ECONOMIC EVALUATION OF RESPIRATORY MEDICATION THERAPY ADHERENCE CLINIC (RMTAC) ON ASTHMA PATIENTS IN MALAYSIA

by

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LIST OF ABBREVIATIONS

AQLQ	Asthma Quality of Life Questionnaire
CBA	Cost-Benefit Analysis
CEA	Cost-Effectiveness Analysis
CEAC	Cost-Effectiveness Acceptability Curve
CI	Confidence Interval
CUA	Cost-Utility Analysis
ED	Emergency Department
EQ-5D	European Quality of Life – 5 Dimensions
FEV_1	Forced Expiratory Volume in 1 second
HR	Hazard Ratio
HRQoL	Health-Related Quality of Life
ICER	Incremental Cost-Effectiveness Ratio
OR	Odds Ratio
QALY	Quality-Adjusted Life Year
RM	Ringgit Malaysia
RMTAC	Respiratory Medication Therapy Adherence Clinic
RR	Relative Risk
SABA	Short-Acting Beta Agonist
SG	Standard Gamble
USA	United States of America

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PENILAIAN EKONOMIK

KLINIK KEPATUHAN UBAT RESPIRATORI (RMTAC)

PADA PESAKIT ASMA DI MALAYSIA

ABSTRAK

Tujuan kajian ini dijalankan adalah untuk menilai kos keberkesanan sebuah klinik respiratori yang diuruskan oleh pegawai farmasi sebagai suatu tambahan kepada klinik perubatan yang sedia ada (RMTAC), *versus* klinik perubatan yang sedia ada sahaja (klinik sedia ada). Sebuah Markov model yang mengandungi konsep kepatuhan kepada ubat telah dihasilkan. Penilaian ekonomik ini adalah berdasarkan tempoh sepanjang hayat dan kitaran bulanan, daripada perspektif pembekal perkhidmatan penjagaan kesihatan (Kementerian Kesihatan Malaysia), dan hasil penilaian ini ditaksir dalam kos per QALY diperoleh dan kos per kemasukan hospital dicegah. Kebarangkalian keadaan kesihatan kawalan asma-kepatuhan kepada ubat diperolehi daripada pangkalan data RMTAC, kos daripada sumber-sumber awam, utiliti daripada kajian pertaruhan standard pada pesakit asma Malaysia, dan lain-lain input daripada sumber sekunder telah digunakan untuk memaklumkan model berkebarangkalian ini. Analisa subkumpulan telah dijalankan ke atas jantina dan kumpulan umur yang berbeza. Analisa senario dijalankan untuk menilai ketidakpastian struktur dan metodologi model ini. Pada nilai ambang kos keberkesanan RM29,000 per QALY diperoleh, RMTAC didapati lebih murah dan lebih berkesan pada ICER -RM9,862.65 (-25,833.49 – (-3,711.69)) per QALY diperoleh dan -RM1,358.68 (-1,686.11 – (-924.31)) per kemasukan hospital dicegah. Kebarangkalian RMTAC ialah kos berkesan adalah sebanyak 99% untuk kedua-dua hasil penilaian QALY diperoleh dan kemasukan hospital dicegah. RMTAC juga

didapati dominan untuk kumpulan umur lain dan analisa senario pada ketidakpastian metodologi model. Walaubagaimanapun, RMTAC didapati tidak kos berkesan apabila tiada lawatan susulan selepas discaj dari RMTAC, dalam analisa senario pada ketidakpastian struktur model. Secara kesimpulannya, pelaksanaan RMTAC di Malaysia mempunyai kebarangkalian yang tinggi menjadi kos berkesan untuk semua peringkat umur. Kajian yang lebih lanjut adalah perlu untuk memastikan bahawa pelaksanaan keputusan ini tidak melangkaui keseluruhan belanjawan perkhidmatan penjagaan kesihatan negara.

