EFFICIENCY AND OPTIMIZATION MODELLING OF HEALTHCARE RESOURCES FOR TREATING TYPE 2 DIABETES MELLITUS PATIENT WITH BASAL INSULIN REGIMEN IN MALAYSIA

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LIST OF ABBREVIATIONS

AF	Atrial Fibrillation
BIA	Budget Impact Analysis
BMI	Body Mass Index
BOA	Budget Optimization Analysis
BP	Blood Pressure
CBA	Cost-Benefit Analysis
CDM	Core Diabetes Model
CE	Cost-Effectiveness
CEA	Cost-Effectiveness Analysis
CHF	Congestive Heart Failure
CK-MB	Creatinine Kinase Myocardial Band
CPG	Clinical Practice Guideline
cTnI	Cardiac Troponin I
cTnT	Cardiac Troponin T
CUA	Cost-utility analysis
CVD	Cardiovascular Disease
DES	Discrete Event Simulation
DPP-4	Dipeptidyl Peptidase-4
DRG	Diagnosis-Related Group
eGFR	Estimating Glomerular Filtration Rate
EQ-5D	EuroQoL 5-Dimensions
EQ-VAS	EuroQoL visual Analogue Scale
GLP-1	Glucagon-Like Peptide-1
GP	General Population
HDL	High-Density Lipoprotein
HIV	Human Immunodeficiency Virus
HF	Heart Failure
HRQoL	Health Related of Quality of Life
HTA	Health Technology Assessment
HUI	Health Utilities Index
ICER	Incremental Cost-Effectiveness Ratio

IHD	Ischemic Heart Disease
ICD	International Classification of Diagnosis
LAIA	Long-Acting Insulin Analogue
LDL	Low-Density Lipoprotein
LPO	Local Purchase Order
LY	Life Year
MI	Myocardial Infarction
NDRM	National Diabetes Registry Malaysia
NICE	National Institute for Health and Clinical Excellence
OAD	Oral Antidiabetic Drug
QoL	Quality of Life
PCI	Percutaneous Cardiac Intervention
PVD	Peripheral Vascular Disease
QALY	Quality-Adjusted Life Year
RCT	Randomized Controlled Trial
RF	Renal Failure
SD	Standard Deviation
SF-6D	Short Form 6D
SG	Standard Gamble
SGLT-2	Sodium-Glucose Co-Transporter-2
SMBG	Self-Monitoring Blood Glucose
SOPD	Surgical Out-Patient Department
T1DM	Type 1 Diabetes Mellitus
T2DM	Type 2 Diabetes Mellitus
TTO	Time Trade-Off
UKPDS-OM2	UKPDS-Outcome Model Version 2
US	The United States of America
VAS	Visual Analogue Scale
WHO	World Health Organization

LIST OF APPENDICES

KECEKAPAN DAN PENGOPTIMUMAN SUMBER KESIHATAN UNTUK MERAWAT PESAKIT DIABETES MELLITUS JENIS 2 DENGAN REGIMEN INSULIN BASAL DI MALAYSIA

ABSTRAK

Kajian ini bertujuan menentukan pengagihan peruntukan yang optimum untuk insulin analog jenis bertindak lama (LAIA) di kalangan pesakit Diabetes Melitus Jenis 2 (T2DM) apabila menerima satu penambahan bajet yang tetap. Objektif ini dicapai melalui tiga fasa kajian. Dalam fasa pertama, nilai-nilai input yang diperlu untuk analisis penilaian ekonomi diperolehi melalui data sekunder dan kajian keratan lintang. Fasa kedua melibatkan analisis keberkesanan kos untuk menentukan jumlah tambahan *quality-adjusted life year* (QALY) dan jumlah kos LAIA antara dan insulin NPH di kalangan pesakit yang disasarkan. UKPDS-OM Versi 2.0 telah digunakan untuk menganggarkan kesan komplikasi jangka panjang berkaitan dengan penyakit diabetes, sementara satu model menganalisis kos-utiliti telah disediakan untuk membandingkan kesan kejadian hipoglycemia yang teruk di antara LAIA dan NPH insulin. Output dari model-model ini telah digabungkan untuk mendapatkan jumlah tambahan QALY dan jumlah kos yang diguna dalam 40 tahun, antara LAIA dan NPH insulin. Nilai-nilai ini kemudian digunakan sebagai input dalam model pengoptimuman bajet di dalam fasa ketiga. Keputusannya menunjukkan bahawa pesakit T2DM yang menerima LAIA (terutamanya insulin Detemir) diunjurkan mendapat tambahan daripada tahun hayat (LY) terdiskaun dan QALY terdiskaun berbanding dengan NPH insulin, terutamanya mengambil kira kesan hipoglycemia yang teruk. Penemuan daripada analisis pengoptimuman bajet menunjukkan bahawa pengagihan yang terbaik ialah bajet tambahan diagagihkan kepada pesakit warga tua (60 tahun ke atas) dan mempunyai

tahap HbA1C yang tinggi berbanding dengan pengagihan peruntukan secara sama rata kepada semua subkumpulan. Jumlah QALY tambahan yang diperoleh dalam 40 tahun untuk pesakit berumur 60 tahun dengan HbA1c melebihi 10% adalah antara 63.61 (insulin Glargine sahaja) dan 311.83 (insulin Detemir sahaja) apabila satu tambahan 10% kepada bajet semasa. Campuran penggunaan insulin glargine dan insulin detemir membolehkan penyebaran penggunaan LAIA lebih tinggi (>360 orang pesakit), dengan jumlah QALY tambahan yang dicapai yang lebih baik (>63.61). Dalam analisis pengoptimuman bajet, pilihan fungsi objektif adalah kritikal semasa membuat keputusan. Pembuat keputusan mesti menentukan sejauh mana mereka mahu tahap QALY maksima dicapai dalam sistem kesihatan. Kesimpulannya, model pengoptimuman yang dibentangkan dalam kajian ini secara langsung memaklumkan kepada pembuat keputusan ialah cara membuat keputusan yang optima dalam pengagihan sumber yang terhad apabila satu pengenalan intervensi baru diperkenalkan di kalangan pesakit T2DM.

