDI inhaler, experts estimated that an asthma patient would need 1 inhaler for the two-month cycle. With Fluticasone MDI, it was estimated that an asthma patient would need 2 inhalers per cycle. The cost of treating asthma is presented in table 12.

Table 12: Cost of Treating Asthma per Cycle

Medication Combination	**Cost (USD)**	**Source**
One Salbutamol 100 microgram Inhaler + 2 Fluticasone MDI inhaler	42.03	(Ministry of Health (Ghana), 2010)
Salbutamol 100 microgram Inhaler + Budesonide DPI 200 microgram inhaler (1 each)	23.40	(Ministry of Health (Ghana), 2010)
Salbutamol 100 microgram Inhaler + Beclometasone 100 microgram inhaler (1 each)	20.90	(Ministry of Health (Ghana), 2010)
Mean Cost per Cycle	28.78	-
Standard Error	6.67	-

4.9.10 Willingness-to-pay Threshold

The willingness-to-pay threshold for Ghana was set to be equal to three times the country's GDP per capita. Ghana's GDP per capita for 2015, according to the World Bank ("Ghana Home," n.d.) was USD 1381.40. Hence, the willingness-to-pay threshold equals USD 4,144.20 (≈ USD 4,100).

5 RESULTS

5.1 Base-Case Cost-Effectiveness Analysis Results

The expected cost of treating 1000 patient with prostaglandin analogues (USD 3,886,100) is higher compared to beta blockers (USD 2,663,700). Similarly, QALY gained from prostaglandin analogues (14,231) is higher compared to beta blockers (14,126). The incremental cost-effectiveness ratio (ICER) is USD 11,600 per QALY gained (Table 13).

Table 13: Summary of Results

Intervention	Cost (USD)	QALY	Incremental Cost (USD)	Incremental QALY	ICER
Beta Blockers	2,663,700	14,126	-	-	-
Prostaglandin analogues	3,886,100	14,231	1,222,400	105	11,600

This implies that that if we choose prostaglandin analogues as first line treatment for POAG patients in Ghana instead of beta blockers, we would gain additional QALYs at an additional cost of USD 11,600 per each QALY gained.

The ICER is greater than three times the GDP per capita of Ghana (USD 4,100). This implies that prostaglandin analogue is not a cost-effective first-line medication for the treatment of POAG in Ghana.

