# การวิเคราะห์ต้นทุน-ประสิทธิผลของเครื่องสูดยาแบบผงแห้ง และเครื่องสูดยาแบบใช้สารผลักดันร่วมกับการใช้สเปซเซอร์ ในการรักษาผู้ป่วยเด็กโรคหืดที่มีอาการหอบเฉียบพลัน: กรณีศึกษาของโรงพยาบาลจุฬาลงกรณ์

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วิทยานิพนธ์นี้เป็นส่วนหนึ่งของการศึกษาตามหลักสูตรปริญญาวิทยาศาสตรมหาบัณฑิต
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# COST-EFFECTIVENESS ANALYSIS OF DRY POWDER INHALER AND METERED DOSE INHALER WITH SPACER IN ACUTE EXACERBATIONS OF CHILDHOOD ASTHMA: A CASE STUDY OF KING CHULALONGKORN MEMORIAL HOSPITAL

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กรรณิกา หนูม่วง : การวิเคราะห์ต้นทุน-ประสิทธิผลของเครื่องสูดยาแบบผงแห้ง และเครื่องสูดยาแบบใช้สารผลักดันร่วมกับการใช้สเปซเซอร์ ในการรักษาผู้ป่วยเด็กโรคหืดที่มีอาการหอบเฉียบพลัน: กรณีศึกษาของโรงพยาบาลจุฬาลงกรณ์. (COST-EFFECTIVENESS ANALYSIS OF DRY POWDER INHALER AND METERED DOSE INHALER WITH SPACER IN ACUTE EXACERBATIONS OF CHILDHOOD ASTHMA: A CASE STUDY OF KING CHULALONGKORN MEMORIAL HOSPITAL) อ. ที่ปรึกษา : รศ. ดร. พงศา พรชัยวิเศษกุล, อ. ที่ปรึกษาร่วม : ศ. นพ. ภิรมย์ กมลรัตนกุล, 109 หน้า. ISBN : 974-14-2906-1.

การศึกษานี้ มีวัตถุประสงค์เพื่อวิเคราะห์และเปรียบเทียบต้นทุน-ประสิทธิผลของเครื่องสูดยาแบบผงแห้งและเครื่องสูดยาแบบใช้สารผลักดันร่วมกับการใช้สเปซเซอร์ สำหรับนำส่งยาซัลบิวตามอล เพื่อใช้ในการรักษาผู้ป่วยเด็กโรคหืดอายุ 5 ถึง 18 ปีที่มีอาการหอบเฉียบพลันระดับความรุนแรงน้อยถึงปานกลาง

การศึกษานี้เป็นการวิจัยชนิดศึกษาย้อนหลัง ซึ่งใช้ข้อมูลทางคลินิกจากการวิจัยสหสถาบัน โดยเลือกโรงพยาบาลจุฬาลงกรณ์เป็นสถานที่สำหรับการวิเคราะห์ทางเศรษฐศาสตร์ ผู้ป่วยจำนวน 80 รายที่มีอาการหอบเฉียบพลันระดับความรุนแรงน้อยถึงปานกลางเข้าร่วมในการศึกษา และติดตามผลการรักษาเป็นเวลา 3 วัน จำนวนผู้ป่วยที่เท่ากัน (40 ราย) ถูกแบ่งกลุ่มโดยการสุ่ม เพื่อให้ได้รับยาซัลบิวตามอลนำส่งโดยเครื่องสูดยาแบบผงแห้งหรือเครื่องสูดยาแบบใช้สารผลักดันร่วมกับการใช้สเปซเซอร์ การคิดต้นทุนของการรักษาโรคหืดเป็นไปตามมุมมองของผู้ให้บริการสุขภาพและมุมมองของผู้ป่วย ต้นทุนรวมทั้งหมดของผู้ให้บริการสุขภาพได้จากต้นทุนค่าบริการพื้นฐานรวมกับต้นทุนค่าบริการทางการแพทย์ และต้นทุนรวมทั้งหมดของผู้ป่วยได้จากต้นทุนทางตรงที่เกี่ยวข้องกับการรักษาพยาบาลรวมกับต้นทุนทางอ้อม โดยต้นทุนทั้งหมดที่แสดงในการศึกษานี้มีค่าเป็นเงินบาทในปี พ.ศ.2548 ผลลัพธ์ของการศึกษานี้คือจำนวนและอัตราร้อยละของผู้ป่วยที่ประสบความสำเร็จในการรักษาเมื่อเวลาผ่านไป 60 นาที

จากผลการศึกษา พบว่าไม่มีความแตกต่างกันอย่างมีนัยสำคัญของอัตราร้อยละของผู้ป่วยที่ประสบความสำเร็จในการรักษา เมื่อเปรียบเทียบระหว่าง 2 กลุ่มการรักษา ถึงแม้จะมีแนวโน้มของอัตราร้อยละที่สูงกว่าในกลุ่มผู้ป่วยที่ได้รับยาสูดผ่านทางเครื่องสูดยาแบบผงแห้งก็ตาม (92.5 % และ 90.0%) ค่าเฉลี่ยของต้นทุนรวมทั้งหมดของผู้ให้บริการสุขภาพและของผู้ป่วยเมื่อได้รับยาสูดผ่านทางเครื่องสูดยาแบบผงแห้ง มีค่าต่ำกว่ากลุ่มเปรียบเทียบอย่างไม่มีนัยสำคัญทางสถิติ ที่ระดับความเชื่อมั่น 95% (180.98 บาท และ 239.63 บาท ตามมุมมองของผู้ให้บริการสุขภาพ; 355.99 บาท และ 496.27 บาท ตามมุมมองของผู้ป่วย) นอกจากนี้ยังพบว่าสัดส่วนต้นทุน-ประสิทธิผล และต้นทุนที่เพิ่มขึ้นต่อ 1 หน่วยประสิทธิผลที่เพิ่มขึ้น มีความคุ้มค่าในกลุ่มผู้ป่วยที่ใช้เครื่องสูดยาแบบผงแห้ง และเมื่อมีการเปลี่ยนจากการใช้เครื่องสูดยาแบบใช้สารผลักดันร่วมกับการใช้สเปซเซอร์ไปเป็นการใช้เครื่องสูดยาแบบผงแห้ง พบว่าต้นทุนต่อ 1% ที่เพิ่มขึ้นของผู้ป่วยที่ประสบความสำเร็จในการรักษาจะลดลง 25.42 บาท และ 60.79 บาท ตามมุมมองของผู้ให้บริการสุขภาพและมุมมองของผู้ป่วย ตามลำดับ โดยการวิเคราะห์ความไวของการทดสอบก็แสดงผลสอดคล้องกัน

สาขาวิชา เศรษฐศาสตร์สาธารณสุข ลายมือชื่อนิสิต.....กรรณิกา หนูม่วง.....
ปีการศึกษา 2548 ลายมือชื่ออาจารย์ที่ปรึกษา.....
ลายมือชื่ออาจารย์ที่ปรึกษาร่วม.....

## 4885807029 : MAJOR HEALTH ECONOMICS
KEY WORD : COST-EFFECTIVENESS / DRY POWDER INHALER / METERED DOSE INHALER / ACUTE EXACERBATION / CHILDHOOD ASTHMA

KANNIKA NUMUANG: COST-EFFECTIVENESS ANALYSIS OF DRY POWDER INHALER AND METERED DOSE INHALER WITH SPACER IN ACUTE EXACERBATIONS OF CHILDHOOD ASTHMA: A CASE STUDY OF KING CHULALONGKORN MEMORIAL HOSPITAL. THESIS ADVISOR : ASSOC. PROF. PONGSA PORNCHAIWISESKUL, Ph.D. THESIS CO-ADVISOR : PROF. PIROM KAMOLRATANAKUL, M.D., M.Sc., 109 pp. ISBN 974-14-2906-1.

The objective of this study was to analyse and compare the cost-effectiveness of the dry powder inhaler (DPI) with the metered dose inhaler (MDI) and spacer for delivering salbutamol in the management of mild to moderate acute exacerbations of asthma in children aged 5 to 18 years.

A retrospective analysis was performed based on clinical data from a multicenter, randomized clinical trial. King Chulalongkorn Memorial Hospital was chosen as the model for this economic evaluation. A total of 80 patients with mild to moderate acute exacerbations of asthma were enrolled into the study, and followed up for 3 days. Equal number of patients (n = 40) were randomized to receive salbutamol administered via either the DPI or the MDI with spacer. The provider's and patient's perspectives were used to estimate costs of asthma treatment among patients. The total provider costs of delivering each treatment to the asthmatic patients was the sum of total routine service costs and total medical care costs. The total patient costs or total costs was calculated from the sum of total direct medical costs and total indirect costs. All costs in this study are presented in 2005 Baht. Outcome measures were the number and percentage of successfully treated patients at 60 minutes (defined as those with clinical scores reduce $\geq$ 50% from baseline, or clinical scores $\leq$ 3 as measured using the Modified Wood's Clinical Scores)

There were not significant differences between the 2 treatment groups in the number and percentage of successfully treated patients, although there was a trend in favour of the DPI group compared with the MDI and spacer group (92.5% vs 90.0%). The means of total provider costs and total patient costs were also lower in the DPI group (Baht 180.98 vs Baht 239.63, and Baht 355.99 vs Baht 496.27, respectively), however, these differences were not statistically significant at 95% CI. The results from the cost-effectiveness analysis showed in favour of the DPI. This indicated that by switching to the DPI from the MDI with spacer, the costs for each additional percentage of successfully treated patients would be reduced by Baht 25.42 and Baht 60.79 according to the provider's and patient's perspectives, respectively. Sensitivity analysis demonstrated that these results were relatively robust over a wide range of assumptions.

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| Field of Study | Health Economics | Student's signature: KANNIKA NUMUANG |
| Academic Year | 2005 | Advisor's signature: |
| | | Co-advisor's signature: P. Kamolratanakul |

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# CHAPTER I

# INTRODUCTION

## 1.1 Background

Asthma is defined as a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role. The chronic inflammation causes an associated increase in airway hyperresponsiveness that leads to recurrent episodes of wheezing, breathlessness, chest tightness and coughing, particularly at night or in the early morning. These episodes are usually associated with widespread but variable airflow obstruction that is often reversible either spontaneously or with treatment.

Asthma is a problem worldwide, and the disease's social burden and costs to public and private health care systems are substantial. There is good evidence that asthma prevalence has been increasing in many countries, but as yet there are insufficient data to determine the likely causes of this increase and of the described variations in and between groups of population. The present burden of asthma on patients and on the whole society is so high that the World Health Organization (WHO) recognizes the importance of asthma, and considers asthma as a major public health problem.

There is growing evidence that the prevalence of asthma is rising in all age groups, especially in children. Asthma is the most common chronic disease of childhood, and its prevalence continues to increase throughout the world. Childhood asthma can have a profound effect not only on the child but also on the parents or caregivers in term of distressing respiratory symptoms, sleep disturbance, inability to undertake normal play or social activities, and time lost from school or work. In addition to negative effects on quality of life, childhood asthma can be associated with substantial economic costs.

In recent years, childhood asthma has become the major childhood chronic disease not only in developed countries but also in developing nations. This is evident from results of Phase I of the collaborative International Study on Asthma and Allergic Disease in Childhood (ISAAC) in 1998, which demonstrated that prevalences of childhood asthma from most developing countries are similar to those observed in developed nations.

Undertreatment and/or suboptimal management of asthma is associated with acute exacerbations of the disease, which lead to increased utilization of expensive medical services, such as emergency room services, hospitalization and physician services. Hoskins *et al*. (2000 quoted in Atherly, Williams and Redd 2003) found that 50% of the total resource use costs were accounted for by 22% of the patients who had experienced asthma attacks. Acute asthma may be defined as airway obstruction that becomes clinically manifest over a relatively short period of time. The clinical manifestations include some combination of shortness of breath, cough, wheezing and chest tightness. The obstruction may be mild and self-limited, or may be life threatening if not immediately addressed.

Current guidelines, such as Global Initiatives for Asthma (GINA), the National Guidelines for Diagnosis and Treatment for Childhood Asthma and the National Asthma Education and Prevention Program, have recommended short-acting inhaled beta2-agonists (usually salbutamol) as the medication of choice for treatment of acute exacerbations of asthma, and are useful for the pretreatment of exercise-induced asthma.

Anti-asthma medications can theoretically be administered by many different routes, including inhalation, ingestion or parenteral by subcutaneous, intramuscular or intravenous injection. There is a considerable advantage to the inhaled route because this delivers the drug directly to the site of action in the airways in concentrations that are likely to be effective, while systemic side effects are minimized or even avoided. This helps to achieve equivalent therapeutic response by using lower doses of a drug than will be required if it is to be given orally or parenterally. The additional advantage for this mode of drug delivery is the rapidity of onset of action, particularly when using beta-agonists for bronchodilation.

A number of different inhalation devices are available. They can be broadly divided into three categories, i.e. metered dose inhalers (MDIs), dry powder inhalers (DPIs) and nebulizers.

Pressurized MDIs (pMDIs) are the most widely prescribed inhaler devices as they are cheap, and have a uniform technology containing a wide variety of anti-asthma drugs. However, most patients cannot use pMDIs correctly as they require good coordination of patient inspiration and inhaler activation to ensure correct inhalation and deposition of the drug in the lungs. Even with the correct inhalation technique, pMDIs are inefficient, delivering only 1/3 of the emitted dose to the lungs, and less than half of the emitted dose to the peripheral airways compared to DPIs. Use of a spacer can reduce drug deposition in the oropharynx, but these devices are bulky and inconvenient to use and carry by the patient which may reduce compliance. Furthermore, pMDIs require an optimal inspiratory flow, a full inspiration from functional residual capacity and a breath hold of at least 6 seconds after inhalation, and so intensive training and regular technique re-testing is necessary. Unlike DPIs, pMDIs have no dose counters or inhalation feedback and control mechanisms, and as they use propellant gases, may cause throat irritation and occasionally paradoxical bronchconstriction. In addition, with the implementation of the 1987 Montreal Protocol and phasing out of chlorofluorocarbons (CFCs), newer CFC-free inhaler devices using ozone-friendly hydrofluoroalkanes (HFAs) have been developed.

Other devices include breath-actuated pMDIs that enable the patient to prime the inhaler which is then only activated when the patient takes a breath, avoiding the need to coordinate actuation with breathing.

DPIs are effective alternative devices that are not dependent on propellants (e.g. CFCs) for drug delivery. Instead, they allow the patient's inspiratory flow to activate, and carry drug particles into the lungs. DPIs are appropriate for older children and adults. The DPIs are often easier to use than the MDIs because they are breath-actuated inhaler, precluding the need to coordinate inspiration with inhaler activation, but some children may not be able to generate an adequate peak inspiratory flow rate. There is general agreement that the MDI is more difficult to master than is the DPI,

and differences exist in patient preference and deposition patterns with different DPIs. Ease of use and acceptability of DPIs and MDIs have been assessed in some comparative studies using preference questionnaires, and several studies have shown that patients prefer the DPIs to the MDIs.

Nebulizers have been used for asthma therapy in pediatrics for many years. With this mode of medication delivery, large doses of a wide range of medication can be delivered to patients of any age, with no special breathing technique required. Unfortunately, nebulizer therapy are expensive, inconvenient, time consuming, require a power source, need regular maintenance, and can cause greater adverse effects than MDIs and DPIs.

The available delivery system each has advantages and disadvantages, and considerations for choosing devices for individuals are important. No device is suitable for all patients. When selecting a device, the patient's age, physical abilities, lifestyle and cultural factors all need to be considered.

When prescribing an inhaler device for a patient with asthma, it is important to select the right drug, in the right dose, and to deliver it in a device that the patient is comfortable with, and can use effectively. Significant improvements in both concordance and inhaler technique can result from involving the patient directly in the process of inhaler selection. The patient's confidence with the device should also be considered. If the patient is involved in the selection process, the device has more chance of being used. However, patient empowerment should not mean that cost-effectiveness becomes an irrelevant issue within the asthma consultation. As with any prescribing decision, inhaler selection should be fully considered based on evidence of effectiveness and safety, as well as appropriateness for the patient and cost effectiveness. In addition, the cost of the drug used in specific devices varies widely. National and international guidelines are inconsistent in their recommendations for prescribing inhaler devices, and there are no explicity evidence based on which is the most efficient.

## 1.2 Rationale

The rising cost of asthma care, however, is at odds with moves to tighten health care budgets. Asthma has been the target of intense activity in the areas of clinical practice guidelines, disease management, drug formulary design and other efforts that are at least in part aimed at reducing medical expenditures and increasing quality for asthma care. Because asthma has become such an important topic to the public, decision makers must be mindful of the social as well as clinical aspects of this disease in their efforts to control the costs of asthma care.

As new and frequently more expensive drugs are developed, there is a need to assess both their effectiveness in reducing or controlling asthma symptoms, and determine their long-term cost-effectiveness. For example, the introduction of more expensive drugs may lead to better management of asthma symptoms and reduced total costs on health services.