ECONOMIC EVALUATION OF RESPIRATORY MEDICATION THERAPY ADHERENCE CLINIC (RMTAC) ON ASTHMA PATIENTS IN MALAYSIA

ABSTRACT

This study aimed to evaluate the cost-effectiveness of a pharmacist-led respiratory clinic as an adjunct to the usual physician care (RMTAC), *versus* usual physician care alone (usual care clinic). A dynamic adherence asthma Markov cohort model was developed. The economic evaluation was based on a lifetime horizon and cycle length of one month, from the healthcare provider's (Ministry of Health) perspective, with the outcomes assessed in cost per QALY gained and cost per hospitalization averted. Probabilities of asthma control-adherence states from RMTAC database, costs from public sources, utilities using standard gamble method on Malaysia's asthma patients, and other inputs from secondary data sources were used to inform the probabilistic model. Subgroup analysis was conducted against 30 and 70-year old cohorts. Scenario analyses were conducted to evaluate the structural and methodological uncertainties of the model. In the economic evaluation, RMTAC was found to be cheaper and more effective, at an ICER of -RM9,862.65 (-25,833.49 – (-3,711.69)) per QALY gained and -RM1,358.68 (-1,686.11 – (-924.31)) per hospitalization averted. The probability of RMTAC being cost-effective was 99% of the time, for both QALY gained and hospitalization averted outcomes. RMTAC was also found to be dominant across other age subgroups, and in the scenario analysis for methodological uncertainties. However, RMTAC was found to be not cost-effective when there is none follow-up visit after discharged from the RMTAC, in the scenario analysis for structural uncertainties. In conclusion, implementing

RMTAC in Malaysia has high probability of being cost-effective across all age groups. Further investigation is necessary to ensure that implementing this decision does not exceed the overall national healthcare expenditure.

CHAPTER 1

INTRODUCTION

1.1 Epidemiology of asthma

Asthma is a heterogeneous chronic respiratory disease that is usually characterized by chronic airway inflammation. It is defined by a history of respiratory symptoms such as wheeze, shortness of breath, chest tightness and cough that vary over time and in intensity, together with variable expiratory airflow limitation" (Global Initiative for Asthma (GINA), 2014).

It is heterogeneous because it has different underlying disease processes among asthma patients. These include allergic asthma, non-allergic asthma, and late onset of asthma which can influence the extent of positive response towards drug therapy, depending on the type. Asthma patients who have comorbidities such as obesity and rhinitis can also worsen their manifestation of respiratory symptoms, which are otherwise triggered by common factors such as temperature changes and pests.

Over the years, global asthma prevalence has been increasing (Global Initiative for Asthma (GINA), 2014) with no sign of decrease (Anandan et al., 2010). It is estimated to increase to 400 million persons suffering from asthma in year 2025 (Masoli et al., 2004). In the third National Health and Morbidity Survey 2006 in Malaysia, it was estimated that 4.5% of the population suffers from asthma (Ministry of Health Malaysia - Institute for Public Health, 2008). Although no more recent data is available, it is believed that this number might be underestimated and lower than the current situation, because the rate of asthma increases along with urbanization

(Masoli et al., 2004). Indeed, the latter has been rising in the past decade (The World Development Indicators, 2014).

1.2 Asthma management

Given the fact that asthma prevalence increases with time, many guidelines have been published and updated periodically to improve the care of this disease since three decades ago (Myers, 2008). There are two dimensions in management of asthma which is pharmacological and non-pharmacological.

Pharmacological management has evolved in terms of the drugs and its administration since it is first introduced. Short-acting beta agonist (reliever therapy) and inhaled corticosteroids (maintenance therapy) is the mainstay of the asthma therapy. Single and combination of drugs have been designed and manufactured in various inhaler devices, in addition to oral tablets and nebulising solutions. There are generally two types of inhaler devices: metered-dose aerosol and breath-actuated dry powder forms. Their use depends on the availability of the inhaler in the market, and suitability of the inhaler to a patient.

Non-pharmacological management covers adjunct strategies such as smoking cessation, indoor allergen avoidance, breathing techniques, and vaccination that could help to improve asthma outcome (Global Initiative for Asthma (GINA), 2014). In this context, non-pharmacological management also relates to patient self-management through asthma action plan and patient education such as on inhaler techniques, trigger factors, medications, symptoms monitoring, and medication adherence. An asthma action plan guides and informs an asthma patient what to do

(self-manage) especially during presence of respiratory symptoms, and when to seek for urgent or emergency medical assistance. Such plan can be further individualised by giving instructions on how and when to increase the dosage of inhaled corticosteroids (Gibson and Powell, 2004).

On the surface, pharmacological management may seem to be sufficient as a stand-alone in asthma management. However, in fact, it is very much encouraged by asthma management guidelines to incorporate non-pharmacological management as part of an enhanced asthma care (British Thoracic Society and Scottish Intercollegiate Guidelines Network, 2012, Global Initiative for Asthma (GINA), 2014). Favourable health outcomes can be potentially achieved when both are used together.

1.3 Asthma-related health outcomes

The two main goals of asthma management are to achieve good symptom control and reduce future risk of asthma exacerbation. Both of these are the domains of asthma control. Asthma control is thus defined as the extent to which the various manifestations of asthma are reduced or removed by treatment (Global Initiative for Asthma (GINA), 2014).