EFFICIENCY AND OPTIMIZATION MODELLING OF HEALTHCARE RESOURCES FOR TREATING TYPE 2 DIABETES MELLITUS PATIENT WITH BASAL INSULIN REGIMEN IN MALAYSIA

ABSTRACT

The study aims to determine the optimal allocation of long-acting insulin analogues (LAIA) among patients with Type 2 Diabetes Mellitus (T2DM) within a fixed budget. The objective was achieved via a three-phase study. In the first phase, the input values for economic evaluation analysis were obtained from secondary data and cross-sectional study. The second phase involved cost-effectiveness analysis to determine the total quality-adjusted life years (QALYs) gained and costs for LAIA and NPH insulin among the targeted patients. UKPDS-OM Version 2.0 was used to estimate the impact of long-term diabetes-related complications, while simple cost-utility analysis was conducted to compare the impact of a severe hypoglycemic event between LAIA and NPH insulin usage. The outputs of these models were combined to obtain total QALY gained and the total cost over 40-year for LAIA versus NPH insulin. These values were then used as inputs for the budget optimization model in phase three. The result showed that T2DM patients treated with LAIA (especially insulin detemir) were projected to benefit from improved life year (LY) and QALYs compared to NPH insulin, especially when accounting for the impact of severe hypoglycemia. The findings from the budget optimization analysis showed that the best scenario for the additional budget was to allocate it to the high HbA1c level and elderly patients (above 60 years old), instead of the resources being equally allocated to all subgroups. Total QALYs gained for patients 60 years old with HbA1c exceeded 10%, while reaching between 63.61 (insulin glargine only) and 311.83 (insulin detemir only) for 40-year-

olds for an additional 10% of the current budget. Using both insulin glargine and insulin detemir together allowed higher diffusion (>360 patients) of LAIA, with better QALYs gained (>63.61). In budget optimization analyses, the choice of objective function was critical in decision-making. Decision-makers must determine how closely they would like to actualize the maximum QALY level in the health care system. The optimization model presented here addresses the lack of information needed to inform decision makers ways to allocate limited resources while introducing new interventions among T2DM patients for the best-optimized outcomes.

CHAPTER 1

INTRODUCTION

1.1 The economic burden of Type 2 Diabetes Mellitus

Type 2 Diabetes Mellitus (T2DM) poses a significant burden for the healthcare system and its management takes nearly 1.8% of world global domestic product. The four factors contributing to the burden of diabetes are labour-force dropout, absenteeism, presenteeism, and mortality (Bommer et al., 2017). For instance, in the United States of America, the cost of diabetes management was estimated to be USD245 billion in 2012, with 28% of it consumed by indirect costs like loss of productivity (Bommer et al., 2017) while the cost of managing complications for each T2DM patient over a period of 30 years was estimated at USD47,240 (Caro, Ward, & O'Brien, 2002). In Latin America and the Caribbean, the total economic burden for diabetes was USD65.22 billion in 2000 (Bommer et al., 2017) while in low-income and middle-income countries, it was estimated that the direct and indirect cost of the burden ranged from USD242 to USD4,129 and USD45 to USD16,914 per capita, approximately (Seuring, Archangelidi, & Suhrcke, 2015). It was estimated that the Malaysian government incurred at least RM1.4 billion in public healthcare to manage diabetes and its complications (Mustapha et al., 2017), which is expected to increase especially in the younger population (Hussein, Taher, Gilcharan Singh, & Chee Siew Swee, 2015; Tee & Yap, 2017).

A large portion of the economic burden of diabetes is from the management of diabetes-related complications (Caro et al., 2002; Li et al., 2013). The complications of T2DM can be divided into macrovascular diseases, related to cardiovascular diseases like stroke and myocardial infarction (MI), and microvascular complications including diabetic retinopathy, which leads to blindness, and diabetic neuropathy with the possibility of developing foot ulcers or amputation, and renal failure due to

microalbuminuria (Fowler, 2011). A study from the US concluded that macrovascular diseases, nephropathy and retinopathy, are incurring a significant amount of the expenses in diabetes management (Caro et al., 2002). As well, expenses for the management of diabetes-related complications by the patient increase over time because the age group for diabetes onset is becoming younger (Alberti et al., 2004). For instance, the incidence of T2DM in Japan increased almost fourfold in the age group 6-years-old to 15-years-old and incidences of newly diagnosed T2DM in children and adolescents was between 8% and 45% in the US (Alberti et al., 2004). Furthermore, a retrospective study in Sweden concluded that the age of diagnosis for T2DM is indicative of survival and cardiovascular risk. The study suggested the treatment of T2DM needed to be more aggressive among younger diabetics (Sattar et al., 2019). Another retrospective study conducted in the US found a higher proportion of patients before 45 years old may require insulin treatment, as they are more likely to develop microalbuminuria compared to patients within the usual age group ($\geq$45 years old) after the onset of disease (Hillier & Pedula, 2003).