Since the first pressurized metered dose inhaler (pMDI) was launched more than 40 years ago, monumental advances have occurred in the design of asthma inhalers. The

development of spacer devices, dry powder inhalers (DPIs), and breath-actuated devices has provided patients and physicians with a seemingly endless choice of asthma medications and delivery systems. Despite this, the pMDI has remained one of the most widely used delivery systems, mainly because it is cheap, portable, and delivers an extensive range of anti-asthma medications. However, pMDIs have several drawbacks, including suboptimal use resulting from the failure of patients to properly coordinate inhaler actuation with inspiraton, patients need careful instruction and training on their appropriate use, and no dose counter is present. In addition, the propellants and lubricants in pMDIs can result in paradoxical, acute bronchoconstriction in some patients.

Furthermore, during the last 25 years, environmental concerns over the destruction of stratospheric ozone by chlorine and global warming due to emission of greenhouse gases have resulted in multinational agreements to phase out production, and ban the use of chlorofluorocarbons (CFCs) by the year 2005. The inevitable demise of CFC-containing pMDIs has resulted in a global flurry of research and development activity to find suitable replacement devices. Even currently available substitute propellants have themselves been identified as greenhouse gases, suggesting a somewhat limited future for the pMDI. In Thailand, all CFC-containing MDIs have been phased out since December, 2005. Although alternative propellants have been developed, CFC-free pMDIs have been slow to appear on the market. The transition from the CFC-containing MDIs to CFC-free inhalers, i.e. either DPIs or non-CFC MDIs, will take place over a period of a few years in Thailand.

At the same time, the incidence of asthma has continued to increase worldwide, with up to 20% of children and young adults currently affected. This situation has stimulated the development of alternative, propellant-free inhalant devices for the administration of topical drugs, such as beta2-agonist bronchodilators and corticosteroids, the cornerstones of asthma treatment. As a result, the past decade has witnessed the development of breath-actuated multidose DPIs as the simplest and cost effective solution.

Taking the problems associated with the use of pMDI mentioned above into consideration, DPIs present a better alternative for inhaled asthma therapy. The multidose DPI is a new generation, which has been designed to resemble a pMDI in terms of the small size of the device, but importantly operates without the need for environmentally damaging propellants, and resolve the problem of coordinate actuation and inhalation. In addition, it lacks the lubricants and propellants that have been associated with adverse effects with pMDIs, and contains a dose counter. In comparative studies, the DPI has been shown to be at least as effective as pMDI plus spacer using comparable therapeutic doses of inhaled salbutamol, but is more acceptable and slightly better tolerated. DPIs have overcome many of the disadvantages of pMDIs, however, the prices of DPIs are usually more expensive than MDIs, and there is little research on the cost-effectiveness of different inhaler types, e.g. MDIs compared with DPIs, with the same drug used in children with acute exacerbations of asthma. In addition, the recommendations for inhaler devices from national and international guidelines are either absent, vague or inconsistent.

In light of the burden of pediatric asthma, it is important to assess whether treatment interventions can reduce health care resource utilization, and improve clinical

outcomes. This study is therefore designed to compare the cost-effectiveness of the DPI with the MDI plus spacer for delivering salbutamol to children with acute exacerbations of asthma.

The cost-effectiveness analysis was based on clinical data from a multicenter, randomized clinical trial conducted at 8 centers, i.e. King Chulalongkorn Memorial Hospital, Ramathibodi Hospital, Khon Kaen Rajanakarindha Hospital, Chiang Mai Hospital, Prince of Songkhla Hospital, Queen Sirikit National Institute of Child Health, Nopparatrajathanee Hospital and Police General Hospital. King Chulalongkorn Memorial Hospital was chosen as the model for this economic evaluation because of the availability and accuracy of unit cost information.

## 1.3 Research Question

What is the cost-effectiveness of delivering salbutamol via the dry powder inhaler compared with via the metered dose inhaler plus spacer in the management of mild to moderate acute exacerbations of asthma in children aged 5 to 18 years?

## 1.4 Research Objectives

### 1.4.1 General Objectives

To analyse and compare the cost-effectiveness, adverse events and number of asthma re-exacerbations of the dry powder inhaler with the metered dose inhaler plus spacer for delivering salbutamol in the management of mild to moderate acute exacerbations of asthma in children aged 5 to 18 years.

### 1.4.2 Specific Objectives

1.4.2.1 To compare the number of asthma re-exacerbations in children who use the dry powder inhaler compared to those who use the metered dose inhaler plus spacer.

1.4.2.2 To compare the adverse events of salbutamol in term of tremor, palpitation, hypotension and headache occured in children who use the dry powder inhaler with those who use the metered dose inhaler plus spacer.

1.4.2.3 To compare the cost-effectiveness ratio, and analyse the additional cost per additional effectiveness of delivering salbutamol via the dry powder inhaler compared with via the metered dose inhaler plus spacer in the management of mild to moderate acute exacerbations of childhood asthma.

## 1.5 Scope of the Study

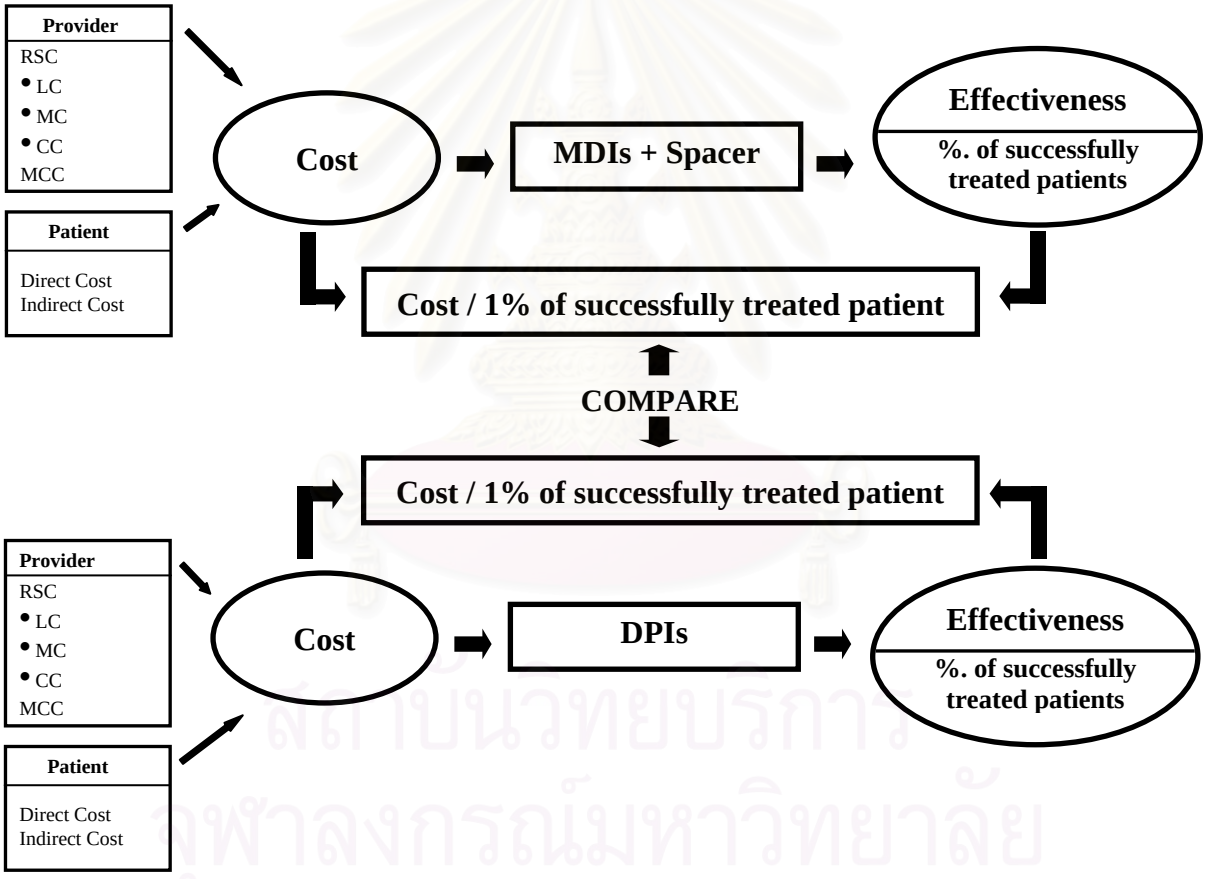
This cost-effectiveness analysis was conducted as a retrospective analysis based on clinical data from a multicenter, randomized clinical trial which enrolled the children with mild to moderate acute exacerbations of asthma who came to the outpatient department (OPD) or the emergency room (ER) of 8 centers in Thailand (i.e. King Chulalongkorn Memorial Hospital, Ramathibodi Hospital, Khon Kaen Rajanakarindha Hospital, Chiang Mai Hospital, Prince of Songkhla Hospital, Queen Sirikit National Institute of Child Health, Nopparatrajathanee Hospital and Police

General Hospital) during March 1, 2005 to December 31, 2005. These patients had to meet the eligibility criteria as identified in the Research Methodology section.

For the purpose of the economic analysis, the dry powder inhaler (DPI) was compared with the metered dose inhaler (MDI) plus spacer. King Chulalongkorn Memorial Hospital was chosen as the model for this economic evaluation. The cost-effectiveness analysis was performed primarily from the health care provider's perspective, and secondarily from the patient's perspective. Cost estimates were derived for both direct medical costs and indirect costs. Cost of provider was calculated from secondary data of cost analysis at King Chulalongkorn Memorial Hospital. The patient costs can be classified as direct medical costs which were charged by the provider and indirect costs incurred due to loss of productivity.

## 1.6 Conceptual Framework

Figure1.1: Conceptual framework of the study




## 1.7 Expected Benefits

This study was conducted to analyse the cost-effectiveness of the dry powder inhaler and the metered dose inhaler with spacer for delivering inhaled beta2-agonist, in an effort to create the use of the most clinical and cost effective treatment, taking account of the ability of the patient to use the inhaler device effectively.

# CHAPTER II

# LITERATURE REVIEW

## 2.1 Prevalence

The results of Phase I of the International Study on Asthma and Allergic Disease in Childhood (ISAAC), in 1998, indicated that the prevalence of childhood asthma varies widely throughout the world. Although prevalences in developing countries (10-20%) are generally lower than those in North America, Europe and Oceania (20-30%), the results indicated that prevalences in developing nations are not as low as was once thought. There are, however, large intracontinental and intercontinental variations among developing countries, perhaps representing differences in ethnicities, cultural practices, urbanization and the effects of industrialization influencing asthma pathogenesis (ISAAC 1998a, 1998b). The health problems of children in the developing world remain overwhelmingly those of poor education, poor housing and poor nutrition.

As in other parts of the world, childhood asthma has become a very common pediatric illness in Asia. Only a decade ago childhood asthma was believed to occur at much lower frequencies among Asian children than among their Western counterparts. This perhaps owes to results of previous investigations, such as one in Thailang (Boonyarittipong *et al*. 1990) and Taiwan (Huang and Hsieh 1997) which indicated that the prevalence rate of childhood asthma in these countries was in the range 1-4%. Nevertheless, results of Phase I of ISAAC (1998a, 1998b), utilizing a standardized epidemiological tool, have indicated that childhood asthma in Asia is as common as in the rest of the world, i.e. 10-15%. An interesting distribution of prevalence rates in Asia became apparent from the ISAAC Phase I study, i.e. that prevalences in more developed nations (such as Japan, Hong Kong, Singapore, etc.) were higher than prevalence rates in China and India. Nevertheless, prevalences in Taiwan and South Korea were lower than those from Southeast Asian nations.

In Thailand, the prevalence of childhood asthma has increased three-fold in less than a decade, rising from 4.3% in 1987 (Boonyarittipong *et al*. 1990) to 13% in 1994 (Vichyanond, Jirapongsananuruk *et al*. 1998), and 14.5% in 2001 (Vichyanond, Kaewsomboon *et al*. 2003). Although there were some variations between questionnaires utilized in these surveys, the differences are not sufficient to explain such large discrepancies.

## 2.2 Clinical Presentation of Childhood Asthma

In a prospective follow-up of 2,000 asthmatic children in Thailand, 50% manifested their initial symptoms within the first 2 years of life. (Tuchinda *et al*. 1987 quoted in Vichyanond, Weinberg and Sole 2001, 379). Since respiratory infections were the major precipitant of asthmatic attacks among these children (84.5%), it was possible that a large number of these subjects were children who wheezed during respiratory tract infection, i.e. wheezing-associated respiratory infections, or were early wheezers as classified by Martinez *et al*. (1995). It was, therefore, possible that asthma in young

children could have been overdiagnosed in Thailand. Nevertheless, a recent review of medical records from a large children's hospital in Bangkok has indicated otherwise. In this review, Vangveerawong (1999) found that it was apparent that asthmatic bronchitis was overdiagnosed by pediatric house officers and a thorough reclassification of diagnoses increased the clinical diagnosis of asthma among 2,312 children from 52% to 80%. With such contradictory results, a prospective study is urgently needed to gain further insight into the pathophysiology of early childhood wheezing in Southeast Asia. Recently, a study from Taiwan looking at Chinese children less than 2 years of age with wheezing and lower respiratory tract infections indicated that a lower value of respiratory compliance is the major risk factor, as had been observed in American children (Martinez *et al*. 1995; Yau, Fang and Hsieh 1999).

### 2.3 Diagnosis of Childhood Asthma in Thailand

Most pediatric asthma specialists in Thailand are familiar with Global Initiatives for Asthma (GINA), the National Asthma Education and Prevention Program (NAEPP) and the National Guidelines for Diagnosis and Treatment for Childhood Asthma. Nevertheless, general practitioners mostly concentrate on pharmacological therapies for asthma rather than on diagnosis, objectives of treatment and prevention of asthma. This reflects an attitude among Thai physicians that asthma is readily recognized during attacks; hence possible underdiagnosis of asthma is expected in children with less obvious presentations. Only 23% of Thai pediatricians in a recent survey indicated they had used a peak flow meter in an evaluation for chronic asthma. This perhaps owes in part to the high price of peak flow meters by local standards and the relative unavailability of the device to physicians. Similarly, use of peak flow meters and spirometry is uncommon in the overall management of asthma (less than 17% of respondents used a peak flow meter in managing acute asthma, and less than 25% used objective lung functions) (Vichyanond, Hatchaleelaha *et al*. 2001). Asthma is therefore diagnosed mostly by history and physical examination, mainly during an acute attack. Complicated cases of asthma are rarely referred to specialists for further evaluation. This owes to a relative lack of knowledge among medical personnel that asthma is an inflammatory disease, and could progress to a more severe condition without timely intervention with appropriate treatment (Vichyanond, Weinberg and Sole 2001).

Despite established informaton that up to 60-70% of asthmatic individuals in Thailand (both adults and children) are sensitized to house dust mites (Kongpanichkul, Vichyanond and Tuchinda 1997 quoted in Vichyanond, Weinberg and Sole 2001, 382), most physicians would consider skin testing to aeroallergens an unnecessary investigation for childhood asthma. Consequently, appropriate environmental control measures for house dust mites (such as hot washing and mattress encasing) and other allergens have received little attention from general practitioners, and pulmonary specialists alike. Recently, the Phadiatop test has been evaluated in Thailand, and has shown a promising sensitivity and specificity in establishing atopic status among Thai children. Nevertheless, its high cost prevents most physicians using it in the diagnosis of asthma (Vichyanond, Weinberg and Sole 2001).

## 2.4 Treatment of Childhood Asthma in Thailand

Asthma treatments include behavioral changes (generally through education), environmental modifications including control of allergens and avoid exposure to risk factors and several different types of medications with various modes of administration. Current pharmacologic strategies include short-acting bronchodilators that act to relieve acute symptoms or asthma attacks and controller treatments, such as corticosteroids, that prevent the occurrence of the asthma attacks.

Although international guidelines for diagnosis and management of asthma have been available for some times, these guidelines require adaptation to individual countries' practices and resources. Such adaptation has been carried out in several countries.

Prescribing styles in Thailand have concentrated more on the use of bronchodilators rather than anti-inflammatory agents despite intensive efforts over the past decade to inform medical communities in Thailand that asthma is an inflammatory disease of airways and lungs. Reasons for such practice are the myths among physicians that prophylactic agents are expensive, not cost-beneficial, and not affordable to most patients and their families. From the survey of pediatricians throughout Thailand done by Vichyanond, Hatchaleelaha *et al*. (2001), corticosteroids and cromolyn were chosen as elements of pharmacotherapy by only 9.6% and 2.4%, respectively. The other reason for not prescribing these two agents was the perceived difficulty of administering aerosol agents to children (and the lack of spacer devices). This is reflected by the fact that a large number of pediatricians chose ketotifen (up to 90.4%) as their preferred prophylactic agent for chronic asthma. In fact, the Thailand Medical Index survey in 1997 indicated that ketotifen accounted for a significant share (8%) of anti-asthmatic drugs prescribed in Thailand.

As for bronchodilator of choice for acute asthma, 81% of pediatricians chose nebulized salbutamol whereas only 13% chose subcutaneous adrenaline (Vichyanond, Hatchaleelaha *et al*. 2001). This has been the result of an intensive campaign on aerosol therapy over the last decade in Thailand. Similar results were seen in a review of in-hospital therapy in the largest teaching hospital in Thailand (Visitsunthorn, Sittichokananon and Tuchinda 1995).