According to GINA, 'well control' means no manifestation of all the following:

1) Activity limitation due to asthma

2) Experiencing daytime symptoms more than twice per week

3) Need for reliever or rescue treatment more than twice per week

positive correlation with both asthma-specific and generic quality of life (Doz et al., 2013, Pereira et al., 2011).

1.4 Medication adherence

A poor asthma control is more likely to be due to external modifiable factors such as inhaler technique, adherence, untreated comorbidities, and allergen exposure than low daily prescribed inhaled corticosteroid dose. Thus, as recommended by guidelines, the aforementioned factors have to be checked and handled appropriately (if any) before pharmacological intervention is considered (British Thoracic Society and Scottish Intercollegiate Guidelines Network, 2012, Global Initiative for Asthma (GINA), 2014).

Among the modifiable factors, it is believed that medication adherence is the most difficult to tackle because it is closely related to human behaviour. Adherence or compliance is defined as "the extent to which a patient acts in accordance with the prescribed interval and dose of a dosing regimen" (Cramer et al., 2008). It is generally comprised of two types: intentional and unintentional. The latter is usually related to forgetfulness, whilst the former is related to personal choice (Elliott et al., 2008). Adherence can be influenced by many factors from epidemiological, sociological, to psychological perspectives. A qualitative asthma study showed that in addition to the patient-physician relationship, patient's beliefs, understanding, and perception towards asthma and its treatments are the main factors affecting patient's willingness to administer his/her medications (van Ganse et al., 2003).

The forgone health benefits of not being adhered to medications can negatively impact the whole society (patients themselves, healthcare payer, healthcare provider, employer, and other related parties) from clinical and economics perspectives. Indeed, non-adherence has been proven to worsen asthma control (Armour et al., 2013), increase risk of future exacerbation (Suissa et al., 2002, Williams et al., 2011), and increase asthma-related mortality rate (Suissa et al., 2000).

1.5 Respiratory Medication Therapy Adherence Clinic (RMTAC)

Acknowledging the importance of medication adherence, the Pharmaceutical Services Division of the Ministry of Health Malaysia has initiated a pharmacist-managed clinic for different types of chronic diseases – Medication Therapy Adherence Clinic (MTAC) in public healthcare facilities. Asthma disease management falls under respiratory MTAC; this clinic shall be named as RMTAC henceforth (Pharmaceutical Services Division, 2010b). RMTAC is first started in year 2008.

Targeted at non-adhered patients, RMTAC is meant to be an adjunct to usual care clinic, where physicians in specialist clinic see patients on routine appointments. The extent of the involvement of non-pharmacological management is higher in RMTAC than usual care clinic. More specifically, pharmacists' main tasks are to understand the root cause of non-adherence, encourage and improve medication adherence through education. The management is tailored according to the issues faced. Other tasks are to promote and guide self-management, and to suggest dose changes to the physicians if and when necessary. On the other hand, usual care clinic relies heavily on pharmacological treatment with little and unstructured non-pharmacological

management given to the patient when deemed necessary and usually lasts no more than two consecutive visits.

Assessments on adherence, knowledge on their medications, inhaler technique, and asthma control are done on each RMTAC visit to monitor improvements. Each patient has to be followed for at least four times a year, and thereafter may be discharged from RMTAC if initial improvements are consistent for at least three consecutive visits. Provided the discharged patient is still under the care of the same healthcare facility, it is required that he/she be reviewed by RMTAC at any point of time to ensure the sustainability of the improvements.

1.6 Problem statement and rationale of study

Although evidences from similar asthma managements show promising effectiveness and cost saving (Yong and Shafie, 2014), there are a number of shortcomings in previous studies. First, RMTAC is fully operated by pharmacists only; the overall findings (on cost and effectiveness) from the review by Yong and Shafie cannot be readily generalized to local setting because the majority of the interventions in the reviewed studies involved more than just pharmacists. Secondly, there are only two known local studies on effectiveness and none on cost or cost-effectiveness of RMTAC despite its 8 years implementation; the qualities of these studies are questionable, and lack generalizability to the whole Malaysia. Thirdly, given the current weak economy climate, there is an increasing pressure for cost containment particularly in public expenditure. This is due to the increasing annual public healthcare expenditure (Malaysia National Health Accounts Unit, 2013) but at the same time the annual budget allocated for the Ministry of Health Malaysia, which is

the major health care provider has been reduced by 1.11% in 2015 (Choong, 2015). Hence, given all these shortcomings it is essential to investigate if the RMTAC is a cost-effective intervention for asthma patients.