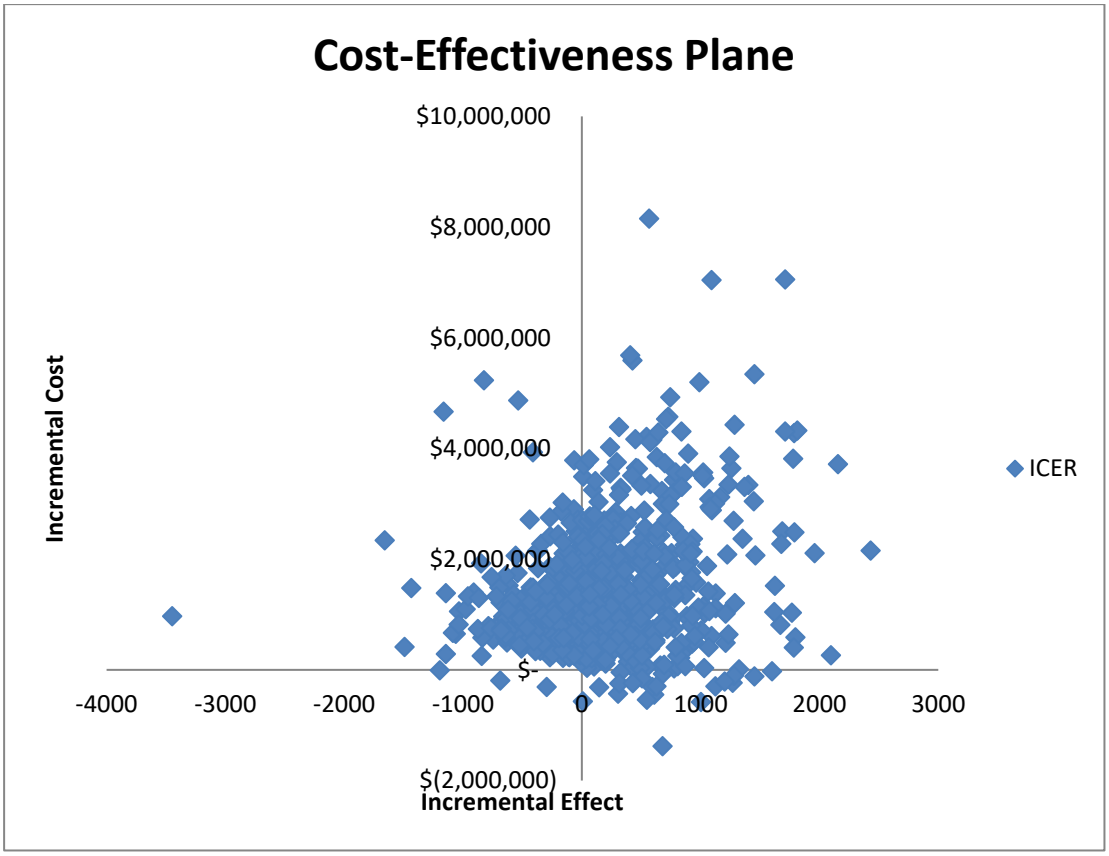
5.2 Sensitivity Analyses

In the one-way sensitivity analysis, the ICER was not sensitive to the probability of developing asthma after the use of beta blockers (Appendix 3). Similarly, the ICER was neither sensitive to the age of the cohort nor the cost of prostaglandin analogues (Appendices 4 & 5).

In the two-way sensitivity analysis, however, the ICER was sensitive to the age of the cohort and the cost of prostaglandin analogues when varied simultaneously. When the age of the cohort was set at 41 years, and the cost of prostaglandin analogues at USD 13.00, prostaglandin analogues became cost-effective (Appendix 6). This implies that, generic latanoprost (costing USD 13.00 per bottle) could be cost-effective for treating POAG patients 41 years old and below.

Results from the probabilistic sensitivity analysis were presented using a cost-effectiveness plane, a cost-effectiveness acceptability curve (CEAC), and a cost-effectiveness acceptability frontier (CEAF). The cost-effectiveness plane (Figure 4) shows the spread of pairs of incremental costs and incremental effectiveness values (ICERs) from running 1,000 Monte Carlo simulations.