The burden of diabetes-related complication, either expenses incurred at an outpatient or inpatient setting, was discussed in previous local literature (Hejazi, Mazlan, Abdullah, & Engkasan, 2015; Mustapha et al., 2017; Nor Azlin, Syed Aljunid, Noor Azahz, Amrizal, & Saperi, 2012; Rohana D et al., 2007). The outpatient cost is between RM454 and RM1,281 for each diabetic patient per year in Malaysia (Mustapha et al., 2017). For inpatient settings, the cost per admission in a hospital, with or without specialists, is nearly RM2,000 (Sharifa Ezat WP, Azimatun NA, Amrizal MN, Rohaizan J, & BS, 2009). Renal failure requires the highest management cost (between RM23,500 and RM36,000 in the event year) compared to other diabetes-related complications (Todorova, Hnoosh, Bloomfield, & Shiu, 2012), while the estimated amount of heart

failure per hospitalization was approximately RM2,700 (Medical Development Division, 2013; Mustapha et al., 2017).

The management of adverse events related to hypoglycemia medication is also a burden for the healthcare payers. For instance, a literature review that was conducted to identify the economic burden of hypoglycemia in patients with Type 1 and T2DM in the US setting concluded that the direct cost for an episode of hypoglycemia requiring assistance from a healthcare practitioner was USD1,161 (Foos et al., 2015). A retrospective study in the US found that the mean costs of hypoglycemia visits were USD17,564 for each hospitalization, USD1,387 for an emergency department visit and USD394 for an outpatient visit (Quilliam, Simeone, Ozbay, & Kogut, 2011). This study concluded that the incidence of hypoglycemia was connected to higher per-episode costs.

1.2 The use of economic evaluation analysis in the healthcare system

Economic evaluation is increasingly employed to make health care decisions. The analyses can provide answers regarding the efficacy and maximized benefits of implementing new procedures by comparing the effectiveness between current and new interventions (Cunningham, 2000; Morris, Devlin, Parkin, & Spencer, 2014). As economic evaluation manages the demand for and informs decision-makers about the cost of implementing the new interventions (Cunningham, 2000; Morris et al., 2014), like, decision to subsidize a healthcare program, they are also informed about the "opportunity cost" or the value of a resource in its best alternative use within limited resources to improve patients' health (Cunningham, 2000). Consequently, economic evaluation is vital for the decision-makers or payers who are involved in the provision

and purchase of healthcare as it gives them leverage in bargaining with pharmaceutical companies supplying new healthcare products (Cunningham, 2000).

The allocation of healthcare resource is complex as it involves a wide range of very different healthcare interventions across different healthcare fields (Cunningham, 2000). For instance, the decision-makers may require a tool to help them decide the allocation of budget across three different types of interventions, like a T2DM prevention campaign, vaccination programs for the elderly, and introduction of new precise medication for cancer, with consideration needed in relation to patients' health status, and the decision needing to be justifiable to the decision-makers and community organizations (Cunningham, 2000). The responsibility of decision-makers is in rationing allocated resources to ensure that the distribution maximizes the health of society which can be seen in an increase of patients' life or reduced infant mortality (Cunningham, 2000). Another approach to resource allocation is that everyone has a 'claim' to the number of healthcare resources which gives them a level of health equal to that of others, and each person has an equal right to access the system. Hence, when making social and economic choices, those who are the least advantaged should obtain maximum benefit (Cunningham, 2000). In conclusion, economic evaluation is one of the tools that provide information applicable to the decisions of service and health personnel to achieve a more equitable and sustainable healthcare system.

1.3 The limitation of cost-effectiveness and budget impact analysis

Cost-Effectiveness Analysis (CEA) and Budget Impact Analysis (BIA) are part of economic analyses tools used to aid decision-makers in deciding treatment options to be employed for any healthcare issue especially in reimbursement of drugs and medical technologies while adhering to a strict financial constraint. It is believed that the reimbursement decision made with reference from cost-effectiveness analysis may lead to a more efficient allocation of resources. CEA allows for an efficient allocation of healthcare resources in the absence of a market, assuming constant returns to scale, independent treatment options, and perfect divisibility (Epstein, Chalabi, Claxton, & Sculpher, 2007). The decision-maker, by using cost-effectiveness threshold, can assess whether a new intervention generates benefits at an acceptable cost. For example, a new medication has a higher chance of being reimbursed by the National Institute for Health and Clinical Excellence (NICE) in the United Kingdom when the ICER value for the new medication, compared to the current medication, falls below GBP30,000.

However, using CEA threshold for the decision-makers to consider a new intervention may not be an appropriate method. All new interventions with the ICER that does not exceed the given threshold may be considered in the funding decisions and this may only encourage pharmaceutical companies or interested parties to tailor their estimates or inputs according to the model. For instance, by manipulating the choice of the comparator and the target of the population, the intervention is ensured not to exceed the given threshold so that their products are listed in the national funding regardless of its net benefits (Bertram et al., 2016). Consequently, incorrect decisions are possible if the analyses do not reflect the policy context accurately since CEA does not reflect the impact of costs for all competing healthcare programs nor does it efficiently resolve allocation issues because it does not identify the opportunity costs of

any decision making (Epstein et al., 2007). Besides, an annual single overall budget is usually received by the healthcare payers in most of the healthcare organizations to fund all healthcare programs, and financial affordability remains an issue because it requires massive allocation in order to implement and support new interventions. Thus, CEA, in general, is a less reliable tool for expenditure planning in any fixed budget.