1.7 Objectives of the study

The general objective of this study is to evaluate the cost-effectiveness of RMTAC plus usual physician care vs. usual physician care using decision analytic model, from the healthcare provider's perspective. From this point forth, 'RMTAC plus usual physician care' is denoted as 'RMTAC', and 'usual physician care' is denoted as 'usual care clinic'. The economic evaluation in this context used decision analytic modelling instead of trial-based data because the latter has limitations such as in types and/or sources of evidences collected, and the time horizon (Drummond et al., 2005a). To overcome these, decision analytical modelling is often adopted by the healthcare policymakers as a guide to decision making in resource allocating under conditions of uncertainty. The specific objectives are:

1. To develop and validate a decision model for RMTAC
2. To determine the parameter inputs of the model
    a) Transition probabilities
    b) Costs
    c) Utilities
3. To evaluate cost-effectiveness of RMTAC program vs. usual care clinic from healthcare provider perspective

1.8 Significance of the study

The results on the cost-effectiveness of RMTAC can primarily inform the healthcare policymakers, particularly the Pharmaceutical Services Division of Ministry of Health Malaysia on the value of RMTAC in public healthcare services. If the results are not promising enough, the service can be reviewed to improve its efficiency.

On the other hand, the developed model can be useful (where appropriate) should any party wishes to develop a similar but better program and compare its cost-effectiveness against RMTAC and/or usual care clinic or other available alternatives, or to compare the cost-effectiveness between asthma drugs, or any other attempts that are related to asthma outcomes. However, the model must always be validated before it is used for purposes other than the objectives of this study.

Thus, the outcomes of this study are able to impact current and future situations, both in different ways.

CHAPTER 2

LITERATURE REVIEW

2.1 Introduction

The aim of this chapter is to summarize the state-of-the-art literature on the cost-effectiveness of enhanced asthma management. Enhanced asthma management is a term given to the non-pharmacological asthma management (will be used interchangeably here) because of its potential to enhance a patient's level of asthma control as adjuncts to usual care, by preventing future asthma symptoms and acute attacks (Global Initiative for Asthma (GINA), 2014). Enhanced management of asthma can involve one or more forms of non-pharmacological treatments, which are formally incorporated into the overall care to provide a better management of asthma. The range of variations, however would, mean that there is a corresponding wide range of cost and effectiveness implications in their implementation. This would complicate the uptake of non-pharmacological treatments in other settings. In addition, there are not as many economic studies as there are effectiveness studies comparing an enhanced management/usual care combination to usual care alone. Therefore a systematic review on economic evaluations of enhanced asthma management was conducted to achieve the aim of this chapter. Further details on its methodology can be found in Yong and Shafie (2014). The systematic review was since updated till December 2015 (price year 2014). Based on the results of the systematic review, the costs and outcomes were further compared and discussed against other literatures. The valuation methods of the health-related quality of life (HRQoL) that were used to generate health utilities were also specifically discussed and compared with the methods used by other available economic asthma models.

Different methods of modeling that were used by other researchers to evaluate the long-term impact of the enhanced asthma management were also reviewed. The models in the systematic review were compared and discussed against other economic asthma models including those for pharmacological management. Finally, the cost-effectiveness of the enhanced asthma management was discussed.

2.1.1 Overview of economic evaluation principles

a. Definition of economic evaluation

- Must involve two or more alternatives (Drummond et al., 2005a)
- Both cost and outcomes are examined (Drummond et al., 2005a)
- The four types of economic evaluations that were considered in the systematic review are as follows:
    - Cost consequences analysis (CCA), involves a way of reporting cost and an array of outcomes in a separate and disaggregated way, so that no incremental ratios are involved (Gray et al., 2010)
    - Cost effectiveness analysis (CEA), involves incremental analysis between the calculated differences in costs and outcomes. The outcomes are in natural units (Drummond et al., 2005a, Gray et al., 2010)
    - Cost benefit analysis (CBA), values both measured health and non-health outcomes in monetary units (Drummond et al., 2005a)
    - Cost utility analysis (CUA), is similar to CEA but uses utilities as a measure of the value of an alternative's effects (Drummond et al., 2005a, Gray et al., 2010)

b. Incremental cost-effectiveness ratio

Incremental cost-effectiveness ratio (ICER) is defined as the ratio of the differences in costs and outcomes between two alternatives (Drummond et al., 2005a).

$$\text{ICER} = \frac{\text{Cost}_B - \text{Cost}_A}{\text{Effectiveness}_B - \text{Effectiveness}_A}$$

where A is the existing alternative and B is the new alternative.

c. Perspective

Perspective is also known as to whom the costs and outcomes accrue in an economic evaluation (Drummond et al., 2005c). Depending on the study question, the perspective could be the healthcare provider, patients, healthcare payer, or societal.

d. Time horizon

Time horizon is the duration of the costs and outcomes evaluated or assessed in an economic evaluation.

e. Discounting

If an economic evaluation is conducted for more than one year, then the costs and outcomes have to be adjusted for differential timing because comparisons need to be made at one point in time. In other words, future costs and outcomes have to be reduced or discounted to the present value due to time preference; it is preferred to have dollars and resources now rather than later, in order to enjoy the benefits obtained in the interim (Drummond et al., 2005c).