As for forms of bronchodilators prescribed for chronic asthma, oral beta-agonists were the most favored group of drugs chosen (88%). Metered dose inhalers and dry powder inhalers accounted only for small percentages of responders (7.7% and 6%, respectively). The reasons for such a prescribing style could include lack of adequate time in busy offices to teach inhaler techniques, ease of use of pills, increasing compliance with oral agents, a social myth that inhaler use was associated with a severe degree of disease condition. Pre-exercise treatment was instructed in only 19% of cases. Small volume spacers for infants were not popular in Thailand, being selected by only 1.2% of Thai pediatricians (Vichyanond, Hatchaleelaha *et al*. 2001).

## 2.5 Inhalation Devices

There are a wide range of inhalation devices available. They can be broadly divided into three categories, i.e. metered dose inhalers (MDIs), dry powder inhalers (DPIs) and nebulizers.

The press-and-breathe pressurized metered dose inhaler (pMDI) was the first inhaler device, introduced in 1956. It contains chlorofluorocarbons (CFCs) as a propellant. The drug is dissolved or suspended in the propellant under pressure. When activated, a valve system releases a metered volume of drug and propellant. This is the most commonly used and usually cheapest device (Blanchard and Golish 2002; Wright, Brocklebank and Ram 2002; NHS Centre 2003). Many problems can be associated with the use of pMDI as followings:

- Patients require careful instruction and training to enable them to use pMDI correctly (Orion Pharma 2001; Fink and Rubin 2005; GINA 2005).
- Even with optimal technique, pMDIs deliver only around 10% of the aerosol to the lungs (Clark *et al*. 1985 quoted in Orion Pharma 2001; Hilman 1991 quoted in Orion Pharma 2001), which may only increase to 20% if a spacer is used (Newman 1985 quoted in Orion Pharma 2001).
- Particles leave the pMDI at a high velocity (around 100 km/hour) resulting in difficulty coordinating actuation with inhalation, particularly in children and the elderly (Weller 1999). The pMDI is used incorrectly by 24-84% of patients, either because of poor education or inability to coordinate device actuation with breathing (Epstein *et al*. 1979 quoted in Orion Pharma 2001; Shim *et al*. 1980 quoted in Orion Pharma 2001; Crompton 1982 quoted in Orion Pharma 2001; Allen 1986 quoted in Orion Pharma 2001). However, even with proper counselling as many as 20% of patients cannot become proficient in using the pMDI (Clark *et al*. quoted in Orion Pharma 2001).
- The pMDIs generate many particles that are too large to reach the lower airways and are deposited in the oropharyngeal region (the mouth and pharynx). This can result in local adverse events, such as taste disturbances, cough, and in the case of corticosteroids, oropharyngeal candidiasis or hoarseness (Orion Pharma 2001; Blanchard and Golish 2002; Peters *et al*. 2002; Barry and Callaghan 2003; Fink and Rubin 2005; GINA 2005).
- More than 80% of the inhaled aerosol from the pMDI are usually swollowed, and can result in systemic effects (Davis 1975 quoted in Dalby and Suman 2003).
- The “cold freon effect” can occur with the pMDI. When the propellant hits the back of the oropharynx, it causes the patient either to stop breathing completely, or at least to breathe through the nose rather than the mouth. This is known to occur in 10% of patients (Crompton 1982 quoted in Orion Pharma 2001; Cromptom 1995 quoted in Peter *et al*. 2002)
- Lubricants and propellants in pMDIs can irritate, or even damage the epithelium in the oropharynx, and in few cases may even worsen the asthma by causing paradoxical bronchospasm (Yarbrough *et al*. 1985 quoted in Orion Pharma 2001; Newman 1990 quoted in Orion Pharma 2001; Cocchetto *et al*. 1991 quoted in Orion Pharma 2001; Khilnani and Banga 2004; Virchow 2005).
- No information about the amount of drug remaining in the device is given, and thus, the inhaler may become empty unexpectedly (Williams and Krucheck 1993; Khilnani and Banga 2004). In one study of patients using pMDIs, more than half had run out of medication at sometime and consequently became wheezy, and nearly all

continued to use their inhalers after the canister had delivered the licensed number of doses (Williams and Krucheck 1993).

- High humidity can cause problems when using pMDIs, because such conditions can cause the drug to aggregate, and pMDIs can not be used effectively below 5°c. Aerosols can also become clogged if the patient breathe into the device (Orion Pharma 2001; GINA 2005).

In the 1970s and ’80s, an alarm was sounded that required a fast and professional response, as well as a dramatic change in inhalation therapy. Depletion of the ozone layer was occurring at a dangerously accelerating rate, heightening the threat of potentially harmful ultraviolet radiation. A primary cause of this potentially devastating problem was the proliferation of CFCs in the atmosphere. CFCs were used in a variety of industrial and medicinal products, including aerosol propellants found in MDIs.

Consequently, as a result of initiatives under the Montreal Protocol on Substances that Deplete the Ozone Layer in 1987 and the subsequent phase out of CFC production under the Clean Air Act in 1996 (Orion Pharma 2001; Woodcock, Morice and Everard 2001; Blanchard and Golish 2002; NHS Centre 2003), this has led to diligent efforts by the pharmaceutical industry to develop alternative aerosol delivery systems that do not use CFCs. The CFCs in pMDIs are now being replaced by hydrofluoroalkanes (HFAs), and the medication insert for dosage of the HFA preparations should be carefully reviewed by the clinicians. For bronchodilators, the doses from CFC and HFA inhalers appear to be equivalent (Dolovich 1999 quoted in GINA 2005). However, for some glucocorticosteroids, the HFA formulations which deliver a greater fraction of smaller particles to the lung, may result in both greater efficacy and greater systemic effects (Leach, Davidson and Boudreau 1998; Harrison *et al*. 1999; Juniper *et al*. 2002 quoted in GINA 2005)

In delivering pMDI therapy to children and infants, it is well understood that the components of the inhalation manoeuvre, e.g. inspiratory volume, inspiratory flow rate and breath-hold at end-inspiration, are difficult or impossible to control. Furthermore, as synchronization of actuation with inhalation of the pressurized aerosol is difficult for all children, the use of holding-chamber devices or spacers with pMDIs will eliminate many of these problems, allowing tidal breathing for inhaling the medication rather than deep breaths (a technique very young children and infants cannot master) (Dolovich and Everard 2001).

Holding chambers and spacers affect a reduction in mass median aerodynamic diameter (MMAD) of the original spray through evaporation and impaction of the larger particles on the walls or valves of the device. Thus, a finer aerosol is provided for inhalation with, potentially, a higher degree of success in getting the therapy into the child’s lungs (Dolovich 1995 quoted in Dolovich and Everard 2001; Khilnani and Banga 2004). Oropharyngeal deposition is also markedly decreased (Orion Pharma 2001; Blanchard and Golish 2002; Peters *et al*. 2002; Khilnani and Banga 2004; GINA 2005; Virchow 2005), reducing the total body dose of drug (Thorsson *et al*. 1998; Dolovich *et al*. 1983 quoted in Dolovich and Everard 2001). Also, with the retention of the larger droplets in the holding chamber or spacer, the “cold freon effect” from both CFC and HFA pMDIs, although less in the latter formulations, and which causes many children to stop inhaling, is eliminated (Dolovich and Everard

2001; Peters *et al*. 2002). This is the same outcome for drugs which have a foul taste. The larger droplets contain more drug and propellant, and by collecting this portion of the dose in the holding chamber or spacer, the overall taste sensed with these formulations becomes more palatable (Dolovich and Everard 2001; Barry and Callaghan 2003). The use of a valved holding chamber or spacer should be viewed as a necessary accessory to the pMDI for pediatric and neonatal delivery of these aerosol therapies.

Although spacers are widely recommended for use with pMDIs, most are bulky and inconvenient to carry, handle, and hide (Orion Pharma 2001; Blanchard and Golish 2002; Peters *et al*. 2002; Virchow 2005). All of these are factors that could reduce patient compliance, particularly when the patient is away from home, at school or travelling (Vidgren *et al*. quoted in Orion Pharma 2001). In addition, build up of electrostatic charge on plastic spacers may reduce effectiveness (Orion Pharma 2001; Peters *et al*. 2002; Barry and Callaghan 2003; Khilnani and Banga 2004), necessitating that they are washed regularly, and replaced around every 6 to 12 months. Some health care professionals recommend that spacers are primed for up to 20 doses to reduce static, which is both inconvenient, and wastes drug (Orion Pharma 2001; Peters *et al*. 2002; Khilnani and Banga 2004). Furthermore, they vary in the efficiency of drug delivery, and may increase cost of treatment (Blanchard and Golish 2002; Peters *et al*. 2002; Barry and Callaghan 2003).

Further development of pMDIs resulted in MDIs that combined the actions of actuation and inhalation, thus eliminating the need for hand-lung coordination. The drug is released from the inhaler device when the user inhales through the mouthpiece, in contrast to the user having to release the drug by pressing with a finger a button on the top of the device, and having to synchronise inhalation with this action. With the pressurized component retained, little addition force is needed to trigger the device. Although some recommend that a spacer is also used with this inhaler type in order to minimize the risk of oropharyngeal deposition, particularly with corticosteroid delivery, in practice spacers are rarely used with breath-actuated devices. The propellant used in breath-actuated inhalers was originally CFC, but this is now being replaced by alternatives (Orion Pharma 2001; Wright, Brocklebank and Ram 2002; Peters *et al*. 2002; NHS Centre 2003).

Dry powder inhalers (DPIs) are driven by inspiratory flow of the patient. DPI devices contain the drug in the form of a dry powder. They lack propellants and other potentially harmful additives, but the micronised drug in most DPI devices is mixed with a coarse carrier substance, usually lactose, which has been shown to cause airway irritation in some asthmatic patients. DPIs work on the principle of mechanical inhalation driven by the user's own inspiratory efforts, i.e. they are breath activated by the user. The energy imparted to the system by the user is used to disperse the drug particles. Disperson is aided through the use of a carrier in many of the devices, together with a variety of physical forces, depending on the device, such as turbulence and/or a grille. Individual DPIs have varying internal resistance, and require different minimum flow rates (Peters *et al*. 2002; GINA 2005).

The mechanism in a DPI eliminates the requirement for synchronization between actuation and inhalation, as required in pMDIs. Therefore, by design, the problems of coordination associated with pMDIs, although to some extent eliminated with the

additional use of a spacer device, are not present in DPIs (Dolovich and Everard 2001; Blanchard and Golish 2002; Peters *et al*. 2002; Barry and Callaghan 2003; Cohn 2003; Khilnani and Banga 2004; Virchow 2005). In general, DPIs and pMDIs are equally portable, although the inclusion of a spacer device with a pMDI reduces its portability as a delivery system. However, a number of disadvantages can be recognized as followings:

- DPIs are driven by inspiratory flow and thus, patients must be able to inhale with enough inspiratory flow to generate the drug aerosol (Orion Pharma 2001; Peters *et al*. 2002; Barry and Callaghan 2003; Cohn 2003; Khilnani and Banga 2004; GINA 2005).
- When no carrier is present in DPIs, the amount inhaled is so small that the patient may have no sensation of having received the dose (Orion Pharma 2001).
- For single-unit DPIs, loading of single-dose inhalers requires understanding and skill (Orion Pharma 2001).
- Oropharyngeal deposition still occurs, and patients should be advised to rinse their mouth with water after inhaling, especially when deliver inhaled corticosteroids, to minimise local side effects (Orion Pharma 2001).
- Storage of some DPIs may be more difficult in humid climates because some dry powder formulations may be sensitive to moisture (Barry and Callaghan 2003; GINA 2005).

Nebulizers use oxygen, compressed air, or ultrasonic power to break up solutions or suspensions of medication into droplets for inhalation. The aerosol is administered by a mask or mouthpiece. Historically, nebulization has been the preferred method for administering beta2-agonists to young patients, or to those patients who are unable to coordinate their inhalation with the actuation of an MDI due to agitation or severe obstruction. A major advantage of the nebulizer is the simple technique required of relaxed tidal breathing. This feature makes the nebulizer a logical choice for the delivery of inhaled medications to infants and young children (Spahn *et al*. 2001; Newman *et al*. 2002; Cohn 2003). However, there is a huge variation in the output from the various devices, and this in turn affects drug delivery and therapeutic response. Drug deposition is variable, and ranges from less than 1% to over 20% of the nominal dose (Spahn *et al*. 2001; Dalby and Suman 2003). In addition, their use is limited by their inconvenience (they are cumbersome and noisy), high cost, and the fact that treatment can take a long time (Orion Pharma 2001; Wright, Brocklebank and Ram 2002; Cohn 2003; NHS Centre 2003; Khilnani and Banga 2004; Neto *et al*. 2005). Furthermore, some patients and parents dislike them (Orion Pharma 2001; Neto *et al*. 2005).

While the effectiveness of nebulization is widely recognized, the method nevertheless has several disadvantages. Studies indicate that nebulization can be an inefficient method of delivering aerosol medication. It has been demonstrated that in a controlled setting, the efficacy of MDI and nebulizer was comparable for home use as well as for hospitalised patients. The nebulizer dispenses more medication than the MDI with spacer, but without added therapeutic benefit (Raimondi *et al*. 1997 quoted in Newman *et al*. 2002; Rodrigo 1998). The potential for excess drug exposure is of concern since the inhalation of beta2-agonists in high doses can cause nonpulmonary adverse effects, such as tremor and anxiety (Rodrigo 1998). The costs associated with nebulization, which include purchasing and maintaining equipment, and supervising its use, make this method of administering bronchodilators more expensive than the

MDI with spacer (Turner and Patel 1997 quoted in Newman *et al*. 2002; Khilnani and Banga 2004). Power requirements, higher drug dosing, and the costs of maintaining nebulizers and their peripheral equipment are particularly burdensome for patients in developing regions of the world (Batra, Sethi and Sachdev 1997 quoted in Newman *et al*. 2002). In addition, different studies have shown that MDIs with spacers are more cost-effective than nebulizers for the administration of bronchodilator agents (Newman *et al*. 2002; Vilarinho, Mendes and Souza 2003; Hsu and Parker 2004).

## 2.6 Clinical Studies of Metered Dose Inhalers (MDIs) and Dry Powder Inhalers (DPIs)

### 2.6.1 MDIs and DPIs for Treating Acute Asthma in Children

The conventional first line treatment of acute asthma for the paediatric population is a beta2-agonist administered in an aqueous solution by nebulization. In recent years, beta2-agonists given by pressurized metered dose inhalers plus a spacer have been shown to be as efficacious as when given via a nebulizer to children with acute asthma (Freelander 1984 quoted in Drblik 2003; Fuglsang and Pederson 1986 quoted in Drblik 2003; Pendergast, Hopkins and Timms 1989 quoted in Drblik 2003; Idris *et al*. 1993 quoted in Drblik 2003; Kerem *et al*. 1993 quoted in Drblik 2003). Maldonado-Alanis *et al*. (1998) evaluated the bronchodilator response of 63 children over 6 hours in a three way parallel study. The results were published as an abstract only, and detailed statistical results were not shown. The initial bronchodilator response for salbutamol was similar between pMDI plus Pulmona® spacer, pMDI plus Ellipse® spacer (200 mg from each) and a nebulizer (at a dose of 150 mg/kg). Salzman and Pyszczynski (1986 quoted in Wright, Brocklebank and Ram 2002) included 15 patients with severe stable asthma in a 2-day open crossover trial of metaproterenol 1.3 mg via pMDI plus Aerochamber® spacer device versus 15 mg via a nebulizer. No statistically significant differences in expiratory airflow were found between the delivery methods. A Cochrane systematic review of 16 trials comparing pMDI plus spacer with nebulizers for the delivery of beta2-agonists for mild and moderate exacerbations of asthma found that clinical outcomes from pMDIs were at least equivalent to nebulizers, and may have some advantages for children (Cates and Rowe 2002 quoted in Wright, Brocklebank and Ram 2002). Children over 5 years and adults with mild and moderate exacerbations should be treated with pMDI plus spacer with bronchodilator dose titration according to clinical response. These findings suggested that other treatment modalities could offer the same advantages, and be used as alternatives in the emergency setting in treating patients with acute asthma.

Dry powder formulations of beta2-agonists are a well established treatment of children with clinically stable asthma, and have been shown to be as efficacious as the pMDI with a spacer (Ahlstrom, Svenonius and Svensson 1989 quoted in Drblik 2003; Fuglsang and Pedersen 1989 quoted in Drblik 2003; Hultquist *et al*. 1989 quoted in Drblik 2003; Laberge *et al*. 1994 quoted in Drblik *et al*. 2003). Recently, the use of DPIs has been investigated as a possible alternative for acute asthma, however, these studies generally have been in adults (Engel *et al*. 1990 quoted in Drblik 2003; Tonnesen *et al*. 1994 quoted in Drblik *et al*. 2003, Nana *et al*. 1998). Several investigations have attempted to address this question in the paediatric population using a limited number of subjects (Rufin 1993 quoted in Drblik *et al*. 2003; Springer *et al*. 1996). The reluctance to use an effort dependent breath actuated device in an

acute setting may be due, in part, to the belief that either inspiratory flow is sufficiently compromised during an acute exacerbation, or children may not be able to perform the inspiratory manoeuvre correctly, thereby affecting the amount of medication being effectively delivered.