In recent times, BIA is increasingly used in addition to CEA to define the extent of budget change after the implementation of a new intervention (Goodman, 2017). It is widely used (including in Malaysia) to assist decision-makers in assessing affordability of an innovative intervention, identifying financial consequences in the adoption and diffusion of any new healthcare interventions on the healthcare system (Sullivan et al., 2014), and understanding its impact on the organization's budget (Goodman, 2017). However, BIA is not linked to any achievement of specific outcome measures. Thus, it is unable to evaluate the maximum aggregate health effectiveness; benefits gained with new interventions, diffusion of that specific intervention and the opportunity loss for budgetary decisions if the decision-makers have a limited budget. Usually, BIA is used to inform the financial impact of a new intervention instead of identifying the new interventions to be prioritized for funding. Hence, in the event of a more complex budgetary rule; or insufficient or limited funding, BIA becomes a less reliable tool to assist healthcare decision makers as it cannot deduce the best intervention to maximize benefits for patients and communities (Crown et al., 2017; Stinnett & Paltiel, 1996).

The limitations of CEA and BIA have encouraged some researchers to employ mathematical optimization models to aid in the decision-making process. (Stinnett & Paltiel, 1996) discussed the constrained optimization model which is able to allocate

healthcare resources efficiently but that is also subject to budget constraints. Budget Optimization Analysis (BOA) can allocate the available resource to optimize the health system and patient care interventions (Crown et al., 2017) because it can inform decision-makers about maximizing net benefits gained from implementing such interventions for the population with any given budget. Moreover, BOA is able to evaluate the distribution of different interventions in an assumed population since it approaches the problem of expenditure allocation by considering the costs and benefits in the face of budgetary constraint and perfect divisibility (Earnshaw et al., 2002). It maximizes or minimizes the objective function (decision variables and constraints) that represents a quantifiable measure of interest to the decision-makers (Crown et al., 2017). BOA identifies an 'optimal' solution that achieves the best outcome while fulfilling the introduced constraints (Crown et al., 2017) and resolving budget distribution issues in any healthcare organization. Hence, BOA is gaining interest, as its primary objective is to ensure the improvement of population health within a restricted financial plan (Crown et al., 2017).

1.4 Problem statement

In Malaysia, the prevalence of diabetes was 20.8% in 2015 (Zanariah et al., 2011), with more than one-half of patients on medication seeking treatments at government facilities (Bakri, 2007). The use of insulin in Malaysian government health facilities was very common, especially insulin recombinant synthetic human for treating T2DM (Abd Aziz et al., 2013). Insulin recombinant synthetic intermediate-acting insulin was the most common basal insulin used in the public healthcare institutes in Malaysia (Abd Aziz et al., 2013).

In the current market, two main types of basal insulin dominate, and they are the intermediate-acting insulin (e.g., Neutral Protamine Hagedorn (NPH) insulin) and Long-Acting Insulin Analogues (LAIA) (e.g., insulin glargine and detemir). LAIA overcome the pharmacokinetic shortcoming of the NPH insulin by genetic modification in the amino acid sequence of the insulin molecule (Petznick, 2011) which enables the LAIA to maintain its level of basal insulin and peak-less compared to intermediate-acting human insulin (Rolla, 2008). Besides, the efficacy of LAIA in the real-life setting is verified with its significantly reduced symptomatic hypoglycemia and nocturnal hypoglycemia risk (at least 21% and 50% respectively) compared with NPH insulin (Bolli, Di Marchi, Park, Pramming, & Koivisto, 1999; Mavrogiannaki & Migdalis, 2012). NPH insulin also found that the rates of overnight hypoglycemia was lower in T2DM patients with LAIA (Mavrogiannaki & Migdalis, 2012). Compared with NPH insulin, LAIA improved the fasting blood glucose level and reduced the HbA1c by 0.03% (Mavrogiannaki & Migdalis, 2012). The increase of body weight is a common issue in insulin therapy. Weight gain is less in LAIA compared with NPH insulin, especially for insulin detemir (Mavrogiannaki & Migdalis, 2012).

However, the use of LAIA for patients with diabetes mellitus in Malaysia's public hospitals and clinics is low because it was estimated that the use of insulin analogue was approximately 2% to 3% of insulin usage (Sabirin & Ku Abd Rahim, 2012), probably attributed to its high cost (Letchumanan et al., 2013; Sabirin & Ku Abd Rahim, 2012). The acquisition cost of insulin glargine, for instance, is at least three to five times higher compared to NPH insulin (Sabirin & Ku Abd Rahim, 2012).

Although the use of LAIA increased the acquisition costs, its use could save millions due to the decrement in the cost of diabetes complication management (Gordon,

Evans, McEwan, Bain, & Vora, 2013). By switching 10% of T2DM patients to LAIA, the cost of diabetes complication management may be reduced by as much as GBP34 million compared to an increase of GBP5 million in drug acquisition cost (Gordon et al., 2013). Similarly, it is believed that by switching a fraction of T2DM patients to LAIA in Malaysia, it will help to reduce the diabetes care cost in the public healthcare setting. Using LAIA may be saving the resource of healthcare because it reduced the costs like costs associated with hypoglycemia-associated hospitalization, excess blood glucose monitoring costs and additional costs related to suboptimal insulin dosing and therapy nonadherence consequent upon hypoglycemia (Gordon et al., 2013).

The use of LAIA at healthcare clinics and hospitals is always tied to macro-level policies, conditions, guidelines, and resource allocation which influences the usage and diffusion of LAIA at the micro-level (Kapiriri, Norheim, & Martin, 2009; Scheunemann & White, 2011). The decision-makers at the micro-level are always informed that it has a maximum capped expenditure in the annual budget. Most of the time, it is impossible for decision-makers at macro-level to extract money from existing intervention to pay for new ones by which they could maximize health gains. Hence, they are restricted to providing a sum of additional budget for the new intervention, further requiring them to identify the opportunity cost of adopting new interventions (such as LAIA), to avoid uncontrolled expenditure growth and ensure the maximum benefits gained for patients when implemented at the micro-level. Consequently, a tool is essential to help them understand the diffusion of new intervention (i.e. LAIA) based on budget and individual patients' condition to ensure equity of allocation.