2.2 Quality assessment of economic evaluation and evidence

The updated systematic review involved 43 studies. Majority of the studies originated from United States of America, followed by Europe, Asia, and Australia. There was one economic evaluation concerning enhanced asthma management done in year 1991 (Bolton et al., 1991) and at least one in 1994 to 2012. All of the studies were trial-based, except 3 modelling-based studies. There were 4 studies did mixed type of analysis, 6 CEA studies, 3 CUA studies, 3 CBA studies, whilst all others were CCA studies.

A total of 47 (43 single plus 4 multiple economic evaluation methods) economic evaluation analyses were reviewed. The mean (SD) QHES score was 73.4 (9.9). The maximum and minimum scores were 94.7 (Polisena et al., 2007) and 59.0 (Chan and Wang, 2004) respectively. There were 25 (53%) economic evaluations that scored within 50-74 (fair quality) and the remaining 22 (47%) evaluations scored within 75-100 (high quality). There was no obvious pattern of the QHES scores across the years 1991 to 2012.

Only 23 (53%) studies were assessed for their quality of evidence sources using Cooper et al. These included 3 modelling-based studies and 20 non modelling-based studies that involved evidence sources other than their study population in any data component. NA aside, most data components had high quality evidence sources labelled as Rank 1 and Rank 2. The data components 'Baseline clinical data' and 'Resource use' for the study by de Asis and Greene (2004) had a medium quality evidence source because different jurisdiction was involved.

2.3 Costs of enhanced asthma management

In general, the reviewed studies reported four major types of cost: healthcare resource utilization (hospitalization, ED visit, scheduled and unscheduled physician visit), healthcare personnel involved, medication, and productivity. A positive net monetary benefit indicates cost-saving. In the systematic review, most of these reviewed studies had reported their interventions as cost-saving in relation to their comparators. The interventions that involve education and self-management are highly cost- saving (Gallefoss and Bakke, 2001, Ghosh et al., 1998, Shelledy et al., 2005). However, there could be a risk of overstating the 'cost-saving' as there is a number of cost-saving studies that did not report the total cost of intervention or implementation per patient (Bratton et al., 2001, Bunting and Cranor, 2006, Chan and Wang, 2004, D'Souza et al., 2010, Drummond et al., 1994, Lindberg et al., 2002, Ng et al., 2006, Rossiter et al., 2000, Shelledy et al., 2009, Shelledy et al., 2005, Tagaya et al., 2005, Tschopp et al., 2005, Tschopp et al., 2002).

Because of the lack of information on the cost of intervention, the cheapest and most expensive intervention could only be deduced from those studies that reported their cost of intervention. The cheapest intervention among these 43 studies was the enhanced services Nurse Support group that costs only Int$17 per patient (Xu et al., 2010), followed by a symptom-based self-management plan with Int$44 per patient (de Asis and Greene, 2004). The most expensive was the direct observation by nurses that costs Int$5,320 per patient (Noyes et al., 2013). Having said these, a strict comparison can only be made if the method used in costs estimation is common across studies. One striking example is the comparison between the cheapest and most expensive intervention as mentioned above. Both interventions involved nurse

services, but one adopted time-based method (Xu et al., 2010) and the other just simply divided the total salaries involved by the number of patients (Noyes et al., 2013) to obtain the cost of nurse service per patient. From a costing perspective, the time-based method gives a more accurate cost estimate because unlike the other method, time-based does not contain biased assumption that the personnel works the designated task all round working hours. Therefore, the intervention cost per patient in Noyes et al. could have been overestimated. In fact, many of the studies did not explicitly report their costing method either (Bolton et al., 1991, Donald et al., 2008, Ghosh et al., 1998, Greineder et al., 1999, Johnson et al., 2003, Neri et al., 1996, Rhee et al., 2012, Sullivan et al., 2005, Sullivan et al., 2002, Tinkelman and Wilson, 2004, Woods et al., 2012).