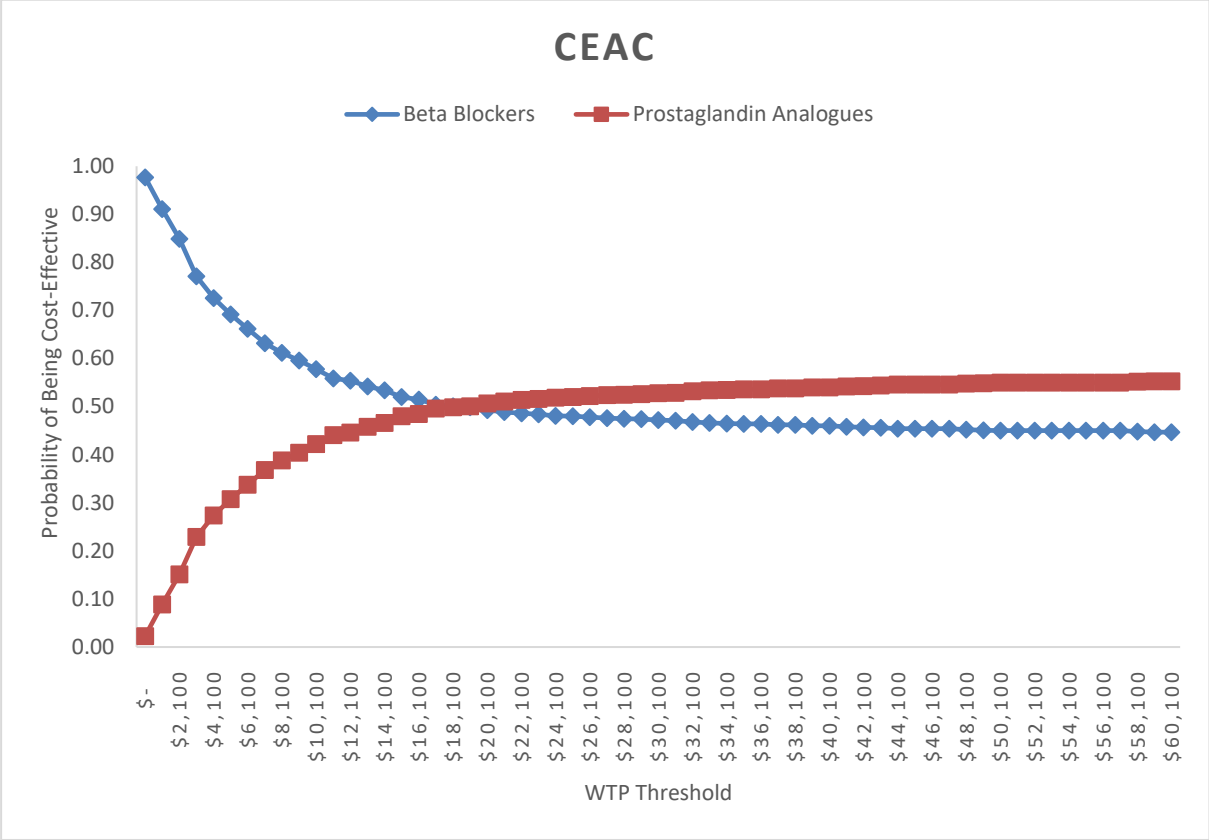
Figure 4: Cost-Effectiveness Plane



In the cost-effectiveness plane, 977 (almost 98%) of the cost-effectiveness pairs are concentrated on the northeast and northwest quadrants. This suggests that prostaglandin analogue is more costly than beta blockers, although this cannot be said with 100% certainty. The locations of the ICER points on the cost-effectiveness plane, however, makes it highly uncertain to tell whether prostaglandin analogue is more effective than beta blockers: 41% fell in the northwest and southwest quadrants, while 59% fell in the northeast and southeast quadrants.