1.5 Objectives of the study

The general objective of the study was to determine the optimal allocation of LAIA among patients with Type 2 Diabetes Mellitus (T2DM) within an additional fixed budget. Three sub-objectives were developed to achieve the general objective. These were as follow:

I. To develop the model of CEA and BOA.
II. To identify and estimate the parameter inputs for BOA and CEA.
III. To estimate the optimum allocation resource method for LAIA among the population of T2DM where efficiency is maximized, subject to various cost-constraints.

1.6 Significant of the study

This is the first study of its kind to evaluate the allocation of resources from the macro-level, incorporating various considerations, including the diffusion of benefits among receivers within the available budget, and providing vital insights into the importance of budget optimization analysis by assisting stakeholders in the procurement of novel, innovative, and expensive medical products. The tool developed in the study may be employed at micro-level to achieve optimum use of the allocated budget especially for newly launched medications and devices in healthcare institutions.

CHAPTER 2

LITERATURE REVIEW

2.1 The use of economic evaluation analysis for healthcare prioritization

Economic evaluation is a method used to compare the costs and benefits of alternative health care interventions (Drummond, Sculpher, Claxton, Stoddart, & Torrance, 2015). It deals with inputs and outputs which can be described as the costs and consequences like the overall benefits expected to be received when the interventions are considered (Drummond et al., 2015). There are many approaches to economic evaluation and different techniques providing a different measurement of consequences even though the measurement of costs for both alternatives are in monetary units (Drummond et al., 2015). Three common economic evaluation approaches are summarized in table 2.1, including the measurement characteristics of the various forms of economic evaluation.

Table 2.1 Summary of the characteristics of economic evaluation analysis

Type of study	Measurement/ valuation of costs in both alternatives	Measurement/ valuation of consequences
Cost-benefit analysis	Monetary units	Monetary units
Cost-effectiveness analysis	Monetary units	Natural units (e.g., life-years gained, disability days saved, points of blood pressure reduction, etc)
Cost-utility analysis	Monetary units	Healthy years (usually measured as QALY)

Cost-benefit analysis (CBA) compares the benefits against the costs of a healthcare program, where all the benefits are valued in monetary terms including the uncertain outcomes, such as the effects on survival and health (Drummond et al., 2015). In CBA, an intervention or treatment is considered ‘worthwhile’ when the monetary value of all the benefits exceeds the costs, and the measure of benefit encompasses a

broader range of benefits; in particular, non-health benefits (Brazier, Ratcliffe, Salomon, & Tsuchiya, 2007). The advantage of using CBA is that it can measure a wide range of benefits, including non-health benefits (Brazier et al., 2007). Three techniques can be used for obtaining the monetary value of health outcome in CBA. They are (i) human capital, (ii) revealed preferences, and (iii) stated preferences of willingness to pay (Drummond et al., 2015). Different approaches to obtaining the health outcomes has their limitation that may be affected the estimation of the health outcome. For instance, the weakness of revealed preference approach was that the outcome may be affected by the job and wage (Brazier et al., 2007). The willingness to forgo is higher for the respondent with higher earnings compared to the respondent with lower earnings even though both respondents face similar risks. Arguably, CBA states that the health effects could be valued in monetary units because monetary value was attached to the health (and life) of a person (Brazier et al., 2007; Drummond et al., 2015). In view of its limitations, this method is rarely used (Brazier et al., 2007) these days.

Cost-utility analysis (CUA) and CEA are the most common tools used for economic evaluation because they provide a method for comparing alternative interventions across a range of outcomes; specifically, a direct ranking of the costs and benefits of specific strategies for preventing or treating a disease (Arnold, 2010). CEA is considered the best method of achieving a given objective, usually measured in its 'natural' units, and presents results in terms of cost-per-unit. The overall goal of CEA is to provide a single measurement, known as the incremental cost-effectiveness ratio (ICER), which relates to the amount of benefit derived by making an alternative treatment choice to the differential cost of that option. 0 shows the formula to calculate ICER value.

Equation 1 $$= \frac{\text{Cost for intervention} - \text{Cost for standard treatment}}{\text{Effectiveness for intervention} - \text{Effectiveness for standard treatment}}$$

On the other hand, CUA, which can be considered a subset of CEA, compares the costs of alternative health care programs with their utility, which is usually measured in terms of QALYs. QALYs combine survival and quality of life into a single value while the quality of life (QoL) component is measured using a metric known as a health utility (Arnold, 2010). Consequently, the advantage of using CUA is that it allows the comparison of ICER across different diseases containing different 'natural' units.

2.2 Essential components of an economic evaluation

In economic evaluation, the critical inputs are (i) utility, (ii) costs, (iii) type of model, (iv) comparison of efficacy between new and current interventions, and (v) patients' demographic data (Drummond et al., 2015). Measuring different health outcomes may demonstrate the effectiveness of treatment, yet it is difficult to allocate healthcare resources efficiently when the outcome is not standardized. Therefore, to enable comparisons across different areas of healthcare, a standard measure is needed.