Although there were no economic evaluations on potentially fatal asthma subgroup of patients in the systematic review, interventions for patients with potentially fatal asthma (Doan et al., 1996, Levenson et al., 1997) are highly cost-saving, because this group of patients usually utilise more healthcare resources during hospitalization than those patients with non-fatal asthma attack; fatal asthma usually requires intensive medical care with mechanical ventilator support (Greenberger, 1999).

2.4 Outcomes of enhanced asthma management

Due to the large number of studies, the effectiveness of enhanced asthma management was reviewed based on the common types of intervention evaluated and outcome measures used. There were generally 3 types of intervention reported: education, self-management, and environmental control. Majority of studies have more than one type of intervention; some may be combination of education and self-

management, education and environmental control, or all three. Education intervention can incorporate a variety of topics including disease, inhaler technique, adherence, and trigger factors. Education intervention is not just confined to the patients but also to health care professionals. Self-management can be delivered either by written plans or via the internet. Peak-flow and symptom-based are the two most common types of self-management. On the other hand, the four most common types of outcome measure used in the reviewed studies were the healthcare resource utilization (number of ED visits, hospitalization, scheduled and unscheduled physician visits), number of symptom-free days (and others alike including days off work or school, days of limited activity), quality of life, and lung function. Healthcare resource utilization typically reflects the frequency of acute asthma exacerbation, which could happen regardless of the asthma control status (Global Initiative for Asthma (GINA), 2014). On the other hand, the number of symptom-free days (and others alike) and lung function reflect the frequency and magnitude of the symptoms manifestations and hence how well the asthma control is. As for the quality of life, it is a measure of how asthma (both asthma control and acute exacerbation components) affects or impacts one's quality of life, pertaining to both asthma disease-related and overall quality of lives. These four types of outcome measure are similar to those recommended by Reddel et al. (2009).

Overall, this systematic review shows that these interventions benefited all severity levels of asthma (from mild to severe asthma). However, it is difficult to deduce which type of intervention is the most effective, because none yielded consistent results. Not every intervention scored improvement in each of their outcome measure; in most cases (86%), there was no significant difference in the healthcare

resource utilization between the evaluated groups. A modest reduction in healthcare resource utilization was found in a systematic review (Crocker et al., 2011), which supports the insignificant difference in this outcome measure found in studies that involved environmental control (Kattan et al., 2005, Sullivan et al., 2002). On the other hand, most of the combined interventions between education and self-management reviewed (53%) have significant differences in healthcare resource utilization, symptom-free days (and others alike), and lung function. These findings share the same significant results from a meta-analysis (Gibson et al., 2003). However, the results on the significant improvement in quality of life in the meta-analysis cannot be considered to be similar to that in this systematic review. This is because more than half of the studies that measured quality of life did not find any significant difference between their comparison groups (Bratton et al., 2001, Donald et al., 2008, Gordois et al., 2007, Kauppinen et al., 1998, Kauppinen et al., 1999, Kauppinen et al., 2001, Lindberg et al., 2002, Schermer et al., 2002, van der Meer et al., 2011, Xu et al., 2010). A further discussion on this outcome measure is in section 2.6.

The presence of bias or 'contamination' could have been the main cause of insignificant differences in outcomes between the three groups in Drummond et al's study (1994). This is justified by the fact that each physician could have several patients randomized into one of the three groups. This performance bias could have been better managed or avoided if the physicians were randomly allocated instead, as was the case in Schermer et al (2002). Intervention that involves regular reviews through telephone calls by Xu et al. (2010) and Donald et al. (2008) have no significant differences in the measured outcomes. However this does not necessarily

mean that telephone calls as part of intervention is not effective in children nor adults, because both of the studies had an initial education intervention for all study participants (both intervention and control groups). Hence the true effectiveness of subsequent follow-up telephone calls to the intervention group could have been diluted. Indeed, without prior education exposure to both study groups, telephone calls as part of intervention has been proven to be effective in the study by Watanabe et al. (1998). Although the results from Polisena et al. (2007) showed that giving asthma action plans are not effective (no significant differences in the measured outcomes), this is not quite valid because the true duration and frequency of patients obtaining an asthma action plan in the past 6 months were not considered in the outcomes analysis. On the contrary, other studies that incorporated asthma action plans have significant differences in their measured outcomes and their plans were updated as needed throughout the study follow-up period (Bunting and Cranor, 2006, Greineder et al., 1999, McLean et al., 2003).

2.5 Utility-based HRQoL measures in enhanced asthma management

In the systematic review, there were 18 studies that assessed health-related quality of life (HRQoL) as one of their outcome measures. HRQoL is defined as "the value assigned to duration of life as modified by the impairments, functional states, perceptions, and social opportunities that are influenced by disease, injury, treatment, or policy" (Feeny, 2000). It is an important measure that complements primary measures such as asthma symptoms and exacerbation; it provides information on the impact of the disease progress to the patient's well-being. In fact, it is one of the recommended outcome measures to be used in clinical trials (Reddel et al., 2009).