Some studies to date have sufficient evidence shown that DPIs can be used in children with acute asthma. Drblik *et al*. (2003) compared one such DPI with a pMDI and a spacer, in their efficacy of delivering equally effective doses of terbutaline sulphate to children presenting to the emergency department for first line treatment of an acute asthmatic episode. Results shown that the DPI and pMDI plus spacer are similar in terms of benefit and side effects in the treatment of acute moderate to severe asthma attacks in this study population. Du Toit *et al*. (2003) assessed the bronchodilator efficacy and side effect profile of a salbutamol DPI device when used in a busy Allergy Clinic. In addition, they sought to assess the attitudes of nursing staff, parents and patients, after the DPI device had been used. The findings of this independent study confirm the favourable RCCH Allergy and Asthma Clinic experience when using the salbutamol DPI device for the acute relief of symptomatic asthma. In spite of the possible bias introduced by the open label study design, they concluded that the device was both effective and safe in children with symptomatic asthma. In addition, the salbutamol DPI device was considered to be effective and easy to use by patients and staff alike.

### 2.6.2 Doses of Salbutamol Used for Asthma Attacks in Children

A selective beta2-adrenergic agonist (usually salbutamol) is administered by inhalation to accomplish the primary goal of rapidly reversing airway obstruction. The recommended doses of short-acting beta2-agonists, e.g. salbutamol, for treating asthma attacks in children specified in the Global Initiative for Asthma (GINA 2005) are 4 to 8 puffs every 2 to 4 hours, or may administer every 20 minutes up to 3 treatments with medical supervision, and are similar to doses recommended in the National Asthma Education and Prevention Program (NAEPP 2002) and A Guide to the Essentials of Good Clinical Practice in Management of Asthma (Khaled and Enarson 2005).

Recent studies have demonstrated the utility of using a MDI with a spacer device and DPI to deliver adrenergic agonists in the face of acute asthma.The doses lied within the recommended range are found in part on studies that used salbutamol administered via DPIs or MDIs with or without spacers. In study conducted by Leversha *et al*. (2000), children in MDI group were given 600 mcg of salbutamol by MDI plus spacer, and the treatment were repeated every 20 minutes as needed. In one study, an average of 8 puffs (range 4 – 14 puffs) was required to achieve an acceptable improvement in airflow rate with minimal side effects (Benton *et al*. 1989 quoted in Larsen and Colasurdo 2001, 200).

### 2.6.3 Adverse Events of Salbutamol Administered via DPIs Compared with via MDIs

Adverse events or side effects of short-acting beta2-agonists, such as salbutamol, on the whole are directly related to the concentration of drug getting into the systemic circulation. Thus in high doses, skeletal muscle tremor, headache, a feeling of

agitation and palpitations can occur. However, there is a tendency for tolerance to systemic side effects to develop fairly rapidly. High doses can also produce hyperglycemia, hypokalemia, and increase circulating fatty acids. At high doses, there will be some effects on the beta2-receptors in the heart, which could produce a ventilation/perfusion imbalance. In severe acute asthma with hypoventilation, high-dose beta2-specific agonists might increase shunting of blood through under-ventilated lung, and thereby produce hypoxemia (Warner, Naspitz and Rizzo 2001).

An open, crossover and randomized study was carried out by Bondesson *et al*. (1998) in order to compare the safety and efficacy of salbutamol inhaled using the DPI and using a pMDI. Twelve patients with moderate to severe asthma, aged 47-68 years, were included in the study. On two separate days, patients received a total dose of 1600 micrograms of salbutamol administered in a cumulative dose fashion: 100, 100, 200, 400 and 800 micrograms at 3-min intervals. The DPI caused a small (but statistically significantly greater than with pMDI) increase in heart rate, QTc interval and tremor. Blood pressure was unaffected by the treatments. No adverse events of clinical relevance were reported. In conclusion, salbutamol inhaled via the DPI was more potent, and seemed to have a better therapeutic ratio than salbutamol inhaled via pMDI. Both treatments were equally well tolerated. Three RCTs in adults found a higher pulse rate in patients using the DPI than those using pMDI, suggesting greater systemic absorption with the DPI device (Johnsen and Weeke 1988 quoted in Wright, Brocklebank and Ram 2002; Ekstrom *et al*. 1995 quoted in Wright, Brocklebank and Ram 2002; Bondesson *et al*. 1998 quoted in Wright, Brocklebank and Ram 2002).

In the study conducted by Neto *et al*. (2005), children in the nebulizer, MDI with non-valved homemade spacer, and DPI groups had a higher variation in their heart rate than those in the MDI with commercial spacer group. Tremors were more frequent in nebulizer and MDI with non-valved homemade spacer than in the MDI with commercial spacer and DPI groups, a finding that runs counter to the literature, probably due to the greater bronchodilator deposition in the oropharynx and in the gastrointestinal tract, with consequently higher systemic absorption. No hypokalemia was detected after 60 minutes of bronchodilator administration, but we should view these results with caution, since they did not measure serum potassium levels at the beginning of the study.

However, some studies have shown that the overall incidence of adverse events was very low, and no serious adverse events, or clinically important changes in vital signs occurred during the studies. In addition, there was no treatment-associated differences in safety parameters, and no significant differences of adverse events provoked by DPIs compared with MDIs (Ahrens *et al*. 1999; Singh and Kumar 2001; Newhouse, Patel and Parry-Billings 2003).

### 2.6.4 Inhaler Techniques

The effectiveness of inhaler devices depends on more than just the devices themselves. Patient technique is crucial to effective drug delivery, and will depend on factors such as patient experience, education, physical ability and effective teaching of technique.

The studies have shown that the pMDI is used incorrectly by 24-84% of patients, either because of poor education or inability to coordinate device actuation with breathing (Epstein *et al*. 1979 quoted in Orion Pharma 2001; Shim *et al*. 1980 quoted in Orion Pharma 2001; Crompton 1982 quoted in Orion Pharma 2001; Allen 1986 quoted in Orion Pharma 2001).

A systematic review of RCTs and observational studies supports the anecdotal impression, and prejudice that pMDI devices are not used as effectively as DPIs (Brocklebank *et al*. 2001). The percentage of patients with correct technique (assessed by a scoring system of correct steps) was 43% compared with 55% for pMDI with spacer, and 59% for DPIs. However, teaching had a positive effect, and eliminates significant differences between devices by increasing the percentage of patients with correct technique to 63% for pMDI, and 65% for DPIs. Differences in effective patient technique therefore appear to owe more to the lack of teaching than to inherent differences in the devices themselves. All patients should receive appropriate instruction and guidance on effective technique when prescribed inhaler devices, and this should be regularly reinforced.

Fink and Rubin (2005), noted that common problems with MDIs include improperly coordinating actuation with the beginning of inspiration thereby reducing the amount of medication inhaled, the occurrence of actuation near end-inspiration can reduce the inhaled dose, failure to shake prior to the first actuation after a period of hours or days may increase dose variability and consistency across the life of the MDI, and reducing the canister temperature to below 15°C substantially reduces the emitted dose. The study also identified some common problems associated with DPI use. For example, when using a DPI, the patient's inspiratory effort is key to the mechanical energy that releases the drug from the inhaler. Failure to produce the minimum inspiratory flow for a specific DPI substantially reduces the inhaled dose, as does exhalation into a DPI.

### 2.6.5 Patient Preference and Compliance

Current delivery options for inhaled therapy are DPIs, MDIs, and nebulizers. Variables such as efficacy and safety are pivotal considerations when choosing a device, but acceptability is also important because it may affect treatment compliance.

Some patients, especially children, find MDIs difficult to use because they require coordination between actuation of the device and inhalation. Large volume spacers can be used in conjunction with MDIs to address this problem. Unfortunately, due to their size, spacers might be inconvenient and aesthetically unacceptable, especially for older children.

Ease of use and acceptability of DPIs and MDIs have been assessed in some comparative studies using preference questionnaires. Several studies have shown that patients prefer the DPI to the conventional MDI (Boe *et al*. 1992 quoted in Morice *et al*. 2002; Vilsvik *et al*. 1993 quoted in Morice *et al*. 2002; Lenney, Innes and Crompton 2000 quoted in Morice *et al*. 2002). Vilsvik *et al*. (1993 quoted in Morice *et al*. 2002) found that 55% (87/158) of patients preferred the DPI (manufactured by AstraZeneca, Sweden) to the MDI ($P < 0.00l$), whereas Schlaeppi *et al*. (1996) found that the DPI manufactured by GlaxoSmithKline was preferred over the DPI

manufactured by AstraZeneca by 65% (104/159) of patients (P < 0.001). Pediatric patients also have found the DPI manufactured by GlaxoSmithKline easier to handle than the DPI manufactured by AstraZeneca (Williams and Richards 1997). Furthermore, a meta-analysis of 800 patients from 9 comparative studies showed that patients preferred the DPI manufactured by Orion Corporation to the DPI manufactured by AstraZeneca, the DPI manufactured by GlaxoSmithKline, and the MDI (Ahonen *et al*. 2002).

Acceptability data were assessed as an outcome variable in 3 studies comparing a DPI with an MDI for delivery of beclomethasone dipropionate to adult and pediatric patients with asthma. When patients in clinical trials were allowed the free use of different inhaler types, the large majority prefered DPIs as evident in the articles regarding the use of DPI manufactured by Orion Corporation and the DPI manufactured by Innovata Biomed (Morice, Andrews and Taylor 2000; Stradling *et al*. 2000; Anand *et al*. 2001). However, because the main purpose of each trial was to assess the efficacy and safety of the treatments, acceptability data were not fully reported. Patients answered questions regarding their preference of an inhaler device (DPI v.s. MDI) and additional questions about specific aspects of the DPI, including handling, ease of use, and usefulness of the dose counter.

Wettengel *et al*. (2002) compared the DPI manufactured by GlaxoSmithKline with the DPI manufactured by Orion Corporation in a group of 185 asthmatic patients, using an eleven-point questionnaire. Patients rated the DPI manufactured by Orion Corporation higher on 8 questions. Jager *et al*. (2000) studied the acceptance of and preference for the DPI manufactured by AstraZeneca in comparison with the DPI manufactured by Orion Corporation in a group of 79 powder-naive asthmatic patients. They found that 59% preferred the DPI manufactured by Orion Corporation, 33% chose the DPI manufactured by AstraZeneca, and 7% rated them the same. Zetterstrom *et al*. (2000), studying a group of 32 patients with asthma and/or bronchial hyper-reactivity, observed that 65% found the DPI manufactured by Orion Corporation very easy to use, and 35% found it easy. Out of 16 patients who had previously used the DPI manufactured by AstraZeneca, 16% rated the DPI manufactured by Orion Corporation much better, 44% rated it better, and 38% rated it as high as the DPI manufactured by AstraZeneca. Tukiainen *et al*. (2002 quoted in Giner *et al*. 2004) compared acceptance of devices, together with other factors, among a group of asthmatic patients (103 used the DPI manufactured by Orion Corporation, and 58 used the DPI manufactured by AstraZeneca). The DPI manufactured by Orion Corporation was found to be better accepted than the DPI manufactured by AstraZeneca in that study. Serra-Batlles *et al*. (2002 quoted in Giner *et al*. 2004) found that their powder-naive patients preferred the DPI manufactured by GlaxoSmithKline over the DPI manufactured by AstraZeneca and, in particular, valued the dose counter, ease of use, design and the attached cover. Features appreciated about the DPI manufactured by AstraZeneca included its small size, discreetness and ease of holding, and those features were rated highly in other studies too. Schweisfurth *et al*. (2002) studied the acceptance of 2 inhalers in a group of asthmatic patients (159 used the DPI manufactured by Orion Corporation, and 167 used the DPI manufactured by AstraZeneca), and also found the former better accepted than the latter. Giner *et al*. (2004) investigated a group of patients' preferences among 3 DPIs, i.e. the DPI manufactured by GlaxoSmithKline, the DPI manufactured by Orion Corporation and the DPI manufactured by AstraZeneca, and

to analyzed the features that were most important for motivating choices. They found that the DPI manufactured by Orion Corporation was the first choice for 53% of patients, the DPI manufactured by AstraZeneca for 27%, and the DPI manufactured by GlaxoSmithKline for 20%. The DPI manufactured by Orion Corporation was rated the highest by the patients in the study. The scores were a long way from the maximum score, so research into developing an ideal inhaler musy continue.

It is possible that a preferred inhaler may improve patient competence and compliance. This is an important consideration for clinicians faced with a choice of alternative replacement devices. The most effective inhaler for any given patient is the one that the patient will use on a regular basis and in an effective manner. Patient compliance with inhaled medication is poor, and patients often report compliance rates in excess of those objectively measured.

In one study (Bender *et al*. 1998 quoted in Barry and Callaghan 2003), adherence with inhaled beta-agonists and corticosteroids in asthmatic children was tracked using an electronic monitor (Metered Dose Inhaler Chronolog). Patients seldom took all of their medications as prescribed, and failed to take any inhaled corticosteroid doses on a median of 42% of days or inhaled beta-agonists on 28% of days despite prescribed daily use. Medication non-adherence was correlated with lower levels of asthma knowledge and greater family dysfunction. Patients tended to dramatically over-report medication use.

In another study (Milgrom *et al*. 1996 quoted in Barry and Callaghan 2003), children who had asthma for which they were receiving both inhaled corticosteroids and beta-agonists, the median use of inhaled corticosteroids reported by patients on their diaries was 95%, whereas the median actual use was 58%. More than 90% of patients exaggerated their use of inhaled steroids, and yet diary entries of even the least compliant subjects reflected a high level of adherence. Low compliance rates were associated with increased exacerbations of disease - the median compliance with inhaled corticosteroids was 13.7% for those who experienced exacerbations, and 68.2% for those who did not.

Other studies using electronic timer devices attached to metered dose inhalers have also shown poor compliance. Even where subjects knew that compliance was being monitored, on only half of the study days was the prescribed medication taken, whether this was self-administered by adults or children or where a parent supervised administration. Older children tended to be less compliant than younger ones. Poorly compliant patients were at increased risk of exacerbations, and in one study (Jonasson, Carlsen and Mowinckel 2000 quoted in Barry and Callaghan 2003), placebo administration was associated with worse compliance than drug treatment, perhaps suggesting that patients will be more compliant if their medication is effective. In the same study, patients were followed for over 2 years. Compliance fell from 77% at the start of the study to 49% in the treatment group after 27 months, and to 32% in those receiving placebo.

Although there is no evidence that compliance is improved by changing to a different inhaler device, small unobtrusive devices are often marketed on the basis that they are more acceptable to the patient, and will therefore be used more. Patient satisfaction studies are, in general, undertaken by the drug or device manufacturing companies.

Therefore selection of an inhaler device for the asthmatic patient should be based on prescribing a device that the patient will use, and encouraging adherence to prescribed treatment. Clinicians should be aware of the limitations of each type of device, and the optimum methods of use for each.

## 2.7 The Cost-Effectiveness Analyses

### 2.7.1 Cost Issues in Asthma

Worldwide, there is considerable interest in the economic effect of asthma, as evidenced by numerous cost-of-illness studies. These studies are difficult to compare because of differences in definitions of costs and sources of unit costs, and differing time periods and exchange rates. Mindful of these difficulties, the Global Initiative for Asthma conducted a review of 6 asthma cost-of-illness studies (GINA 1995 quoted in Weiss and Sullivan 2001). That review of asthma costs in developed countries suggested an average annual societal burden ranging from $326 to $1,315 per afflicted person (1991 US dollars). Approximately 40% to 50% of the total asthma costs were attributed to direct medical expenditures..

The economic cost of asthma is considerable both in terms of direct medical costs (such as hospital admissions and the cost of pharmaceuticals) and indirect medical costs (such as time lost from work and premature death) (Weiss and Sullivan 2001; Masoli *et al*. 2004). Direct costs represent approximately 1–3 % of total medical expenditures in most countries. In 1998, the economic burden of asthma in the United States was estimated to be US$ 12.7 billion. Indirect cost account for over 50% of the total cost. Asthma-related costs are largely attributable to pharmaceuticals, hospitalizations and visits to emergency departments as well as days of work lost. Intangible costs such as those incurred by a low quality of life are very difficult to measure. Both the direct and indirect costs of asthma to an employer are substantial (Birnbaum *et al*. 2002 quoted in Bousquet *et al*. 2005).

In developing countries, childhood asthma has significant adverse effects on the child's daily activities, schooling, family life and finances. In India, the median monthly expenditure on a child's medication was reported to be rupees 333, i.e. about one third of monthly per capita income (Lodha *et al*. 2003 quoted in Bousquet *et al*. 2005).