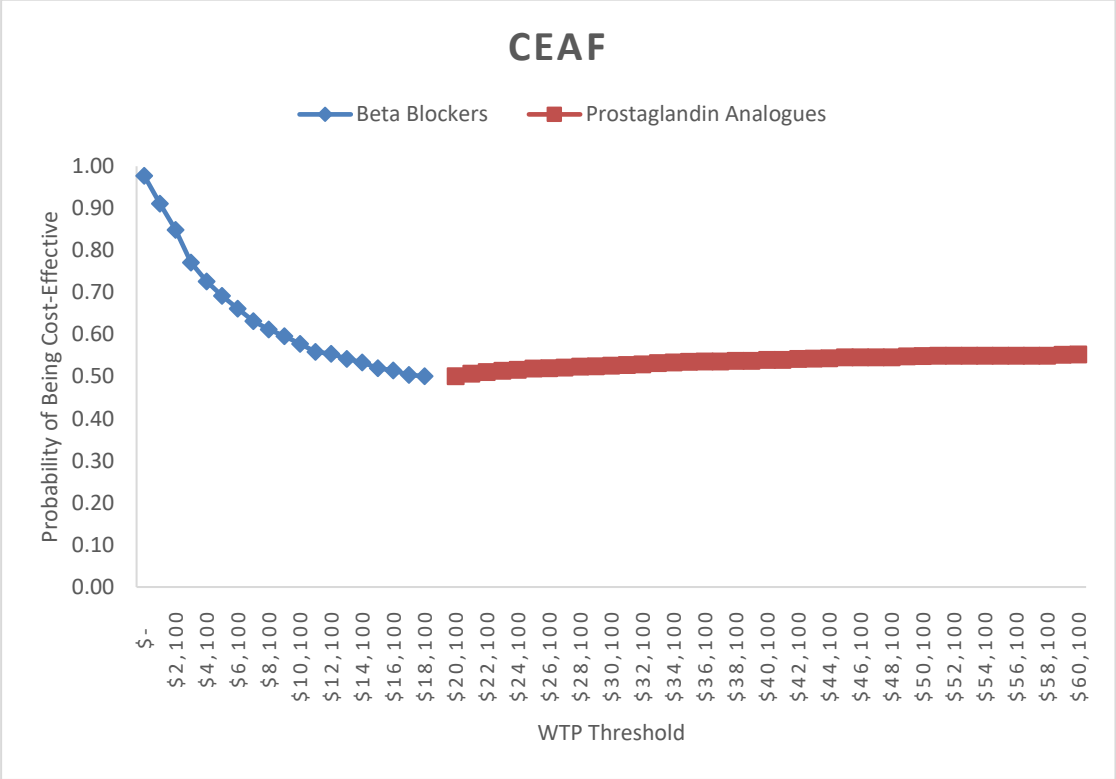
In the cost-effectiveness acceptability curve (CEAC), presented in Figure 5, the y-axis indicates the probability that prostaglandin analogue is cost-effective compared to beta blockers, given a range of willingness-to-pay threshold values (on the x-axis). At a willingness-to-pay threshold of USD 0 per QALY gained, the probability of prostaglandin analogues being cost-effective compared to beta blockers was 0.02. The CEAC, however, shows that the probability of prostaglandin analogues being cost-effective increases as the willingness to pat for additional QALYs increases. When the willingness-to-pay threshold increases to USD 4,100, the probability of prostaglandin analogue being cost-effective compared to beta blockers increases to 0.27. At the same willingness-to-pay threshold, the probability of beta blockers being cost-effective was 0.73. This seems to suggests that prostaglandin analogue is not cost-effective compared to beta blockers. However, this cannot be said with absolute certainty since the probability of prostaglandin analogue being cost-effective is greater than 0.

Figure 5: Cost-Effectiveness Acceptability Curve



The cost-effectiveness acceptability frontier (CEAF) in Figure 6 indicates the probability that the alternative with the highest net-benefit will be cost-effective. Hence the decision uncertainty (or error probability) is 1 minus the value of the frontier. Like the CEAC, the CEAF shows that, at the willingness to pay threshold of USD 4,100, the comparator (beta blockers) is cost-effective. The probability of beta blockers being cost-effective is 0.73 with error probability of 0.27.