HRQoL measurement instruments can be categorized based on the scope of their construct (generic vs. specific), and how the construct is developed (non-preference vs. preference). Among the 16 studies that used non-preference based, 6 of them used both generic and asthma specific versions (Kauppinen et al., 1998, Kauppinen et al., 1999, Kauppinen et al., 2001, Lindberg et al., 2002, Shelledy et al., 2009, Xu et al., 2010), 9 of them used only asthma specific versions (Bratton et al., 2001, Chan and Wang, 2004, Donald et al., 2008, Franco et al., 2007, Gallefoss and Bakke, 2001, McLean et al., 2003, Schermer et al., 2002, Tschopp et al., 2005, Tschopp et al., 2002), and 1 of them used only generic version (Lucas et al., 2001). No doubt that these non preference-based instruments measure HRQoL extensively through a number of domains or dimensions, however the scores across all the assessed domains or dimensions are often unable to be aggregated into a meaningful single score. For example, what the overall HRQoL would mean if the score in pain domain is lower than that in social activity domain. Although a CEA is still possible for each domain or dimension as the outcome measure, it may not be very useful for comparison across other diseases or interventions within the same disease.

Due to this limitation, preference-based instruments are preferred over the non-preference based because they are able to generate a meaningful single summary value or preference score that is known as utility or valued HRQoL. In addition to being preference-based, a utility that is measured on an interval scale with perfect health and death as anchors fulfills the criteria for use in a CUA (Torrance, 1997). This utility, when combine with the number of life years become the Quality-Adjusted Life Years (QALY) which is the common outcome measure (as QALYs gained) of a CUA. QALYs gained is also the preferred outcome measure for many

countries, in their evidence submission to their healthcare decision making bodies/entities for reimbursement (Eldessouki and Smith, 2012).

Preference-based instruments can be further classified into direct (Standard Gamble (SG), Time-trade Off (TTO), Visual Analogue Scale (VAS)) and indirect method of preference measurement. The latter is a multi-attribute health status classification instrument that indirectly measures preferences and it is more common due to its ease of use. These measures score the patient's descriptive responses with pre-determined weightage. An example of this indirect preference-based instrument is the EuroQol-5D, which was used by one of the two studies reviewed (Steuten et al., 2007, van der Meer et al., 2011). Another study that used indirect preference-based instrument is Gordois et al. (2007), which used the Assessment of Quality of Life questionnaire.

With two reviewed studies that have used VAS to measure preferences (Schermer et al., 2002, van der Meer et al., 2011), this method is more preferred to the SG and TTO possibly because it is easy to be administered by patients and it is not costly to the researchers (Torrance et al., 2001). However, when the models of pharmacological management that have QALYs gained as outcome measure are compared with the studies reviewed here, it seems that direct preference-based methods are overall less commonly used and that only one model used TTO to elicit preferences (Paltiel et al., 2001); the use of EQ-5D (Morishima et al., 2013, Price et al., 2009) and mapping Asthma Quality of Life Questionnaire scores to EQ-5D utilities (Campbell et al., 2010, Dewilde et al., 2006, Paggiaro et al., 2013) are the

two most common methods, other than using an asthma specific indirect measure for pediatrics (Gerald et al., 2010) and disability weights (Mogasale and Vos, 2013).

2.6 Economic models of enhanced asthma management

Except for the 3 studies that found no significant differences between their comparators (Drummond et al., 1994, van der Meer et al., 2011, Xu et al., 2010), findings from other 44 studies showed that these interventions benefited all severity levels of asthma (from mild to severe asthma). And among these, even the longest trial duration of 5 years by Kauppinen et al. (2001) is not enough to ascertain the long-term impact of enhanced asthma management on costs and outcomes. A trial is often faced with budget constraints that limit the length of their follow-up period. There are also limited types and/or sources of evidences that can be collected in a trial.

In order to overcome limitations that arise from trial-based economic evaluation, researchers often opt for modelling-based economic evaluation because as the outcomes can be projected to as long as a lifetime horizon, it is also cost-saving. This method is also known as decision analytical modeling; it is often adopted by the healthcare policymakers as a guide to decision making in resource allocating under conditions of uncertainty. From healthcare economic evaluation perspective, a decision analytic model is a mathematical simulation model (Briggs et al., 2006b). Briefly, it defines a set of consequences and/or complications of the evaluated alternatives as events over time and across populations based on data drawn from primary and/or secondary sources using mathematical concepts, resembling as much real life situation as possible (Briggs et al., 2006b, Nuijten and Starzewski, 1998,

Weinstein et al., 2001). As such, empirical models such as regression, health-belief, and behavioral models are not considered here. Although a regression model itself has mathematical properties, it is insufficient to fit the definition of a mathematical simulation model.