A study of US families, conducted from 1977 to 1980, showed average annual costs of $1087 per child with asthma (n = 25) (Marion, Creer and Reynolds 1985 quoted in Weiss and Sullivan 2001). A more recent study from Australia, with similar methods and a much larger sample of children with milder asthma (n = 193), showed a mean annual cost per child of 212.48 Australian dollars, increasing to 884 Australian dollars for children who had been hospitalized (Toelle *et al*. 1995 quoted in Weiss and Sullivan 2001). Canadian investigators found that the annual costs per patient in South Central Ontario varied greatly on the basis of disease severity, age, smoking status, drug coverage, health plan and retirement status (Ungar *et al*. 1998 quoted in Weiss and Sullivan 2001). One study of particular interest characterized asthma costs in lesser developed countries. The investigators conducted a mail survey of health care providers in 24 countries throughout Africa and Asia; many of the countries had a limited supply of asthma-related drugs. The results indicated the estimated costs of

asthma drugs ranged from 3.8% to 25% of the patient's monthly income (Watson and Lewis 1997 quoted in Weiss and Sullivan 2001). Another study of 8 low- and middle-income countries found that costs and availability of asthma medications varied widely, representing a potentially important barrier to care (Ait-Khaled *et al*. 2000 quoted in Weiss and Sullivan 2001). These results support the evidence of rising costs of asthma care thoughout the world, and the disease's social burden and costs to public and private health care systems are substantial. The costs of medical treatments for asthma can represent a substantial proportion of family income. In addition, because asthma has become such an important topic to the public, decision makers should be mindful of the social as well as clinical aspects of this disease in their efforts to control the costs of asthma care. As new and frequently more expensive drugs, e.g. DPIs, are developed, there is a need to assess both their effectiveness in reducing or controlling asthma symptoms, and determine their cost-effectiveness as conducted in this study.

Emergency department (ED) visits and hospitalizations are key cost components of asthma care. Several studies have attempted to better quantify these costs. One of these studies examined the costs of 214 persons with asthma-related ED visits not resulting in hospitalization. The ED costs for these individuals ranged from an average of $248 for children 5 years and younger to $457 for adults 18 years and older (Segal, Ried and Mackowiak 1995 quoted in Weiss and Sullivan 2001). These costs were similar to those described in another study of more than 3000 adults who had an average ED cost of $234 per visit (Stanford, McLaughlin and Okamoto 1999 quoted in Weiss and Sullivan 2001). In this same study average hospitalization costs for asthma were $3103, however, they ranged from approximately $2000 for patients classified as having mild asthma on admission to more than $15,000 per hospitalization for patients defined as having the most severe disease.

There are economic studies of children with asthma, one conducted within a single health care organization and the other based on a national population sample, both explore the marginal cost of asthma above other health care costs. These studies concluded that for children with asthma, there seem to be additional nonasthma-related costs associated with comorbid upper and lower respiratory conditions (Lozano, Connell and Koepsell 1995 quoted in Weiss and Sullivan 2001; Lozano *et al*. 1999). One of these studies examined a low-income Medicaid population, and found that asthma costs for African-American children were 24% higher than the costs for white children, primarily because of higher costs associated with hospitalizations and ED visits (Lozano, Connell and Koepsell 1995 quoted in Weiss and Sullivan 2001). Higher use of ED and inpatient services for asthma among African-American children using Medicaid (compared with white children) could not be fully explained by poverty or inadequate health insurance. Furthermore, these children appeared to make disproportionately few office visits for asthma, suggesting suboptimal use of preventive services for asthma. By contrast, the comparable use of well-child visits in the 2 groups suggested the problem may not be inaccess to care in general, but there may be specific problems in the successful management of chronic diseases, such as asthma, among African-American children. African-American race was associated with an increased risk for remaining high users of hospital resources, however, the race was neither sensitive nor specific in identifying persistent high use of hospital resources. Persistent high levels of hospital resource utilization may be influenced by additional factors, such as comorbid conditions (e.g. sinusitis), the

improper use of drug therapy, or demographic factors and socioeconomic status (e.g. family size). The identification of factors associated with persistent high use of hospital resources will allow the asthma disease management programs to target specific populations for special intervention.
Stevens *et al*. (2003) estimated that 1 to 5-year-old children with wheeze in the UK cost the health service a total of 53 million UK pounds (GBP). The greatest expenditure, 34 million GBP, was for primary care, representing 65.2% of total healthcare costs. Prescription costs represented 20.4% (11 million GBP) of total healthcare costs. Caring for preschool children with wheeze in the UK cost the health service 0.15% of its total budget in 1998/1999. The total costs to society of caring for the 0.88% of preschool children who attended hospital for asthma or wheeze in a year represented a further 2.6 million UK pounds. Primary prevention strategies at the population level promise more cost savings than any attempt at decreasing hospitalisations in those more severely ill.

Wang, Zhong and Wheeler (2005) estimated direct medical costs and school absence days among school-age children who had treatment for asthma during 1996. They estimated indirect costs as costs of lost productivity arising from parents' loss of time from work and lifetime earnings lost due to premature death of children from asthma. All costs were calculated in 2003 dollars. In 1996, an estimated 2.52 million children aged five to 17 years received treatment for asthma. Direct medical expenditure was $1009.8 million ($401 per child with asthma), including payments for prescribed medicine, hospital inpatient stay, hospital outpatient care, emergency room visits and office-based visits. Children with treated asthma had a total of 14.5 million school absence days; asthma accounts for 6.3 million school absence days (2.48 days per child with asthma). Parents' loss of productivity from asthma-related school absence days was $719.1 million ($285 per child with asthma). A total of 211 school-age children died of asthma during 1996, accounting for $264.7 million lifetime earnings lost ($105 per child with asthma). Total economic impact of asthma in school-age children was $1993.6 million ($791 per child with asthma). They concluded that the economic impact of asthma on school-age children, families, and society is immense, and more public health efforts to better control asthma in children are needed.

Achieving greater disease control in patients with asthma will reduce the number of hospitalizations associated with asthma, and may ultimately produce a reduction in both direct and indirect costs. Improved control may occur at the expense of increased medication and general practitioner costs, but in the long run these costs will be offset by a reduction in the cost of uncontrolled asthma, such as those associated with additional physician visits, hospitalization and days off work.

New products have to justify their price over cheaper generics already available on the market. Pharmaceutical companies are faced increasingly with the need to justify their pricing applications with health economic data. A high drug price may be acceptable if the medication helps to decrease the costs of the disease to society or reduce the even higher costs of hospital care.

### 2.7.2 Clinical Outcomes and Effectiveness of Asthma Treatments

Outcomes studies address the effectiveness of interventions. Some reports use specific outcome measures and instruments to assess variables that impact the practice of

medicine and patient care. Outcomes studies often go beyond the physician's viewpoint, and consider patients' opinions about their care, and its effect on their quality of life. Data obtained through outcomes studies should provide payers, physicians, patients and other decision makers with facts that promote informed choices about health care.

Effective outcomes studies should (Aon Consulting 2002):

- Indicate cost-effectiveness, i.e. cost of interventions and which are the best value for the money.
- Lead to better use of the resources in order to improve care, and reduce costs.
- Generate information about what therapies and technologies achieve optimal results in terms of patient satisfaction and clinical outcomes, as well as cost-effectiveness.
- Be able to be used to develop and improve guidelines for disease management.
- Be useful in evaluating community health improvement, patient monitoring and practice styles.

A number of outcome measures are used to determine effectiveness of asthma treatment for the purpose of the economic analysis. Some examples of effectiveness measure use are followings:

- The number or proportion of patients meeting the desired end point or patients who achieve treatment success (Steinmetz *et al*. 1998; Volmer *et al*. 1999; Stempel *et al*. 2000; Bisgaard *et al*. 2001).
- The number or proportion of symptom-free days (SFD). A SFD is defined as a 24-hour period in which no asthma symptoms (Steinmetz *et al*. 1998; Lundback *et al*. 1999; Stempel *et al*. 2000; Everden *et al*. 2002; Jonsson *et al*. 2004; Miyagawa *et al*. 2006). The SFD has been recommended as an outcome measure in guidelines for economic evaluation in asthma (Sullivan *et al*. 1996 quoted in Jonsson *et al*. 2004)
- The number or proportion of episode-free days (EFD). An EFD is defined as a day without an asthma attack, need for rescue medication or sleep disturbance caused by asthma and the absence of an adverse event (Lundback *et al*. 1999, Stempel *et al*. 2000, Weiss *et al*. 2004; Ericsson *et al*. 2005).
- The number of asthma exacerbations (Liljas, Stahl and Pauwels 1997; Bisgaard *et al*. 2001; Jonsson *et al*. 2004)
- Others.

### 2.7.3 The Previous Cost-Effectiveness Analyses of Breath-Actuated Inhalers and Metered Dose Inhalers (MDIs)

There are many different devices available for inhalation therapy in the treatment of asthma. Comparative studies between them are often poorly designed, and may be unable to detect a difference between two devices.

There are a number of economic analyses of asthma interventions, but to date few of these have analysed the cost effectiveness of different inhaler types with the same drug in the required population, and meet the agreed standards for economic evaluation in health care.

Liljas, Stadhl and Pauwels (1997) conducted an open randomised parallel-group study, 1004 patients with asthma in 7 countries were randomised to receive asthma treatment via two different kinds of inhalers: an aerosol pMDI and a DPI (manufactured by AstraZeneca). The patients were treated for 52 weeks with inhaled corticosteroids and/or inhaled beta2-agonists. Because of the difficulty of comparing costs between countries, each country was analysed separately. Canadian patients constituted the largest subpopulations (445 patients), and were therefore used in this analysis. From the analysis, they concluded that the effectiveness of treatment (measured as the number of exacerbations and days with exacerbation) was significantly better for patients treated via the DPI than via the pMDI ($p = 0.03$). Furthermore, the total annual costs of treatment were, on average, $Can 331 less ($p < 0.01$) for patients using the DPI than for those using the pMDI (mainly due to lower costs for hospitalization and medication). The cost differences between inhaled corticosteroids and inhaled beta2-agonists were significantly in favour of treatment via the DPI ($p < 0.01$). Thus, the results of this study suggest that treatment via the DPI is a cost-effective strategy in patients with asthma in Canada.

There are two studies represented the health economic analyses of asthma treatment given via breath-actuated inhaler compared with traditional MDI. Kelloway and Wyatt (1997) evaluated the cost-effectiveness of treatment with beta-agonist pirbuterol delivered by either a manually operated MDI or a breath-actuated inhaler. They found that no significant differences between the two groups appeared in baseline or follow-up outcomes, which were assessed by self-reported health status and spirometry. However, patients receiving pirbuterol from BAIs used 23% less than those patients who received the drug from MDIs. Another study conducted by Langley (1999) reviewed the impact of the use of technologically dissimilar beta-agonist aerosols (the Maxair Autohaler® (pirbuterol acetate) breath-actuated aerosol and the traditional albuterol press-and-breathe inhaler) on the treatment costs of asthma. At the descriptive level, costs of treatment for patients using the press-and-breathe inhaler are estimated to be 16.5% greater than costs for patients using the breath-actuated inhaler. In the multivariate analysis, the presence of the breath-actuated inhaler (in a dummy variable analysis) was not only statistically significant ($P < 0.05$), but entered with the expected negative sign. Estimated cost impacts under various model specifications are consistent with the magnitude of the cost differences reported in the descriptive analysis. Total cost savings with the Maxair Autohaler® ranged from 8.7% to 11.7%, with medical cost savings estimated at 14.6%.

# CHAPTER III

# RESEARCH METHODOLOGY

## 3.1 Research Design

This cost-effectiveness analysis was a retrospective analysis based on clinical data from a multicenter, randomized clinical trial conducted in Thailand (8 centers, i.e. King Chulalongkorn Memorial Hospital, Ramathibodi Hospital, Khon Kaen Rajanakarindha Hospital, Chiang Mai Hospital, Prince of Songkhla Hospital, Queen Sirikit National Institute of Child Health, Nopparatrajathanee Hospital and Police General Hospital). This clinical study was conducted to compare the efficacy and safety of salbutamol administered via metered dose inhaler (MDI) with spacer, dry powder inhaler (DPI) and nebulizer in the management of mild to moderate acute exacerbations of asthma in children. The patients were assessed for treatment response, adverse events and asthma re-exacerbations during the 3-day treatment period.

For the purpose of the economic analysis, the DPI was compared only with the MDI plus spacer. No comparison was made with the nebulizer as this treatment arm was considered to be less cost-effective than DPI and MDI plus spacer which was evident from the results of many published studies. This study was conducted from the perspective of the provider and patient. King Chulalongkorn Memorial Hospital was chosen as the model for this economic evaluation.

The patients who came to the outpatient department (OPD) or the emergency room (ER) of King Chulalongkorn Memorial Hospital during March 1, 2005 to December 31, 2005, and met the eligibility criteria were enrolled into the study. Following recruitment, the patients were randomized into 2 treatment groups. The statistician generated the block randomization with random numbers, and supplied to the investigator. Randomization was performed by providing each center with random numbers contained in blinded envelops created by the investigator. Each number was assigned to either MDI with spacer or DPI before the start of the trial using a computerized randomization procedure.

The patients were divided into 2 groups in this cost-effectiveness analysis. The experimental group (DPI) comprised patients who received salbutamol by the DPI (Buventol® Easyhaler® 100 mcg/dose, Orion Corporation, Finland), and the comparative group (MDI with spacer) received salbutamol by the MDI (Ventolin® Evohaler® 100 mcg/dose, GlaxoSmithKline, U.K.) with Volumatic® spacer (Volumatic®, Glaxo Wellcome, U.K.).

A detailed clinical evaluation (history and examination) was recorded on a case report form (CRF), and the severity (mild, moderate and severe) of the acute episode assessed by using the Modified Wood's Clinical Score, which consisted of the assessment of cyanosis, inspiratory breath sound, accessory muscle used, wheezing and cerebral function. Investigations including the Modified Wood's Clinical Score,

demographic characteristics, asthma history, vital signs (pulse rate, respiratory rate and blood pressure) and oxygen saturation were recorded at baseline. After assessment of severity of the asthma attack, all patients were treated according to the approved protocol, and no life saving treatment was withheld.

The patients were given 6 puffs of salbutamol (600 mcg) administered either by the MDI with spacer or by the DPI. For the comparative group (MDI plus spacer), the spacers were primed with 5 puffs from the MDI before use in order to prevent the electrostatic charge. This charge attracts the aerosol particles to the surface of the spacer, and can significantly reduce the dose available from inhalation.

Each patient was given salbutamol doses repeated every 20 minutes if the clinical score > 3, and ceasing administration when achieving the study end point (clinical scores reduce $\geq$ 50% from baseline or clinical scores $\leq$ 3), or up to a maximum of 3 treatments.

The patients were sequentially assessed by a single observer (physician) to assess the response to inhaled salbutamol. Investigations and observations including the Modified Wood's Clinical Score, oxygen saturation, respiratory rate, pulse rate and blood pressure were recorded at baseline, 20 minutes after each treatment, and finally at 60 minutes (T = 0, 20, 40 and 60 minutes). During the treatment period, all patients were assessed for adverse events by the physician, and the results were recorded on the case report form (CRF). Safety of each treatment was assessed by monitoring the nature and frequency of adverse events in term of tremor, palpitation, hypotension and headache by measurement of respiratory rate, pulse rate, blood pressure, tremor and other symptoms.

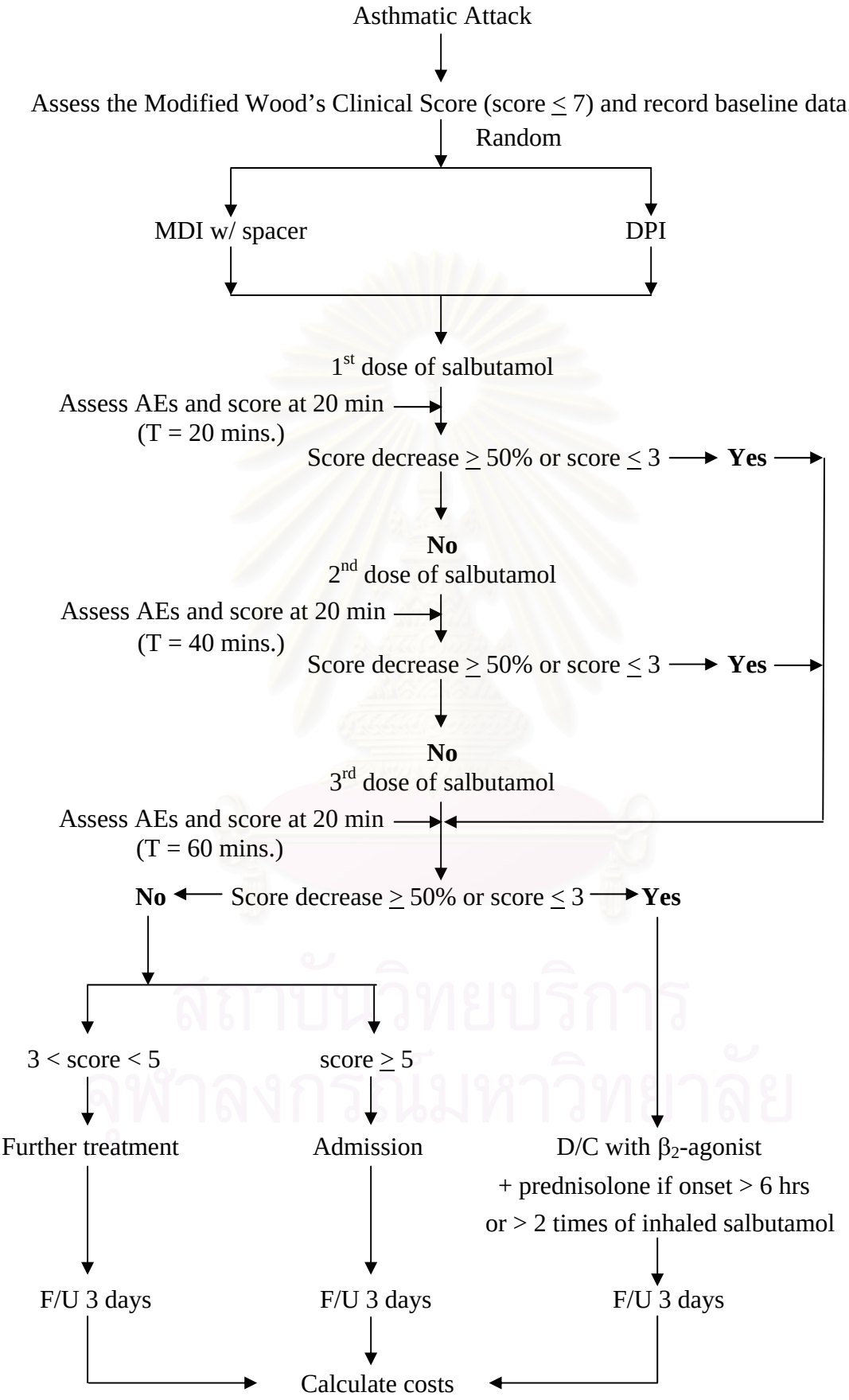
The patients reverted to receive further treatment according to the standard guidelines if their clinical scores were more than 3, but less than 5 (3 < clinical score < 5) at 60 minutes, and they were admitted in the hospital if their clinical scores $\geq$ 5. The patients with good response after receive inhalation of salbutamol for one hour, were discharged after stabilization. The patients discharged from the OPD or ER were prescribed bronchodilator, prednisolone (if onset of asthma was more than 6 hours, or the patient received more than 2 treatments of inhaled salbutamol during stay in the OPD or ER), and continued taking their usual asthma prophylaxis. Families were advised to return to the OPD or ER if the prescribed asthma treatment did not result in improvement of asthma symptoms. Re-presentation to the OPD or ER within the 72 hours after discharge was noted. The patients were re-assessed for adverse events, symptoms and number of asthma re-exacerbations on day 3 after discharge from the hospital.