QALY is a generic measure of disease burden, including both patients' quality and quantity of life lived. In brief, the QALY approach is necessarily a weighting scheme where the time spent in ill health (measured in years) is multiplied by a weight measuring the relative desirability of the illness state to yield a number that represents the equivalent number of years in full health (Gafni, 1994), and is favourably used in health economics to summarize the measurement of health outcomes (Whitehead & Ali, 2010). In order to generate QALYs, health utilities such as Health-Related of Quality of Life (HRQoL) weight are generated directly or indirectly (also called generic preference-based measures) by defining health states (Whitehead & Ali, 2010).

The three most widely used techniques for eliciting preferences are visual analogue scale (VAS), time trade-off (TTO), and standard gamble (SG) (Drummond et al., 2015). An alternative to these three, and a widely used method, is to bypass the measurement task by using one of the pre-scored multi-attribute health status classification systems, such as the commonly used questionnaire, including the EuroQol (EQ)-5-Dimensions (EQ-5D), the Short Form 6D (SF-6D), and the Health Utilities Index (HUI) (Drummond et al., 2015). The instruments differ, such as in the dimension or severity of health state, the number and description of levels defined for each dimension, the population on which the preferences are based, and in terms of the valuation method: the TTO was used to value the EQ-5D, whereas the SF-6D and HUI involve SG (Whitehead & Ali, 2010).

VAS consists of a line on one page, approximately 10 cm in length, with clearly defined endpoints with or without other marks along the line (Drummond et al., 2015). The top of the scale indicates the "best imaginable health," whereas the bottom of the scale indicates the "worst imaginable health". The respondents gave their preferred health state by writing a value between the line. TTO approach is more complex compared to the VAS. The TTO method gives preferences for health states by leading a subject to imagine living in a defined number of years in an imperfect health state (Attema, Edelaar-Peeters, Versteegh, & Stolk, 2013). Individuals rate the health state on the scale. The choice is between living for the rest of their life in an impaired health state (i.e., T2DM), or living in full health for a shorter period (Attema et al., 2013). The participants were asked to put a value for a imperfect health state with the different length of full health state until the respondents have the conclusion that it is indifferent between imperfect health state and full health state (Attema et al., 2013; Whitehead & Ali, 2010). Compared to VAS, TTO studies are conducted in the context of health

technology assessment (HTA) to inform the healthcare field policy makers in making resource allocation decisions (Attema et al., 2013). SG is recommended to measure individuals' preferences under uncertain conditions and to express the outcome of different therapeutic choices in "utility values" and health program evaluation (Gafni, 1994). In SG, an element of risk is involved in the decisions faced by individuals, which is to choose between the certainty of remaining in a particular health state or to take a gamble of either being in full health or risking death (Whitehead & Ali, 2010). The probability of experiencing death is varied until the individual is indifferent between the certainty and the gamble (Whitehead & Ali, 2010).

The particular range of costs included in an economic evaluation analysis depends on four points: (a) perspective of the study, (b) if the comparison is restricted to two or more of the programs immediately under study, (c) if some costs are more likely to confirm a result that would be obtained by consideration of the narrower range of the costs and (d) the relative or the magnitude of the costs (Drummond et al., 2015; Slothuus, 2000).

It is essential to specify the perspective, such as societal perspective, the Ministry of Health, other government ministries, the patient, the employer, and the agencies providing the program because an item may cost differently from different angles (Drummond et al., 2015). For instance, patient expenditures are considered cost when the societal perspective is used instead of the Ministry of Health's point of view. The costs commonly excluded from comparison is restricted to the treatment immediately under the study because the costs will not affect the choice between the given programs (Drummond et al., 2015). The consideration of patients' costs merely confirms a result that might be obtained from the health sector and the operating costs within it (Drummond et al., 2015). For example, treating a given condition by restricting

access to surgery may not only lower cost for the patient, but may also lower financial burden on the healthcare system (Drummond et al., 2015). The evaluator may not consider patients' cost and the choice of program is very unlikely to be changed; hence, it is redundant to consider these costs because it is unlikely to give major impact to the study results (Drummond et al., 2015).

After the relevant types of costs have been identified, the individual items must be measured and valued before the economic evaluation analysis is conducted (Drummond et al., 2015). The cost consists of two elements: (a) resource use and (b) price (Drummond et al., 2015). The measurement of resource use is dependent on the context of the study, which can be collected from case reports if the analysis is being conducted alongside a prospective clinical study (Drummond et al., 2015). In order to avoid confusing patients or users, it is suggested that the costs be traced up to one year for study (Drummond et al., 2015). Another issue to contend with is the inclusion of future unrelated costs, like consumption costs and costs for diseases that are unrelated to the intervention, which are being evaluated, and the occurring costs during the added year of life which might be excluded. This is considered because existing data is inadequate, failing to capture the future resource usage of all unrelated diseases (Drummond et al., 2015). However, there were suggestions that future unrelated costs should be included if an intervention is undertaken, subject to a budget constraint, as a result might affect the prioritization (Slothuus, 2000). The costs included in the economic analysis are dependent on the objective and context of the evaluation (Slothuus, 2000). Table 2.2 lists the number of cost items, adopted from a report wrote by Ulla Slothuus, under different perspectives.