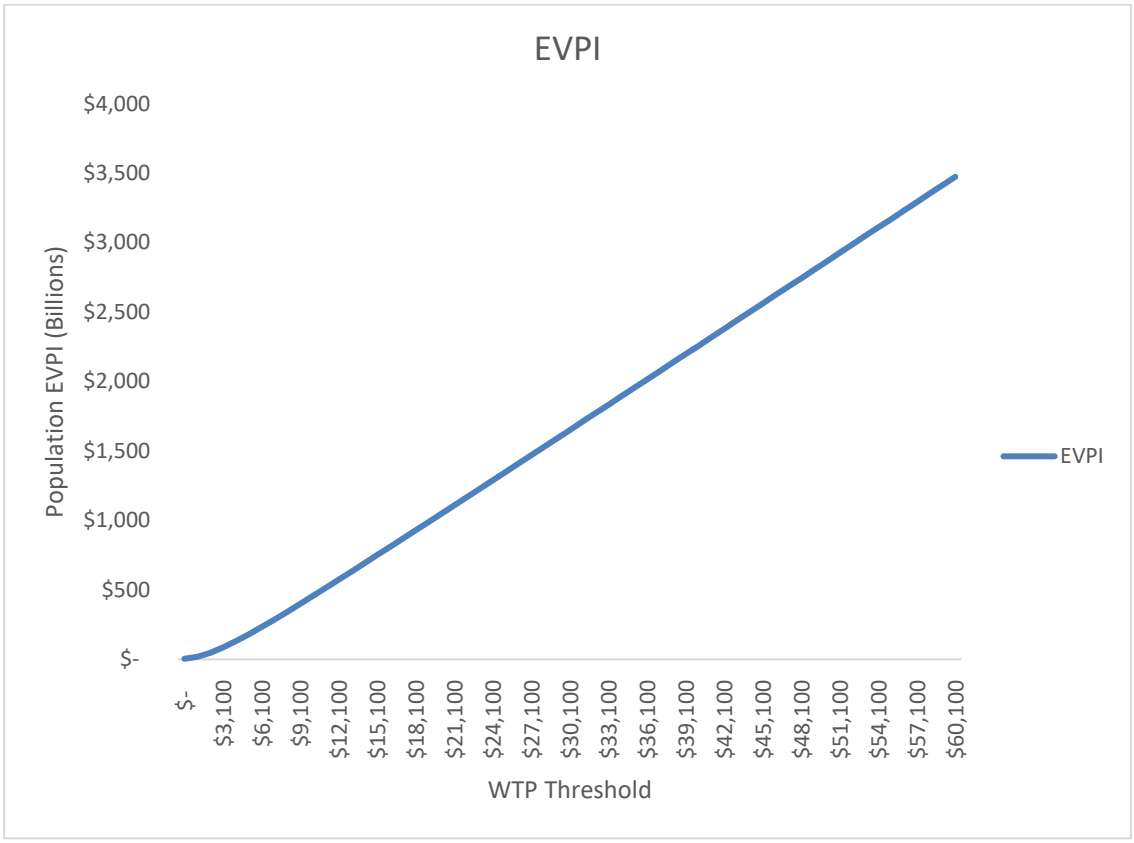
Figure 6: Cost-Effectiveness Acceptability Frontier



5.3 Expected Value of Perfect Information (EVPI)

Figure 7 shows population EVPI for a range of willingness-to-pay threshold values between USD 0 and USD 60,100. Given a willingness to pay threshold of USD 4,100, the population EVPI is USD 131 billion. This implies that further research would be potentially cost-effective if expected cost of further research is less than USD 131 billion. Beyond this value, further research is not worthwhile.

Figure 7: Population EVPI



6 DISCUSSION

There has been a growing concern in Ghana, recently, that anti-glaucoma medications listed on the country's National Health Insurance Scheme's (NHIS) medicines list are not adequate to manage glaucoma. This has led to calls from many stakeholders for prostaglandin analogues, particularly latanoprost, to be added to the NHIS medicines list. However, the cost-effectiveness of prostaglandin analogues is yet to be established. The health care system of Ghana is faced with many challenges. Perhaps the greatest challenge that the health care system faces is inadequate funding. The latest available figures indicate that Ghana spends only USD 58 per capita on health care annually (see Table 1). The resource constraints of the country make it highly important to establish the cost-effectiveness of prostaglandin analogues before recommending it to the National Health Insurance Authority. This study reports an economic evaluation modelling framework to compare the cost-effectiveness of prostaglandin analogues with beta blockers as first line treatment for primary open angle glaucoma in Ghana.

6.1 Cost-Utility Analysis

Results from this study indicate that prostaglandin analogue is more effective, but also more costly, compared to beta blockers. The results also show that prostaglandin analogue is not a cost-effective alternative to beta blockers as a first-line medication for primary open angle glaucoma in Ghana, given the current economic situation of the country. A two-way sensitivity analysis on the age of the cohort and the cost of prostaglandin analogues (latanoprost), however, showed that prostaglandin analogues (specifically generic latanoprost) could be cost-effective for treating primary open angle glaucoma patients 41 years and below. This finding, especially with respect to age, seems to suggest that the full benefit of prostaglandin analogues can only be observed in the long run. Thus, even at USD 13.00 per bottle, prostaglandin analogue was not cost-effective for the cohort used in the base-case analysis (55 years) because the cohort had a higher probability of death, and therefore died out too quickly to benefit fully from the intervention. However, it became cost-effective for a younger cohort (41 years and below), with a lower probability of death.