The provider's and patient's perspectives were used to estimate costs of asthma among children. Cost estimates were derived for both direct medical costs and indirect costs. Direct non-medical costs were not taken into account because data were lacking. The direct costs of asthma were estimated as asthma-related medical costs. Calculation of the direct medical costs of asthma management were based on resources consumed by patients in the intention-to-treat population during the treatment phase of the study. Information on asthma-related direct healthcare resource use was collected during the study using CRFs. The cost of provider was calculated from secondary data of cost analysis at King Chulalongkorn Memorial Hospital. The total provider costs were the sum of total routine service costs and total medical care

costs. The patient costs included the direct medical costs and indirect costs. The direct medical costs were the costs which were charged by the provider, and the indirect costs were estimated as costs of caretakers' loss of productivity due to asthma-related school absence days. The direct medical costs and indirect costs together added up to the total costs of patients.

The study was conducted in accordance with good clinical practice (GCP), and was approved by the various local ethical committees. All patients and their parents received oral and written information about the study, and gave their written informed consent to participation.

Figure 3.1: Flow Diagram of the Method



### 3.2 Subjects

The patients aged 5 to 18 years with acute exacerbations of asthma who came to the outpatient department (OPD) or the emergency room (ER) of King Chulalongkorn Memorial Hospital during March 1, 2005 to December 31, 2005 were eligible for enrollment in the study. All patients included in the study met the asthma diagnosis criteria based on the Global Initiative for Asthma (GINA) guidelines. They were patients with diagnosed mild to moderate severity of the acute episode assessed by using the Modified Wood's Clinical Score. At an initial visit, the clinical score was required to be $\leq$ 7. An informed consent was obtained from patients' parent or guardian prior to recruitment.

Criteria for exclusion were the presence of other conditions such as heart disease, chronic liver disease, chronic kidney disease, chronic lung disease, bronchopulmonary dysplasia, brittle asthma, and severe exacerbation requiring ET intubation or admission in the hospital. The patients who were allergic or contraindicated with salbutamol should be excluded due to the potential for hypersensitivity reactions. The patients who had repeated exacerbation of asthma within 7 days after entry into this study, patients who received steroids for the presenting exacerbation of asthma before coming to hospital and those who couldn't use the dry powder inhaler were also excluded.

### 3.3 Data Collection

The patients were followed during the 3-day treatment period. After recruitment, they were assessed at baseline, 20 minutes after each treatment and finally at 60 minutes (T = 0, 20, 40 and 60 minutes), and re-assessed on day 3 after discharge from the hospital. Data on health care utilization, study drugs, concomitant therapy, tests, adverse events and the number of asthma re-exacerbations were recorded in a case report form (CRF). The number of days absent from school as a result of a child's asthma during the treatment period were recorded on day 3. The patient data were collected at King Chulalongkorn Memorial Hospital between March 1, 2005 and December 31, 2005.

#### 3.3.1 Cost Data

The economic analysis was conducted primarily from the provider's perspective and secondarily from the patient's perspective. Calculation of the resource use and the direct medical costs of asthma management were based on resources consumed by patients during the treatment phase of the study. Estimates of resource utilization were extrapolated from the clinical trial data set in the retrospective analysis. All cost data taken into account were presented in 2005 Baht, and when unit costs were from other years, these costs were adjusted for inflation using the consumer price index (CPI) for medical and personal care.

#### 3.3.1.1 Healthcare Provider's Costs

Cost of provider was calculated from secondary data of cost analysis at King Chulalongkorn Memorial Hospital during March 1, 2005 to December 31, 2005.

Total direct medical costs of treatment were calculated by applying unit costs to health care resource use recorded during the study. Resource use was identified from data recorded by the patient and by the physician in the case report forms (CRFs).

The following health care resource use was collected throughout the trial for all patients:

- Hospital contacts (OPD visits, ER visits, inpatient hospital days, intensive care unit days).
- Physician and nurse contacts.
- Volumatic® spacer (included in the MDI plus spacer treatment arm only, and not included in the DPI arm).
- Medications (study drugs, rescue medications and other asthma-related prescription drugs. Asthma-related prescription drugs included any medications that were taken by patients during the treatment period of the study to treat asthma symptoms, acute asthma exacerbations or treatment-related adverse events).
- Laboratory tests.
- Others.

The cost incurred by the provider is the real cost of delivering the service to the patients. Total direct cost (TDC) was calculated from labor costs (LC), material costs (MC) and capital costs (CC) of King Chulalongkorn Memorial Hospital incurred during March 1, 2005 to December 31, 2005.

All sections of King Chulalongkorn Memorial Hospital were classified into 3 cost center categories, i.e. non-revenue producing cost center (NRPCC), revenue producing cost center (RPCC) and patient service (PS). TDC of each unit was calculated from the LC, MC and CC. The total costs incurred by the administrative/ supportive units were allocated to their respective service units using the appropriate allocation criteria. Routine service costs (RSC; overhead costs) of delivering the services to asthmatic patients included all components of costs in all sections of King Chulalongkorn Memorial Hospital during the study period, except MC of the RPCC (radiological, laboratory and pharmaceutical sections) because these components of costs varied among patients who received different interventions. Therefore, they were calculated separately as medical care costs. The unit costs of routine services were then calculated by dividing the RSC by the total number of patients' visits or the total number of patients' days during the year studied (March 1, 2005 to December 31, 2005), as appropriate. For examples were given below:

$$\text{Unit Cost of RSC (OPD)} = \frac{\text{RSC of OPD}}{\text{Number of Visits}}$$

$$\text{Unit Cost of RSC (IPD)} = \frac{\text{RSC of IPD}}{\text{Number of Patients' Days}}$$

Thus, the full cost or the total provider costs of delivering each intervention to asthmatic patients was the sum of the total RSC (routine service unit costs multiplied by the number of patients' visits or the number of patients' days for each intervention, as appropriate) and the MC of the RPCC for each intervention, the so-called "medical care costs".

There were 5 steps of unit cost calculation as follows:

1.) Cost Center Identification and Grouping
   - Non-revenue producing cost center: NRPCC
   - Revenue producing cost center: RPCC
   - Patient service: PS

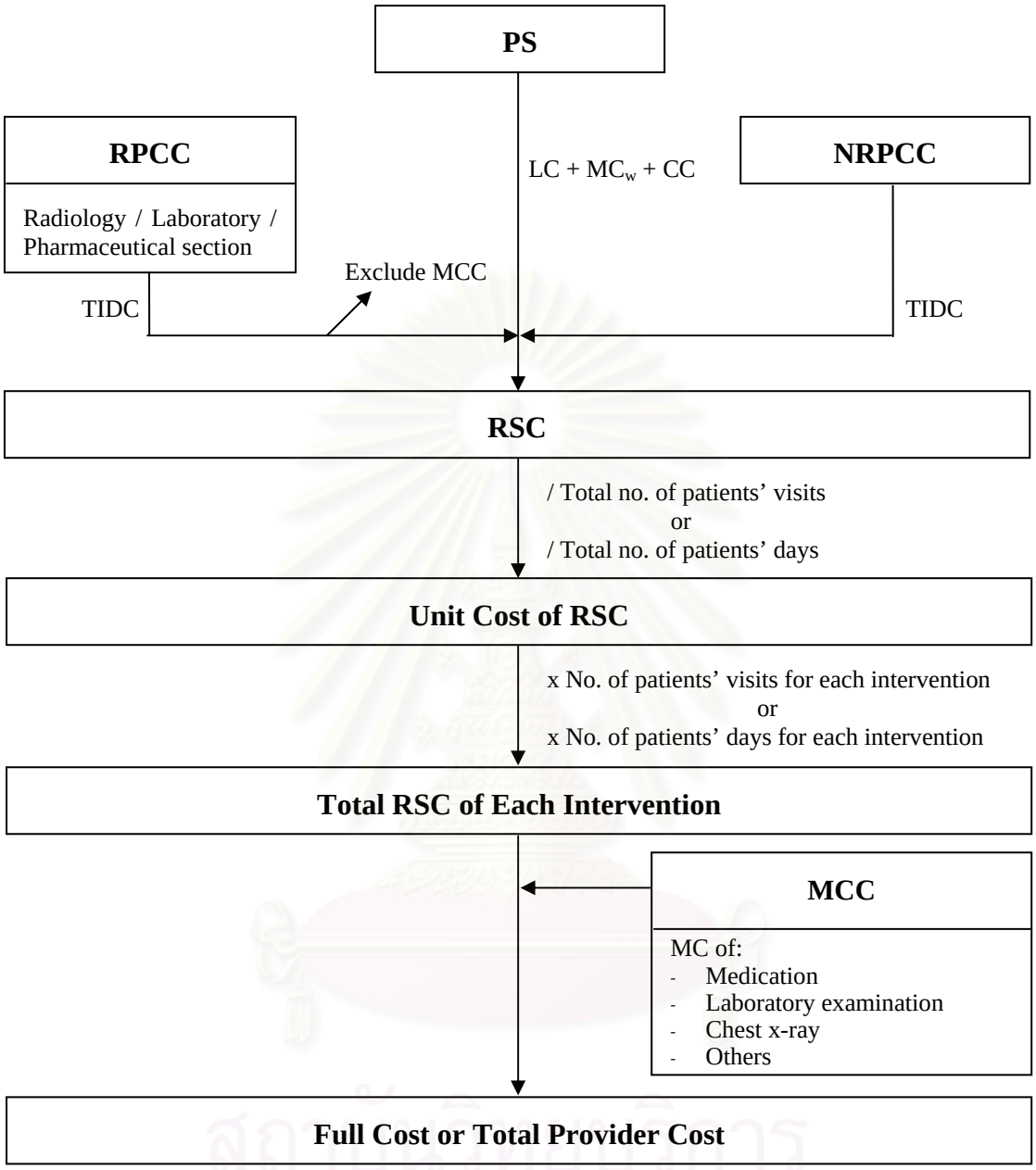
2.) Direct Cost Determination
   Total Direct Cost = Labor Cost + Material Cost + Capital Cost
   Labor Cost
   - Personnel: physicians, nurses, health workers, technicians etc.
   - Include salaries and fringe benefits.

   Material Cost
   - Medications: study drugs, rescue medications, concurrent prescription drugs related to the treatment of asthma, asthma exacerbations or treatment of adverse events
   - Supplies: spacer, equipments, etc.
   - Operation and Maintenance: electricity, water, etc.

   Capital Cost
   - Equipments: laboratory instruments, etc.
   - Land and Building: hospital, wardes, etc.
   - Vehicles

3.) Allocation Criteria Determination
4.) Full Cost Determination
5.) Unit Cost Calculation

Figure 3.2: Conceptual Framework of Total Provider Cost Calculation




Remarks:

| | | |
|---|---|---|
| CC | = | Capital cost |
| LC | = | Labor cost |
| MC | = | Material cost |
| $MC_w$ | = | Ward material cost |
| MCC | = | Medical care cost |
| NRPCC | = | Non-revenue producing cost center |
| PS | = | Patient service |
| RPCC | = | Revenue producing cost center |
| RSC | = | Routine service cost |
| TIDC | = | Total indirect cost |

#### 3.3.1.2 Patient's Costs

The patient's perspective was used to estimate costs of asthma treatment among patients. The patient's costs or total costs were calculated from the sum of total direct medical costs and total indirect costs. This study only examined direct medical costs and indirect costs (i.e. days lost from work by patients'parents). Direct non-medical costs (e.g. transportation, child care, environmental changes to avoid allergens) were not evaluated and not taken into account because data were lacking. The direct medical costs were the costs which were charged by the provider. In this study, the direct medical costs were split into 2 sections, i.e. those which occurred within King Chulalongkorn Memorial Hospital, and those that were incurred outside of it.

For calculating the direct medical costs, the following costs were considered according to the patient's perspective.

- Costs of hospital contacts (OPD visits, ER visits, inpatient hospital days, intensive care unit days).
- Costs of physician and nurse contacts (either at the doctor's office or the patient's home, and telephone calls).
- Costs of medications (study drugs, rescue medications and other asthma-related prescription drugs. Asthma-related prescription drugs included any medications that were taken by patients during the treatment period of the study to treat asthma symptoms, acute asthma exacerbations or treatment-related adverse events).
- Laboratory tests.
- Others.

From the patient's perspective, the cost of spacer was not included in the calculation of medication costs for patients in the MDI with spacer group because the patients were not charged for this cost. All physicians participating in this study didn't prescribe the spacer for using at home, and the cost of spacer used during the treatment at hospital were not charged by the provider, so this cost were not taken into account in the economic analysis according to the patient's perspective.

The indirect costs were included in the patient's costs. The indirect costs were calculated using the human capital approach based on information regarding absence from school. That was, regardless of the job the individual had, whether the individual was a man or a woman, or whether the individual worked or went to school, the unit costs attached to these absences would be equal. Parents or caretakers often had to take time off work to care for the asthmatic children, and these would also be counted as productivity costs. The number of school days lost was equated with the number of days lost from work for the caretaker. As the individuals only were asked whether they have missed any days from school, and not the number of hours missed for these days, it would be assumed that the individuals worked or went to school for 8 hours per day on average. For children, absence from school was valued by using the national average daily earnings of the caretakers. The costs of caretakers' loss of productivity due to school absence days were calculated by multiplying the number of working days lost by the national average daily earnings. The national average daily earnings were estimated by dividing the the national income of Thailand in 2005 by the number of employed population in 2005 and by the number of days in 1 year (365

days). The direct medical costs and indirect costs together made up the total costs according to the patient's perspective.

### 3.3.2 Clinical Outcomes

The outcomes for comparison between groups were the clinical signs which were used to assess the severity of asthmatic crises, i.e. cyanosis, breath sounds, accessory muscle use, wheezing and cerebral function. These outcomes together made up the Modified Wood's Clinical Score. The assessments were made at 0, 20, 40 and finally at 60 minutes by a single observer (physician) to assess the response to inhaled salbutamol. The patients with clinical scores reduce $\geq$ 50% from baseline, or clinical scores $\leq$ 3 were considered to achieve the study end point.

The primary outcome was the response to inhaled salbutamol, which was measured by the Modified Wood's Clinical Score. The number and percentage of successfully treated patients at 20, 40 and 60 minutes defined as those with clinical scores reduce $\geq$ 50% from baseline, or clinical scores $\leq$ 3 were calculated.

The secondary outcomes were the number of asthma re-exacerbation within 3 days after discharge and the occurrence of adverse events provoked by inhaled salbutamol. An asthma re-exacerbation was defined as a worsening of the child's asthma symptoms in terms of cough, wheeze, dyspnea, absence from school due to asthma symptoms and/or required the parents to contact the hospital or physician. The assessment of adverse events in terms of tremor, palpitation, hypotension and headache was performed during the 3-day treatment period.

### 3.3.3 Clinical Effectiveness

A number of outcome measures were used to determine treatment effectiveness for the purpose of the economic analysis. These included the number and percentage of successfully treated patients at 60 minutes.