Table 2.2 Cost items to be included under different study perspectives

Cost element	Societal	Patient and patient family	Self-insured employer	Public or private insurer	Managed-care plans
Medical care (aggregate)	All medical care costs	Out-of-pocket expenses	Covered payments	Covered payments	Covered services
"Units"	All units	Those paid out-of-pocket	Those covered	Those covered	Those covered
"Price"	Opportunity cost	Amount paid out-of-pocket	Amount paid + admin cost	Amount paid + admin cost	Marginal cost
Patient time cost for treatment or intervention	Cost of all time used	The opportunity cost to the patient	Only if it affects productivity, paid sick time, admin cost	None	None
Marketed caregiving	All costs	Out-of-pocket expenses	Covered payments	Covered payments	Covered payments
Un-marketed informal caregiving	All costs	The opportunity cost to caregiver	None	None	None
Transportation and other non-medical services	All costs	All costs	None	None	None
Sick leave, disability, other-transfers	Admin cost only	Amount received	Amount paid by employer + own admin	Amount paid by employer + own admin	If any paid

The clinical study is the basis of economic evaluation, providing all sources of data and a framework for overall evaluation (Drummond et al., 2015). The data can be retrieved from clinical studies, including patients' baseline demographic and clinical efficiency of the intervention and comparator, which can inform about the net additional health benefits of a new treatment compared with the existing treatment. Randomized

controlled trial (RCT) is one of the clinical study tools commonly used to measure the cost-effectiveness of healthcare intervention and RCT's value is considered a source of "internal validity" (Drummond et al., 2015). Although RCTs provide high internal validity, not all RCTs are suitable for economic evaluations, and numerous issues and problems are faced by researchers when using data obtained from RCTs, including limited options for comparing therapies, over-detailed measurement in trials, and intermediate outcomes instead of final health outcomes. Other issues for using RCT include an inadequate number of patients on follow-up. As well, the collected data may reflect the effects of the trial rather than that of the resources needed to provide the new intervention (Drummond et al., 2015). Other clinical studies, such as observational studies, can be used for economic evaluation, but the lack of randomization is its most significant disadvantage (Drummond et al., 2015).

2.3 Types of decision modelling

Decision modelling provides a framework for developing expected estimates in a flexible analytic framework, or measuring an option's cost-effectiveness in order for researchers to test the condition of uncertainty (Arnold, 2010; Drummond et al., 2015). The most important aspect of the decision modelling process is that the model must be able to represent sets of reasonable chodiice (Arnold, 2010). The critical elements of the decision-analytic model use probability to reflect the likelihood of events or changes in health and the expected values weighted by the probability of a patient following the treatment pathway in the model to make informed decisions as it measures the frequency of an event in a given sample or population (Drummond et al., 2015).

There are many types of models, such as decision trees and Markov models (Arnold, 2010; Drummond et al., 2015). A decision tree represents individuals' possible

prognoses following some sort of intervention by a series of pathways (Drummond et al., 2015) starting with a specific problem formulation. These could include choice between therapy A and therapy B in a particular condition, of which the decision context is followed by a decision node for each choice and chance nodes, thus describing the possible outcomes implied by the respective choices. However, the limitation of using a decision tree model is that it is not applicable to complicated long-term prognoses, especially chronic diseases. The Markov model is widely used in economic evaluation to handle decision problems where the progression of disease for a patient is based on a series of ‘ states’ (Drummond et al., 2015). In the Markov model, cycles are the probability of a patient occupying a given state, assessed over a series of the discrete period, and the length of these cycles depends on the evaluated disease and intervention (Drummond et al., 2015). In some situations, a decision tree model and Markov model are combined to analyze the expected value of outcomes (Drummond et al., 2015). However, the Markov model is more common compared to the decision tree (Drummond et al., 2015). Therefore, the application of a model is highly dependent on (a) the complexity of the problem, (b) the need to extrapolate model outcomes over extended periods of time, and (c) whether the resource constraints and interactions of various elements in the model are required (Arnold, 2010).

2.4 Budget impact analysis, the important elements

The use of BIA is increasingly required by reimbursement authorities in many countries like Malaysia, South Korea, Taiwan, and Thailand, along with CEA, before formulary approval or reimbursement (Sullivan et al., 2014). It is an approach that estimates the financial consequences of the adoption and diffusion of a new healthcare intervention within a specific health setting or system context, given certain resource constraints (Mauskopf et al., 2007). Therefore, decision-makers prefer using BIA to forecast the budget and plan healthcare budgets at national and regional levels, including healthcare programs by healthcare delivery organizations, and private health insurance plans (Sullivan et al., 2014). The guideline for BIA is presented in the The Professional Society for Health Economics and Outcome Research (ISPOR) task force (Mauskopf et al., 2007; Sullivan et al., 2014) in order to provide a clear standard for improving consistency in the analyses and results of BIA. A freestanding BIA analytic framework, which was recommended by authors as key elements, must account relevant features of the healthcare system, the possible constraints and restrictions, the anticipated uptake of the new intervention, and the use and effects of the current and new interventions (Sullivan et al., 2014).

It is important to consider the features of the healthcare system and insurance coverage decisions during the design of a BIA model because it will influence the given budget (Sullivan et al., 2014). Patients may not be fully covered by reimbursement authorities for new technologies or interventions, and patients may even be required to pay a portion of the expenses as decision-makers enforce administrative and clinical hurdles, offer many treatment options, impose restrictions on the usage of new interventions and conditions for reimbursement of said technology or intervention (Sullivan et al., 2014). For instance, patients who are readmitted within 15 days of

discharge may not be paid according to the reimbursement policy and thus, a new intervention may not be considered in this scenario.

The perspective of the budget holder, too, needs to be considered (Arnold, 2010; Sullivan et al., 2014). The budget holder can be the national health insurance or a national health service, a private insurer or a hospital manager (Arnold, 2010). Different budget holders have different perspectives and this may affect the estimation of the outcome (Sullivan et al., 2014). For example, a pharmacy budget holder will be concerned only with the expenses for drugs, but this may be subsumed for a hospital or regional budget holder (Sullivan et al., 2014).