The probabilistic sensitivity analysis reveals some level of uncertainty surrounding the results of the cost-effectiveness analysis. Results from EVPI suggest that further evidence would be necessary

to reduce decision uncertainty provided that the expected cost of further research does not exceed USD 131 billion.

6.2 Related Studies

There are several studies that seek to establish the cost-effectiveness of treatment interventions for glaucoma. However, studies that compare different anti-glaucoma medications are limited. In Ghana, economic evaluation studies on glaucoma treatment are very scanty. Koffuor et al. (2012) who established the efficacy of anti-glaucoma medications in Ghana did not account for their costs. Wittenborn & Rein (2011) also compared the cost-effectiveness of glaucoma interventions in Barbados and Ghana, but did not consider the cost-effectiveness between different ant-glaucoma medications. Thus, studies that establish the cost-effectiveness of anti-glaucoma medications in Ghana are almost non-existent. As far as I know, this is the first study that seeks to establish the cost-effectiveness between anti-glaucoma medications for treating primary open angle glaucoma in Ghana. The model reported in this study, therefore, provides a relevant framework for further studies on glaucoma treatment costs and health gains.

6.3 Limitations of the Study

The study has several limitations, which could have influenced the incremental cost and/or incremental QALY, and for that matter the ICER. The limitations stem mainly from the key assumptions of the model.

As far as medical treatment is concerned, the only adverse event I considered was asthma. All other adverse events were assumed to be negligible since they could be promptly treated. This assumption may have led to underestimation of costs and overestimation of QALYs under both interventions. It is, however, difficult to know to which direction this limitation would have driven incremental cost and/or incremental QALY. The direction of the effect would depend on the specific adverse events associated with each intervention, the reduction in QALYs due to each adverse event, and the cost involved in treating the respective events. For instance, if the average cost of treating all adverse events associated with beta blockers were known to be higher than that of prostaglandin analogues, then we could conclude that the limitation would lead to overestimation of incremental cost, or vice versa. Similarly, if the average reduction in QALYs due to all adverse events associated with beta blockers were known to be higher than

that of prostaglandin analogues, then we could conclude that the limitation would lead to underestimation of incremental QALY, or vice versa.

Besides, all post-surgery complications were assumed to be negligible. Clearly, this assumption might have led to underestimation of costs in both groups. However, the possible impact of this limitation on incremental cost would depend on how many patients in each intervention group had complications after undergoing surgery.

It was further assumed that POAG patients would not need any anti-glaucoma medication after they have undergone surgery. In practice, however, some POAG patients may have elevated IOP even after surgery, and would therefore need further medical treatment. Ignoring this probability might have led to understatement of costs in both groups

Furthermore, I assumed no extra follow-up costs for POAG patients who developed asthma after the use of beta blockers. This assumption might have led to underestimation of costs associated with beta blockers and, hence, overestimation of incremental cost.

I also assumed that no patient died from asthma that resulted from the use of beta blockers. Neglecting possible asthma-related deaths could have led to overestimation of QALYs gained under beta blockers and, therefore, underestimation of incremental QALYs.

It is also worth noting that the inclusion of probability of asthma in the model could have led to double counting, since some of the POAG patients may have had asthma prior to taking beta blockers. Double counting would mean overestimated incremental QALY and underestimated incremental cost.

Another limitation of the study stems from the assumption that there was no shift in treatment before a patient progressed from early POAG stage. In practice, patients at early POAG stage who show intolerance to beta blockers or prostaglandin analogues may be shifted to another treatment before they progress to the next stage. This assumption might, therefore, have led to underestimation of costs under both interventions. It is, however, unclear whether this could have led to an overestimation or underestimation of incremental cost, since the number of patients who would show intolerance under each intervention is unknown.

Moreover, I assumed that follow-up costs were the same for all POAG patients, although experts indicated that a few patients may need more follow ups in exceptional cases. Such

exceptional cases which were assumed to be insignificant could have led to underestimation of costs in both groups. It is, however, unclear how this limitation could have impacted incremental cost.