A successfully treated patient was one in which clinical score reduce $\geq$ 50% from baseline, or clinical score $\leq$ 3.

## 3.4 Data Analysis

### 3.4.1 Effectiveness-Time Curve

One way to present the difference of effectiveness for the 2 treatment groups was to construct effectiveness-time curves. With this approach, the cumulative percentage of successfully treated patients was plotted on the vertical axis, and the assessed times (T = 0, 20, 40 and 60 minutes) were plotted on the horizontal axis.

### 3.4.2 Cost-Effectiveness Analysis

The cost-effectiveness analysis was conducted from the provider's and patient's perspectives. The mean cost-effectiveness ratio provides an indication of the average costs of achieving a given outcome with each treatment. This was calculated by dividing the mean costs per patient by the number and by the percentage of successfully treated patients at 60 minutes.

Incremental cost-effectivenrss ratios (ICERs) were calculated by dividing the difference in the mean costs between the treatment groups by the difference in the number and by the difference in the percentage of successfully treated patients at 60 minutes for each treatment. ICERs evaluate the net change in both cost and effectiveness between treatments, and calculate additional costs required to achieve additional health gains with a treatment relative to the comparator.

Incremental cost-effectiveness ratio was calculated from the following equation:

$$ICER = \frac{Cost_{DPI} - Cost_{MDI+spacer}}{Effectiveness_{DPI} - Effectiveness_{MDI+spacer}}$$

### 3.4.3 Regression Analysis

Ordinary least squares (OLS) regression analyses were performed using the following models with the aims of identifying which factors had the greatest influence on the costs and estimating the impact of treatment with the DPI, controlling for the effects of other factors that influence health care costs.

$$\ln(TDC) = \alpha_1 + \beta_1 Age + \beta_2 Duration + \alpha_2 Severity + \alpha_3 Gender + \alpha_4 Treatment + \gamma_1(Treatment \times Age) + \gamma_2(Treatment \times Duration) + \gamma_3(Treatment \times Severity) + \gamma_4(Treatment \times Gender) + u$$

$$\ln(TC) = \alpha_1 + \beta_1 Age + \beta_2 Duration + \alpha_2 Severity + \alpha_3 Gender + \alpha_4 Treatment + \gamma_1(Treatment \times Age) + \gamma_2(Treatment \times Duration) + \gamma_3(Treatment \times Severity) + \gamma_4(Treatment \times Gender) + u$$

where

| | | |
|---|---|---|
| TDC | = | Total direct medical costs (according to the provider's and patient's perspectives) |
| TC | = | Total costs (according to the patient's perspective) |
| Age | = | Age of a patient in years |
| Duration | = | Duration of asthma in months counted from the first diagnosis |
| Severity | = | Severity of asthma at the first diagnosis (1 if persistent asthma, 0 otherwise) |
| Gender | = | Gender of a patient (1 if male, 0 otherwise) |
| Treatment | = | Treatment or intervention received by a patient (1 if DPI, 0 if MDI with spacer) |
| $\alpha_1$ | = | Intercept coefficient |
| $\beta_1 - \beta_2$ | = | Slope coefficients |
| $\alpha_2 - \alpha_4$ | = | Differential intercept coefficients (i.e. the coefficients attached to the dummy variables) |

$\gamma_1 - \gamma_4$ = Differential slope coefficients (also called the slope drifter, i.e. the coefficients attached to the interaction terms)

u = Error term

Dependent variables were the total direct medical costs and the total costs. A logarithmic transformation was used for the dependent variables to reduce the impact of the most costly patients, i.e. the outliers. The dependent variable for the first regression analysis was the logarithmically transformed total direct medical costs incurred by the provider or by the patient during the 3-day treatment period between March 1, 2005 to December 31, 2005. The analyses were conducted from the perspectives of the provider and the patient. The second regression focused on the total costs (total direct medical costs + total indirect costs) incurred by the patients during the 3-day treatment period between March 1, 2005 to December 31, 2005. This analysis was conducted from the patient's perspective.

The independent variables included in the regression analyses were "age", "duration of asthma", "severity of asthma at the first diagnosis" (coded as 1 if the patient had persistent asthma, otherwise coded as 0, i.e. if the patient had intermittent asthma), "gender" (coded as 1 for male, otherwise coded as 0, i.e. female), "treatment" (coded as 1 if the patient used the DPI, otherwise codes as 0, i.e. the MDI with spacer), and the interaction terms (i.e. the interactions between "treatment" and other variables)

These independent variables were included to adjust for differences in baseline characteristics between the 2 treatment groups. This correction is important even when the differences between the 2 treatments are not statistically significant because small differences in multiple baseline characteristics can add up to substantial differences in expected outcome. The rationale for these particular adjustments was as follows. Age and gender were included because these variables often influence treatment patterns and may be correlated with severity of illness. Next, the duration and severity of asthma were added in the regression because these may associate with current severity of illness, and vary the treatment patterns.

The hypotheses were that "duration of asthma" and "severity of asthma at the first diagnosis" had a positive effect on the dependent variables, and "age" had a negative effect on the dependent variables. There was not clear hypothesis regarding the variable "gender". The dummy variable "treatment" was hypothesised to be negative, indicating lower costs for patients treated with the DPI.

### 3.4.4 Sensitivity Analysis

The sensitivity analyses were undertaken to explore how robust the results were to changes in underlying assumptions. The sensitivity analyses were conducted by varying key parameters to investigate the effects of uncertainties in the data on the results of the study. The first sensitivity analysis was performed by changing the cost of study drugs. Because of the variation in exchange rate, the drug price can vary from time to time. For cost of study drugs, the sensitivity of the results was assessed using 2 scenarios. The first scenario assumed that the drug cost varied +/- 30% in the cost per puff of the DPI, and in the cost per puff of the MDI for the second scenario. In the second sensitivity analysis, the medians of total direct medical costs and total costs were used in place of the mean values. In the last sensitivity analysis, the direct

non-medical costs (i.e. transportation fee) was included in the cost calculation according to the patient's perspective. The transportation fee was assumed to be Baht 6.00 per trip. The sensitivity analysis for including the direct non-medical costs into the patient's costs was performed using 2 scenarios. The first scenario used the mean total costs for calculating the cost-effectiveness ratios and ICERs, and the second scenario used the median values.

### 3.5 Limitations

There are a number of limitations that should be considered when interpreting the results. Firstly, this study was conducted by choosing King Chulalongkorn Memorial Hospital as the model for the economic evaluation. However, different hospitals may have different health care systems, different treatment patterns and culture differences in health care use, and these may cause different patterns of resource utilization. Secondly, cost of provider was calculated from the secondary data of cost analysis at King Chulalongkorn Memorial Hospital, however, cost may cannot be generalized from one hospital to another because the difference in the cost of health care interventions and medications vary between hospitals, especially in different levels of hospitals. Thirdly, the cost for a day absent from school was estimated by using the human capital approach. This approach, however, would bias against individuals who were unemployed, children below school age, housewives/husbands and retired individuals, which was one of the drawbacks of the human capital approach. Fourthly, the clinical study was conducted during March 1, 2005 to December 31, 2005, as this time period, the seasons (rainy season and/or winter) and adverse weather conditions, such as cool temperatures and high humidity, had been associated with asthma exacerbations, and may be related to the increased number of asthma exacerbations and the decreased response to treatment. Fifthly, this study based on the 3-day which was short duration, therefore, it was not possible to assess the long term cost-effectiveness of the study drugs. In addition, this short duration may underestimate the true costs because hospitalization was a rare but expensive consequence of poorly controlled asthma. The length of the study also made it difficult and impractical to consider indirect costs, which should ideally be incorporated into economic analysis. Finally, this cost-effectiveness analysis was based on small sample size (80 patients) as maybe not enough powered to show the difference between the 2 treatment groups.

### 3.6 Ethics

The study was conducted in accordance with good clinical practice (GCP), and was approved by the various local ethical committees, including King Chulalongkorn Memorial Hospital as shown by the study approval (Appendix B). All patients and their parents received oral and written information about the study, and gave their written informed consent to participation.

# CHAPTER IV

# RESULTS

## 4.1 Baseline Characteristics

A total of 80 patients met the eligibility criteria were included in the study. Equal numbers of patients were randomized to each treatment group. There were 40 patients (20 males and 20 females) in the MDI with spacer group, and 40 patients (28 males and 12 females) in the DPI group. All patients completed the 3-day treatment period, and none of them withdrew from the study.

Baseline characteristics of patients, including demographics, asthma history and health care use were shown in Table 4.1. In terms of hospitalization in previous year and short-acting beta2-agonist use for the patients in the MDI with spacer group, the data were obtained from 38 patients. The reason was that data of 2 patients were not taken into account because data were lacking and not available.

There were not statistical significant differences in age, gender, weight, height, asthma history and use of short-acting beta2-agonists between the 2 treatment groups at baseline. The groups did not differ at baseline in any parameters, so the randomization was successful.

Table 4.1: Demographics and baseline characteristics of the intention-to-treat patients in the MDI with spacer and DPI groups.

| Characteristics | MDI with spacer | DPI | p-Value |
|---|---|---|---|
| No.of patients | 40 | 40 | - |
| Age (year) | 9.28 (2.69) | 8.88 (2.83) | 0.519 |
| Gender (male/female) | 20/20 (50.0% / 50.0%) | 28/12 (70.0% / 30.0%) | 0.110 |
| Weight (kg) | 32.18 (12.17) | 31.25 (11.01) | 0.723 |
| Height (cm) | 135.03 (15.07) | 132.41 (15.86) | 0.461 |
| Duration of asthma from 1st diagnosis (month) | 58.25 (39.43) | 64.98 (41.66) | 0.477 |
| Severity of asthma at 1st diagnosis* (no.of patients) | | | 0.342 |
| Intermittent | 26 (65.0%) | 20 (50.0%) | |
| Mild persistent | 9 (22.5%) | 11 (27.5%) | |
| Moderate persistent | 5 (12.5%) | 9 (22.5%) | |
| Severe persistent | 0 (0.0%) | 0 (0.0%) | |
| Exacerbations in previous year | | | |
| No.of exacerbations/year | 3.11 (4.22) | 2.90 (2.97) | 0.718 |
| No.of patients (yes/no) | 32/6 (84.2% / 15.8%) | 33/7 (82.5% / 17.5%) | 1.000 |
| Hospitalization in previous year | | | |
| No.of hospitalization/year | 0.18 (0.39) | 0.40 (1.03) | 0.427 |
| No.of patients (yes/no) | 7/31 (18.4% / 81.6%) | 10/30 (25.0% / 75.0%) | 0.668 |
| Short-acting $\beta_2$-agonist used | | | |
| No.of drug use/month | 1.97 (4.90) | 2.49 (5.12) | 0.521 |
| No.of patients (yes/no) | 23/15 (60.5% / 39.5%) | 27/13 (67.5% / 32.5%) | 0.685 |

Data are presented as mean value with SD in parentheses, or as number of patients with % in parentheses.
*Severity was diagnosed based on the GINA guideline
Abbreviations: cm = centimeter; DPI = dry powder inhaler; GINA = Global Initiative for Asthma; MDI = metered dose inhaler; SD = standard deviation

## 4.2 Costs

### 4.2.1 Resource Utilization

Information on asthma-related resource use was collected during the study period using the case report forms (CRFs), and asthma-related resource utilization (excluding medication) was summarized in Table 4.2. All visits included in the cost analysis were "unscheduled". Therefore, health care contacts related to the study protocol and routine visits associated with regular asthma management were excluded from the cost analysis.

Taking the perspective of the provider, and looking only resource use occurred in King Chulalongkorn Memorial Hospital, the number of outpatient department visits was lower in the DPI group than in the MDI with spacer group. There were not emergency room visits and intensive care unit admission in both groups. There were not hospitalization in the MDI and spacer group compared with 2 days in the DPI group. One patient belonged to the DPI group with the inpatient department stay of 2 days was hospitalized due to asthma exacerbation and respiratory insufficiency as a result of noncompliance.

When the resource use occurred outside King Chulalongkorn Memorial Hospital and productivity loss were included, thereby taking the patient's perspective, one patient belonged to the MDI with spacer group was hospitalized in Police General Hospital for 1 day due to asthma re-exacerbations, and there was one emergency room visit at Queen Sirikit National Institute of Child Health in the DPI group. For hospitalization, 1 patient belonged to the MDI with spacer group was hospitalized in Police General Hospital for 1 day, and 1 patient with 2 inpatient days in the DPI group was admitted in King Chulalongkorn Memorial Hospital. In addition to this difference, the patient in the DPI group seemed to be hospitalized for a longer period, but in fact , the patient in the MDI with spacer group was admitted for 3 days. However, the resource use was truncated at 3 days after the treatment, and since this patient was admitted on the third day of the treatment phase, so the study would take into account only 1 inpatient day.

Asthma-related production loss due to absence from work of caretakers to care for the asthmatic children was 11 and 9 days in the MDI with spacer and DPI groups, respectively.

When the medical care costs were also considered, the mean and total medical care costs (according to the provider's perspective) were similar between the 2 treatment groups (Table 4.3 and 4.4, respectively). On the other hand, the mean and total medical care costs (according to the patient's perspective) for the DPI group was higher than the MDI with spacer group, mainly due to the cost of chest x-ray incurred by 1 patient belonged to the DPI group (Table 4.5 and 4.6, respectively).

Table 4.2: Summary of asthma-related healthcare resource utilization (excluding medication) and days of production loss during the 3-day treatment period for the intention-to-treat patients in the MDI with spacer and DPI groups.

| **Resource utilization (no.of days or visits)** | **MDI with spacer (n = 40)** | **DPI (n = 40)** |
|---|---|---|
| Unscheduled hospital contacts (KCMH) | | |
| Emergency room visits | 0 | 0 |
| Intensive care unit days | 0 | 0 |
| Inpatient days | 0 | 2 (1) |
| Outpatient visits | 6 (6) | 4 (4) |
| Unscheduled hospital contacts (other providers) | | |
| Emergency room visits | 0 | 1 (1) |
| Intensive care unit days | 0 | 0 |
| Inpatient days* | 1 (1) | 0 |
| Outpatient visits | 0 | 0 |
| Unscheduled physician contacts | | |
| Home visits | 0 | 0 |
| Clinic visits | 0 | 0 |
| Telephone contacts | 0 | 0 |
| Production loss | | |
| Days absent from school | 11 (11) | 9 (6) |

Data are presented as number of days or visits, and number of patients are given in parentheses.
*Patient treated as an inpatient, but data missing in term of department (i.e. intensive care unit or general ward). This patient was assumed to be inpatient in a general pediatric ward, and the data were costed accordingly.
Abbreviations: DPI = dry powder inhaler; KCMH = King Chulalongkorn Memorial Hospital; MDI = metered dose inhaler

### 4.2.2 Healthcare Provider's Costs

The economic analysis was conducted from the provider's perspective, and the total provider costs were estimated as total direct medical costs. Total direct medical costs of treatment were calculated by applying unit costs at King Chulalongkorn Memorial Hospital to health care resource use recorded during the study period. The costs of medications were obtained from the pharmaceutical department, and all costs were presented in 2005 Baht. Cost of oxygen saturation measurement was calculated based on charge from King Chulalongkorn Memorial Hospital, and adjusted to the hospital's cost by the cost to charge ratio (i.e. 0.8325). The unit costs for other health care resources, called unit costs of routine services or overhead costs, were based on data from the cost analysis at King Chulalongkorn Memorial Hospital in 2004. When unit costs were not valued in 2005 Baht or were from other years, the effect of inflation was removed by using the consumer price index (CPI) to inflate or deflate the data. The unit costs of routine services in 2004 Baht were adjusted to be 2005 values by using selected medical and personal care item from the consumer price index. From the report for consumer price index of Thailand (based year 2002), the consumer price index of medical and personal care item in 2004 and 2005 are presented as 102.4 and 104.2, respectively. The unit costs of routine services in 2005 values were calculated by multiplying the unit costs of routine services in 2004 values with 1.02 (derived from 104.2/102.4).

$$\text{Unit cost of routine service in 2005 Baht} = \text{Unit cost of routine service in 2004 Baht} \times \frac{CPI_{2005}}{CPI_{2004}}$$

The cost incurred by the provider was the real cost of delivering the services to the patients at King Chulalongkorn Memorial Hospital, thus the total provider costs of delivering each treatment to the asthmatic patients was the sum of the total routine service costs (unit costs of routine services multiplied by total number of patients'visits or patients'day for each treatment) and total medical care costs.

The mean and total direct medical costs occurred during the study period for the patients in the MDI with spacer and DPI groups were shown in Table 4.3 and 4.4, respectively. The mean total direct medical costs in the DPI group was Baht 333.66 compared with Baht 239.63 in the MDI with spacer group. The difference was not statistically significant ($p = 0.128$). The mean total direct medical costs per patient for the DPI group was higher than the MDI with spacer group, mainly due to the higher routine service costs, in particular hospitalization cost (Baht 126.80 per patient for the DPI group, and none of those in the MDI with spacer group).