The third aspect which needs to be considered in BIA is the use and cost of current and new interventions. The use of current and new intervention can be defined according to the size and characteristics of the eligible population and of the distributions of any characteristics; for instance, the disease severity or stage, comorbidities, age, sex, ethnicity, and other characteristics, because these may impact the budget (Sullivan et al., 2014). When conducting BIA for a chronic disease like T2DM, the target population may consist of new patients, though longstanding patients must also be considered, as the overall total number of the population may increase over time.

The current interventions must be defined at the start of the BIA study and current interventions like ‘no intervention,’ ‘intervention that might be replaced by the new one’ and ‘off-label use’ must be included (Sullivan et al., 2014). However, the off-label use of new interventions should not be considered in the BIA unless upon request by the budget holders as there is little or no effectiveness, and lack of safety data, on such use (Sullivan et al., 2014). In the analytic framework, the variations in usage and cost-relevant details of how the new interventions are used must be addressed (Sullivan

et al., 2014). The introduction of a new intervention in the market may either slowly uptake the current market proportion of intervention or expand the current market (Sullivan et al., 2014). In BIA, there are four possible types of changes between the use of new and current intervention: (1) the new intervention used as a substitution for current intervention, (2) the combination use of new and current intervention, (3) as supportive care and used in patients experiencing intolerance and inconvenience with current intervention (4) implementation of new intervention due to the loss of effect with the current interventions (Sullivan et al., 2014). These changes may impact the outcome of BIA because they may offset the expenses of the new intervention (Sullivan et al., 2014).

The costs considered in BIA do not only include the acquisition cost for the current and new intervention but also condition-related costs and other direct costs (Sullivan et al., 2014). The acquisition cost for the intervention can be determined by multiplying the budget holder's price with the number of people in the eligible population (Sullivan et al., 2014). The condition-related costs are costs of using condition-related healthcare services like number of ward readmissions, disease-progression rate, and symptoms of the disease (Sullivan et al., 2014), which must be accounted for in BIA study. These costs may change due to the introduction of new interventions. For example, the introduction of LAIA as a replacement for NPH insulin may reduce the number of diabetics at the emergency department due to severe hypoglycemia, thus reducing the cost of ER management. Costs which are not related to the budget holder, like improvement in productivity, social services, and other costs outside the healthcare field should not be included in a BIA (Sullivan et al., 2014).

Others elements should be considered during BIA, including time horizon, discount rate, and the uncertainty of the input parameters, as it always estimates the

impact of budget for a time horizon of 3 to 5 years (Arnold, 2010; Sullivan et al., 2014) and the flow of financial consequences which are shown on a yearly basis. Even though CEA applies a discounted rate over a time horizon, it is not recommended for BIA because the budget holder's interest in the impact is expected at each point in time (Sullivan et al., 2014). There are two types of uncertainty in a BIA, input values used and fundamental assumptions. Of which, their values are recommended to be changed to reflect the plausible alternative scenarios (Sullivan et al., 2014).

The reporting of BIA must be fully transparent, with clear presentation of all the sources for inputs and ranges of uncertainties (Arnold, 2010). BIA should be presented in a simple spreadsheet (Sullivan et al., 2014) that must easily reflect health conditions, its natural history, and its consequences for each year after the new drug is introduced into the market. Then readily validated for its structure, content, and outcomes (Arnold, 2010).

2.5 Budget optimization analysis

In recent years, decision-makers in medicine and public health have become more acutely aware of the scarcity of resources available for investment in health. It is challenging for them to optimize the allocation of a fixed amount of resources across a variety of competing programs that promise improved health for patients and communities. They need to consider different prevalence factors and comorbidities and mortality outcomes during the budgeting procedure in the absence of a single criterion to be served as a surrogate during fund allocation.

Linear mathematical programming was suggested by Stinnett and Paltiel (Stinnett & Paltiel, 1996) to replace the general decision rule algorithm. They suggested using a resource allocation model to solve the allocation problem and to accommodate

more complex information regarding returns to scale, indivisibilities, and ethical constraints, including the cost of equity (Stinnett & Paltiel, 1996). The model can allocate a single budget under certain constraints with perfect divisibility (Stinnett & Paltiel, 1996) and is used to help stakeholders faced with multi-objective problems consider different prevalence factors and comorbidities and mortality outcomes in the budgeting procedure where no single criterion serves as a surrogate (Mehrotra & Kim, 2011). As well, the model can be incorporated into budgetary policies to ensure the resources are allocated optimally, efficiently, and equally (Epstein et al., 2007). It can be extended by incorporating more complex budgetary rules about when expenditure can be incurred and the opportunity loss in each budgetary policy (Epstein et al., 2007). It can be applied to analysis of a realistic and policy-relevant problem to determine the possible opportunity loss and gains when implementing an intervention in the healthcare system (Earnshaw, Hicks, Richter, & Honeycutt, 2007; Epstein et al., 2007).

The budget optimization model is commonly applied in healthcare decision-making. It can be used in tandem with the Markov model to determine the possibility of different prevention options that are subject to budget, screening coverage, and vaccination constraints. For instance, this approach provided a greater range of answers that are easier for decision-makers to understand, especially concerning specific diseases such as diabetes (Earnshaw et al., 2002; Feenstra et al., 2011), cervical cancer (Demarteau, Breuer, & Standaert, 2012), and national HIV prevention (Alistar, Long, Brandeau, & Beck, 2014; Lasry, Sansom, Hicks, & Uzunangelov, 2011), and including realistic budget constraints. It can also be combined with multi-criteria decision-making by weighing the prevalence and comorbidity factors according to geography, thus demonstrating the possibility of allocating available resources. For instance, a study from the US uses the budget optimization model to demonstrate the allocation of