Utility measures used in the model may not be accurate. The health utilities associated with the POAG stages were retrieved from the National Collaborating Centre for Acute Care (UK) (2009). According to the authors, however, the methodology adopted to estimate the values had not yet been validated. Besides, the original health utilities were estimated for different ocular conditions causing a defect in visual acuity, and might not be applicable to glaucoma patients since the pattern of visual loss in glaucoma differs from other conditions. It is, however, impossible to tell whether these limitations could have led to overestimation or underestimation of incremental QALY.

Probability of death could have also been underestimated under both interventions. In the absence of data to show that people die from glaucoma, I assumed that the probability of death among POAG patients was the same as that for the general population of Ghana. This assumption ignores the fact that the blind and people with visual impairment may have a higher probability of death from accidents, for instance. It is, however, difficult to determine the direction of the effect this limitation could have had on incremental QALY; it is difficult to determine how many patients under each intervention could have died from visual-impairment-related causes.

I assumed that all patients who progress from early POAG stage are given combination therapy. However, experts stated that some patients are shifted from one monotherapy to another before they are eventually given combination therapy, although the percentage of patients who fall into this category could not be estimated. This limitation may have led to overestimation of costs in both groups. It is, however, difficult to tell how this limitation could have influenced incremental cost.

In addition, the assumption that the severity of the POAG condition is similar in both eyes of a patient may not reflect reality since, in practice, a patient could present with unilateral POAG.

Finally, the WTP threshold adopted in the study may not reflect the actual WTP threshold in Ghana. While the WTP threshold used in the model was based on DALYs averted, the study measured health effect in terms of QALYs gained. QALYs gained and DALYs averted may

not be interchangeable since they are partly based on different assumptions and different methodologies.

6.4 Conclusion

Given the existing evidence, prostaglandin analogues is not a cost-effective alternative to beta blockers as a first-line medication for primary open angle glaucoma in Ghana. Prostaglandin analogues (specifically generic latanoprost) may, however, be cost-effective in treating POAG patients below 41 years. The population EVPI shows that further reseaech to reduce decision uncertainty would be cost-effective if expected cost of further research does not exceed USD 131 billion.

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Appendices

Appendix 1: Life Table for Ghana 2013

Age	Probability of Death	
	Female	**Male**
<1 year	0.042299	0.0521
1-4 years	0.022923	0.024086
5-9 years	0.016682	0.016784
10-14 years	0.010198	0.009866
15-19 years	0.011471	0.013503
20-24 years	0.014199	0.01904
25-29 years	0.016908	0.020019
30-34 years	0.01927	0.021748
35-39 years	0.023739	0.026648
40-44 years	0.027454	0.030997
45-49 years	0.032665	0.039465
50-54 years	0.04376	0.054715
55-59 years	0.056971	0.069616
60-64 years	0.084521	0.101838
65-69 years	0.131772	0.151119
70-74 years	0.208545	0.228736
75-79 years	0.322648	0.345576
80-84 years	0.489874	0.520373
85-89 years	0.701343	0.715682
90-94 years	0.92976	0.947176
95-99 years	0.969188	0.975211
100+ years	1	1

Appendix 2: Unit Costs of Resources, Converted from Ghana Cedis to US Dollars

Resource	**Unit of Pricing**	**Price (GH¢)**	**Price (USD)**
Acetazolamide Tablet, 250 mg	Tablet	0.25	0.06
Pilocarpine Eye Drops (2%)	10 mL bottle	12.5	3.19
Pilocarpine Eye Drops (4%)	10 mL bottle	14	3.57
Mean (Pilocarpine Eye Drops 2% and 4%)		13.25	3.38
Timolol Maleate Eye Drops, 0.5%	10 mL bottle	7.39	1.89
Trabeculectomy (Public Hospitals)	1 procedure	134.08	34.17
Trabeculectomy (CHAG hospitals)	1 procedure	136.95	34.90
Trabeculectomy (Mean of Public and CHAG hospitals)		135.515	34.53
Budesonide DPI, 200 micrograms	Inhaler	73.84	18.82
Salbutamol Inhaler, 100 micrograms	Inhaler	18	4.59
Fluticasone MDI, 125 micrograms	Inhaler	73.47	18.72
Beclometasone dipropionate Inhaler, 100 micrograms	Inhaler	64	16.31
Latanoprost (generic)	2.5 mL bottle	51	13.00
Latanoprost (Xalatan)	2.5 mL bottle	151.25	38.54
Mean (generic latanoprost and Xalatan)		101.125	25.77