The flow of the events over time relates to the purpose of decision-making or the decision problem, level of detail, and complexity which altogether designate the model type. There are few common types of model: decision tree, Markov cohort, Markov Monte Carlo / micro-simulation, dynamic transmission model, and discrete event simulation. Ideally, a model should be reusable if it has the proper characteristics to address similar purpose.

In this economic evaluation, asthma is the target disease and the non-pharmacological management is the intervention to be evaluated. Unlike non-pharmacological management, pharmacological management needs shorter duration to prove its efficacy and cost-effectiveness. And because asthma is a chronic disease and patients will need to have a lifelong treatment, sustainability issue of the pharmacological management effect is not a concern at all as long as administration and medication adherence is not an issue. The situation is quite the opposite for non-pharmacological management because the sustainability of the management depends partly on the patients themselves and partly on the continuous-monitoring process in practice. Inevitably, a longer duration of evaluation is needed for a non-pharmacological asthma management.

There were four modeling-based economic evaluation studies identified in the systematic review; Markov cohort model (Gordois et al., 2007, Steuten et al., 2007), decision-tree model (Mogasale and Vos, 2013), and the model type is uncertain for de Asis and Greene (2004) study. Because of the long duration required to simulate chronic diseases like asthma, a Markov cohort model is deemed more appropriate than a decision-tree model to address the aim of this economic evaluation. In addition, an asthma patient has recurring risk of acute exacerbation which can make a decision-tree model too 'bushy' to handle. Comparing between the two available Markov cohort models, the modeled health states are somewhat quite different. Gordois et al. used asthma severity, whilst Steuten et al. used asthma control and exacerbation to describe the health states. It is felt unsuitable to model asthma severity health states because asthma severity is only a surrogate measure i.e. it is assessed retrospectively from the level of pharmacological treatment required to control asthma symptoms and exacerbations, and it is only assessable if the patient has administered ICS for several months (Global Initiative for Asthma (GINA), 2014). Hence, the changes in asthma severity may take from several months to years. However, asthma control and exacerbation reflect the manifestations of asthma disease and are the primary measures of asthma progress assessment (Global Initiative for Asthma (GINA), 2014). Indeed, when compared with other published models (duplicates removed) for pharmacological asthma management, 11 out of 12 models do not use asthma severity to describe health states (Campbell et al., 2010, Dewilde et al., 2006, Gerald et al., 2010, Gerzeli et al., 2012, Morishima et al., 2013, Paggiaro et al., 2013, Paltiel et al., 2001, Price et al., 2009, Price and Briggs, 2002, Wu et al., 2012, Zafari et al., 2014). In addition to the asthma control and exacerbation health states, these twelve (including Steuten et al.) models have

another striking similarity: none of them directly incorporated medication adherence in their models, although there were some that applied this component externally by examining different scenarios (Zafari et al., 2014) and assumed that patients are adherent to their medications (Campbell et al., 2010, Dewilde et al., 2006).

2.7 Cost-effectiveness of enhanced asthma management

From the systematic review, there were 6 CEA studies (Franco et al., 2007, Gallefoss and Bakke, 2001, Kattan et al., 2005, Noyes et al., 2013, Sullivan et al., 2005, Sullivan et al., 2002), 3 CUA studies (Gordois et al., 2007, Steuten et al., 2007, van der Meer et al., 2011), 4 CBA studies (Bhaumik et al., 2013, Neri et al., 1996, Runge et al., 2006, Tschopp et al., 2005), and 6 studies conducted a mixed type of analysis (de Asis and Greene, 2004, Kauppinen et al., 1998, Kauppinen et al., 1999, Kauppinen et al., 2001, Neri et al., 1996, Schermer et al., 2002), whilst all others were CCA studies.

Among the CEA, CUA, and CBA studies, a mixture of education and self-management implemented by an integrated team of healthcare and allied healthcare professionals is deemed to be the most cost-effective (reported to be dominant). In CCA, costs and outcomes are presented separately without involving incremental analysis. Hence, it will not be possible to deduce whether the intervention is cost-effective or not. It all depends on how the decision-maker prefers to value the desired outcomes from their perspective, on the basis of the reported costs and outcomes. Therefore, although some CCA studies reported a reduction in costs and an improvement in outcome measures, it did not mean that that particular intervention was cost-effective.