NB: (USD 1.00 ≈ GH¢ 3.9240)

Appendix 3: One-way Sensitivity Analysis on Probability of Developing Asthma

Annual Probalility of asthma	Incr. Cost	Incr. QALY	ICER
0.00	1223426	104	11746
0.01	1223151	104	11715
0.02	1222873	105	11684
0.03	1222593	105	11653
0.04	1222310	105	11622
0.05	1222025	105	11591
0.06	1221737	106	11559

Appendix 4: One-way Sensitivity Analysis on Cost of Latanoprost (Excerpt)

Cost of Prostaglandin Analogues	Incr. Cost	Incr. QALY	ICER
13	506494	105	4821
14	562559	105	5355
15	618624	105	5888
16	674688	105	6422
17	730753	105	6956
18	786817	105	7489
19	842882	105	8023
20	898946	105	8557
21	955011	105	9090
22	1011075	105	9624
23	1067140	105	10158
24	1123204	105	10691
25	1179269	105	11225
26	1235333	105	11759

Appendix 5: One-way Sensitivity Analysis on Age of the Cohort (Ercerpt)

Age in Years	Incr. Cost	Incr. QALY	ICER
30	1295960	136	9495
31	1295090	136	9517
32	1294006	136	9541
33	1292658	135	9567
34	1290985	135	9594
35	1289583	134	9622
36	1288580	133	9654
37	1287326	133	9690
38	1285765	132	9730
39	1283826	131	9773
40	1281997	131	9819
41	1280350	130	9872
42	1278289	129	9931
43	1275720	128	9997
44	1272526	126	10068
45	1269536	125	10145
46	1266879	124	10233
47	1263554	122	10332
48	1259409	121	10442
49	1254252	119	10561
50	1249717	117	10690
51	1246130	115	10839
52	1241643	113	11010
53	1236054	110	11200
54	1229102	108	11408
55	1222439	105	11636
56	1216307	102	11899
57	1208639	99	12196
58	1199070	96	12527
59	1187133	92	12887
60	1176394	89	13277
61	1167576	85	13726
62	1156515	81	14231
63	1142638	77	14790
64	1125211	73	15396
65	1109913	69	16051
66	1098006	65	16797

Appendix 6: Two-way Sensitivity Analysis on Age of Cohort and Cost of Latanoprost (Excerpt)

Age in Years	Cost of Latanoprost (USD)					
	13	**14**	**15**	**16**	**17**	**18**
30	3922	4359	4795	5231	5668	6104
31	3931	4369	4806	5244	5681	6118
32	3942	4380	4819	5257	5696	6134
33	3952	4392	4832	5271	5711	6151
34	3964	4405	4846	5286	5727	6168
35	3976	4418	4860	5302	5744	6186
36	3989	4433	4876	5320	5764	6207
37	4004	4449	4895	5340	5785	6231
38	4021	4468	4915	5362	5809	6256
39	4039	4488	4937	5386	5835	6284
40	4058	4509	4960	5411	5863	6314
41	4080	4534	4987	5441	5894	6348
42	4105	4561	5018	5474	5930	6386
43	4133	4592	5051	5511	5970	6429
44	4163	4625	5088	5550	6012	6475
45	4195	4661	5126	5592	6058	6524
46	4232	4701	5171	5641	6111	6581
47	4273	4748	5222	5697	6171	6646
48	4319	4799	5278	5758	6237	6717
49	4369	4854	5339	5824	6309	6794
50	4423	4914	5405	5895	6386	6877