In a comparison of the outpatient department visits between the 2 groups, the mean and total costs of the outpatient department visits were lower in the DPI group than in the MDI with spacer group (Table 4.3 and 4.4, respectively). Accordingly, the mean costs of the outpatient department visits was Baht 65.57 per patient for the patients received the DPI compared with Baht 98.36 per patient for the patients received the MDI and spacer. However, overall routine service costs, including costs of emergency room visits, hospitalization and unscheduled outpatient department visit, were Baht 192.37 per patient for the DPI group compared with Baht 98.36 per patient for the

MDI and spacer group (p = 0.535), this was due to higher cost of hospital admission in the DPI group as shown in Table 4.3.

Table 4.3 showed the average total medical care costs (including costs of medication and tests) per patient by type of drug use presented separately within each treatment group. The total medical care costs per patient were similar between the 2 treatmemt groups, Baht 141.28 in the DPI group compared with Baht 141.27 in the MDI and spacer group. When each item of medical care costs was considered separately, the costs for study medication, oral corticosteroids, rescue medication and other asthma-related medications prescribed during the treatment period were lower in the DPI group. Although the acquisition cost of the study drug was higher for the DPI than for the MDI, the additional acquisition cost of the DPI was partly offset by reductions in medication costs resulting from lower utilization of other asthma medication (i.e. oral corticosteroids, rescue medications and concurrent prescription drugs related to the treatment of asthma, asthma exacerbations or treatment of adverse events). Moreover, the overall costs of the study medication were significantly lower in the DPI group than in the MDI with spacer group. This was due to higher doses of study drug used and including the cost of 1 spacer in the study medication cost for the MDI with spacer group. The spacer was necessary and widely recommended for use with the MDI for asthma therapy in this age group. Thus, the cost for the study medication was significantly lower in the DPI group than in the MDI with spacer group (mean difference of costs about Baht 4.89 and $p < 0.001$). However, the mean and total medical care costs were similar between the 2 groups as can be seen in Table 4.3 and 4.4, respectively. Accordingly, the total medical care costs of asthma management was Baht 141.28 per patient for the patients treated with the DPI, compared with Baht 141.27 per patient for the patients treated with the MDI and spacer. This was due to higher costs of medication prescribed during hospital admission and re-visit, mainly because of the medication prescribed during hospitalization.

Table 4.3: Mean total direct medical costs per patient during the 3-day treatment period for the intention-to-treat patients in the MDI with spacer and DPI groups (according to the provider's perspective).

| Cost item | MDI with spacer* (n = 40) | DPI* (n = 40) | Mean Difference**(SE) | p-Value |
|---|---|---|---|---|
| **Direct medical costs** | | | | |
| Routine service costs | | | | |
| Emergency room | 0.00 (0.00) | 0.00 (0.00) | 0.00 (0.00) | 1.000 |
| Intensive care unit | 0.00 (0.00) | 0.00 (0.00) | 0.00 (0.00) | 1.000 |
| Inpatient department | 0.00 (0.00) | 126.80 (801.97) | (-)126.80 (126.80) | 0.317 |
| Outpatient department | 98.36 (237.12) | 65.57 (199.22) | 32.79 (48.97) | 0.502 |
| Total routine service costs | 98.36 (237.12) | 192.37 (914.51) | (-)94.02 (149.38) | 0.535 |
| Medical care costs | | | | |
| Study medication | 15.94 (2.62) | 11.05 (5.68) | 4.89 (0.99) | < 0.001*** |
| Oral corticosteroids | 3.61 (2.32) | 2.91 (2.36) | 0.70 (0.52) | 0.127 |
| Rescue medication | 21.83 (29.29) | 17.80 (24.17) | 4.03 (6.00) | 0.843 |
| Medication prescribed during hospital admission | 0.00 (0.00) | 10.66 (67.44) | (-)10.66 (10.66) | 0.317 |
| Medication prescribed during re-visit | 5.00 (17.77) | 6.66 (33.04) | (-)1.67 (5.93) | 0.671 |
| Other asthma-related medication | 11.66 (27.50) | 8.96 (16.83) | 2.70 (5.10) | 0.862 |
| Tests | 83.24 (0.00) | 83.24 (0.00) | 0.00 (0.00) | 1.000 |
| Total medical care costs | 141.27 (44.51) | 141.28 (82.16) | (-)0.01 (14.77) | 0.201 |
| **Total direct medical costs** | 239.63 (245.95) | 333.66 (985.77) | (-)94.03 (160.64) | 0.128 |

All cost data are presented in 2005 Baht; when necessary, the costs were adjusted to 2005 Baht using the medical and personal care item of CPI.
*Data are presented as mean value with SD in parentheses, unless otherwise stated.
**Mean difference = MDI with spacer – DPI
***Statistically significant difference ($p < 0.05$)
Abbreviations: CPI = consumer price index; DPI = dry powder inhaler; MDI = metered dose inhaler; SD = standard deviation; SE = standard error of difference

Table 4.4: Total direct medical costs during the 3-day treatment period for the intention-to-treat patients in the MDI with spacer and DPI groups (according to the provider's perspective).

| Cost item | MDI with spacer (n = 40) | DPI (n = 40) | Difference* |
|---|---|---|---|
| **Direct medical costs** | | | |
| Routine service costs | | | |
| Emergency room | 0.00 | 0.00 | 0.00 |
| Intensive care unit | 0.00 | 0.00 | 0.00 |
| Inpatient department | 0.00 | 5,072.08 | (-)5,072.08 |
| Outpatient department | 3,934.24 | 2,622.83 | 1,311.41 |
| Total routine service costs | 3,934.24 | 7,694.91 | (-)3,760.66 |
| Medical care costs | | | |
| Study medication | 637.44 | 441.81 | 195.63 |
| Oral corticosteroids | 144.42 | 116.58 | 27.84 |
| Rescue medication | 873.19 | 712.04 | 161.15 |
| Medication prescribed during hospital admission | 0.00 | 426.53 | (-)426.53 |
| Medication prescribed during re-visit | 199.80 | 266.40 | (-)66.60 |
| Other asthma-related medication | 466.49 | 358.42 | 108.07 |
| Tests | 3,329.60 | 3,329.60 | 0.00 |
| Total medical care costs | 5,650.94 | 5,651.38 | (-)0.43 |
| **Total direct medical costs** | 9,585.19 | 13,346.28 | (-)3,761.10 |

All cost data are presented in 2005 Baht; when necessary, the costs were adjusted to 2005 Baht using the medical and personal care item of CPI.
*Difference = MDI with spacer – DPI
Abbreviations: CPI = consumer price index; DPI = dry powder inhaler; MDI = metered dose inhaler

### 4.2.3 Patient's Costs

The patient's perspective was used to estimate costs of asthma treatment among this patient group. The patient's costs or total costs were calculated from the sum of total direct medical costs and total indirect costs. This study only examined direct medical costs and indirect costs (i.e. days lost from work by patients'parents). Direct non-medical costs (e.g. transportation, child care, environmental changes to avoid allergens) were not evaluated and not taken into account because data were lacking.

The direct medical costs were determined on the basis of the medical charge from the provider. Medications were costed using the patient's prices charged by the pharmaceutical department. The direct medical costs were split into 2 sections, i.e. those which occurred within King Chulalongkorn Memorial Hospital, and those that were incurred outside of it.

The indirect costs were estimated as costs of caretakers' loss of productivity due to asthma-related school absence days. Parents or caretakers had to take time off work to care for the asthmatic children, and these would also be counted as productivity costs. The number of school days lost was equated with the number of days lost from work for the caretakers, and absence from school was given the same value as absence from work. The costs of caretakers' loss of productivity were estimated by multiplying the number of working days lost with the national average daily earnings. The national average daily earnings was derived from the national income of Thailand in 2005 divided by the number of employed population in 2005 (National Statistical Office 2005) and by the number of days in 1 year (365 days). The national income of Thailand in 2005 were not available, so the adjustment was calculated for the national income in 2004, as published by Office of the National Economic and Social Development Board (2005). The national income in 2004 was adjusted for inflation using the GDP deflator, derived from nominal GDP divided by real GDP (Office of the National Economic and Social Development Board 2005).

$$\text{NI in 2005} = \text{NI in 2004} \times \frac{\text{GDP deflator in 2005}}{\text{GDP deflator in 2004}}$$

$$\text{National average daily earnings per capita} = \frac{\text{NI in 2005}}{\text{No.of employed population in year 2005} \times 365 \text{ days}}$$

The mean and total costs calculated from the patient's perspective for the patients in the 2 treatment groups were summarized in Table 4.5 and 4.6, rspectively. In this study, the patient's costs can be classified as direct medical costs paid for the provider and indirect costs. Direct non-medical costs were not taken into account because data were lacking.

From the patient's perspective, the cost of spacer was excluded from the economic analysis because this cost was not charged by the provider, and this differed from the provider's perspective that included the cost of 1 spacer into the study medication

cost. As can be seen in Table 4.5 and 4.6, this exclusion resulted in a decreasing of cost for study medication in the MDI with spacer group, thereby the cost for study medication was significantly lower in the MDI with spacer group ($p < 0.001$), and was mainly due to the lower price for study drug in that group. Although the cost of the study drug was higher in the DPI group, the additional cost of the DPI was partly offset by reductions in costs resulting from lower utilization of oral corticosteroids, rescue medications and other asthma-related medicatons. The mean total medical care costs paid for King Chulalongkorn Memorial Hospital in the DPI group was Baht 169.72 compared with Baht 160.58 in the MDI with spacer group ($p = 0.765$) (Table 4.5). When the hospital care costs were included, the mean total direct medical costs paid for King Chulalongkorn Memorial Hospital in the DPI group was Baht 380.48 per patient compared with Baht 343.93 per patient in the MDI with spacer group, and there was not significant difference between the groups ($p = 0.870$). The mean total direct medical costs was higher for the DPI group, mainly due to the higher costs of hospitalization.

When the direct medical costs paid for other providers were also considered, the mean and total hospital care costs occurred outside King Chulalongkorn Memorial Hospital were lower in the DPI group than in the MDI with spacer group (Table 4.5 and 4.6, respectively). Accordingly, the mean total hospital care costs was Baht 30.73 for patients treated with the DPI, compared with Baht 44.26 for patients treated with the MDI and spacer ($p = 0.986$). The hospital care costs paid for other providers were influenced by a small proportion of patients with high costs, 1 patient belonged to the MDI and spacer group with the inpatient department stay of 1 day was hospitalized due to asthma re-exacerbation, and 1 patient with 1 emergency room visit in the DPI group. The costs for medication were small (Baht 9.10), and there was not significant difference between the 2 groups ($p = 0.155$) as shown in Table 4.6 and 4.5, respectively. The mean and total medical care costs paid for other providers for the DPI group was higher than for the MDI with spacer group, mainly due to the cost of chest x-ray incurred by 1 patient belonged to the DPI group (Table 4.5 and 4.6, respectively). The difference was not statistically significant ($p = 0.579$).

The mean and total productivity costs or indirect costs were higher in the MDI with spacer group than in the DPI group as can be seen in Table 4.5 and 4.6, respectively. The saving in productivity costs (about Baht 19.61 per patient) in the DPI group was resulted from the reduction in the number of days absent from work or school (Table 4.2.), however, the difference of indirect costs was not statistically significant between the 2 treatment groups (Table 4.5).

The direct and indirect costs together added up to the total costs or total patient costs. The mean total costs for the DPI group was Baht 502.60 per patient compared with Baht 496.27 per patient for the MDI with spacer group, and there was not significant difference between the groups ($p = 0.617$). The mean total costs was higher for the DPI group, mainly due to the higher cost of hospitalization in King Chulalongkorn Memorial Hospital.

Table 4.5: Mean total costs per patient during the 3-day treatment period for the intention-to-treat patients in the MDI with spacer and DPI groups (according to the patient's perspective).

| Cost item | MDI with spacer* (n = 40) | DPI* (n = 40) | Mean Difference**(SE) | p-Value |
|---|---|---|---|---|
| **Direct medical costs paid for KCMH** | | | | |
| Hospital care costs | | | | |
| Emergency room | 0.00 (0.00) | 0.00 (0.00) | 0.00 (0.00) | 1.000 |
| Intensive care unit | 0.00 (0.00) | 0.00 (0.00) | 0.00 (0.00) | 1.000 |
| Inpatient department | 0.00 (0.00) | 88.52 (559.85) | (-)88.52 (88.52) | 0.317 |
| Outpatient department | 183.35 (442.02) | 122.23 (371.37) | 61.12 (91.28) | 0.502 |
| Total hospital care costs | 183.35 (442.02) | 210.75 (806.91) | (-)27.40 (145.47) | 0.535 |
| Medical care costs | | | | |
| Study medication | 10.02 (3.15) | 13.27 (6.82) | (-)3.25 (1.19) | < 0.001*** |
| Oral corticosteroids | 4.34 (2.79) | 3.50 (2.84) | 0.84 (0.63) | 0.127 |
| Rescue medication | 26.22 (35.19) | 21.38 (29.03) | 4.84 (7.21) | 0.843 |
| Medication prescribed during hospital admission | 0.00 (0.00) | 12.81 (81.01) | (-)12.81 (12.81) | 0.317 |
| Medication prescribed during re-visit | 6.00 (21.34) | 8.00 (39.69) | (-)2.00 (7.13) | 0.671 |
| Other asthma-related medication | 14.01 (33.03) | 10.76 (20.21) | 3.25 (6.12) | 0.862 |
| Tests | 100.00 (0.00) | 100.00 (0.00) | 0.00 (0.00) | 1.000 |
| Total medical care costs | 160.58 (53.46) | 169.72 (98.68) | (-)9.14 (17.75) | 0.765 |
| **Total direct medical costs paid for KCMH** | 343.93 (450.96) | 380.48 (892.35) | (-)36.54 (158.09) | 0.870 |

(Continued to next page)

Table 4.5. (Continued): Mean total costs per patient during the 3-day treatment period for the intention-to-treat patients in the MDI with spacer and DPI groups (according to the patient's perspective).

| Cost item | MDI with spacer* (n = 40) | DPI* (n = 40) | Mean Difference**(SE) | p-Value |
|---|---|---|---|---|
| (Continued from last page) | | | | |
| **Direct medical costs paid for other providers** | | | | |
| Hospital care costs | | | | |
| Emergency room | 0.00 (0.00) | 30.73 (194.34) | (-)30.73 (30.73) | 0.317 |
| Intensive care unit | 0.00 (0.00) | 0.00 (0.00) | 0.00 (0.00) | 1.000 |
| Inpatient department | 44.26 (279.93) | 0.00 (0.00) | 44.26 (44.26) | 0.317 |
| Outpatient department | 0.00 (0.00) | 0.00 (0.00) | 0.00 (0.00) | 1.000 |
| Total hospital care costs | 44.26 (279.93) | 30.73 (194.34) | 13.53 (53.88) | 0.986 |
| Medical care costs | | | | |
| Medication | 0.23 (1.03) | 0.00 (0.00) | 0.23 (0.16) | 0.155 |
| Chest x-ray | 0.00 (0.00) | 3.16 (19.99) | (-)3.16 (3.16) | 0.317 |
| Total medical care costs | 0.23 (1.03) | 3.16 (19.99) | (-)2.93 (3.16) | 0.579 |
| **Total direct medical costs paid for other providers** | 44.49 (280.80) | 33.89 (214.33) | 10.60 (55.85) | 0.559 |
| **Direct non-medical costs** | N/A | N/A | N/A | N/A |
| **Total direct cost** | 388.42 (610.88) | 414.37 (908.27) | (-)25.94 (173.07) | 0.985 |
| **Indirect costs** | | | | |
| Costs of lost work days | 107.84 (177.33) | 88.23 (243.00) | 19.61 (47.56) | 0.228 |
| **Total indirect costs** | 107.84 (177.33) | 88.23 (243.00) | 19.61 (47.56) | 0.228 |
| **Total costs****** | 496.27 (716.78) | 502.60 (1076.29) | (-)6.34 (204.46) | 0.617 |

All cost data are presented in 2005 Baht; when necessary, the costs were adjusted to 2005 Baht using the medical and personal care item of CPI.
*Data are presented as mean value with SD in parentheses, unless otherwise stated. **Mean difference = MDI with spacer – DPI
***Statistically significant difference ($p < 0.05$) ****Total costs = Total direct costs + Total indirect costs
Abbreviations: CPI = consumer price index; DPI = dry powder inhaler; KCMH = King Chulalongkorn Memorial Hospital; MDI = metered dose inhaler; N/A = not available; SD = standard deviation; SE = standard error of difference

Table 4.6: Total costs during the 3-day treatment period for the intention-to-treat patients in the MDI with spacer and DPI groups (according to the patient's perspective).

| Cost item | MDI with spacer (n = 40) | DPI (n = 40) | Difference* |
|---|---|---|---|
| **Direct medical costs paid for KCMH** | | | |
| Hospital care costs | | | |
| Emergency room | 0.00 | 0.00 | 0.00 |
| Intensive care unit | 0.00 | 0.00 | 0.00 |
| Inpatient department | 0.00 | 3,540.83 | (-)3,540.83 |
| Outpatient department | 7,334.01 | 4889.34 | 2,444.67 |
| Total hospital care costs | 7,334.01 | 8,430.17 | (-)1,096.16 |
| Medical care costs | | | |
| Study medication | 400.67 | 530.70 | (-)130.03 |
| Oral corticosteroids | 173.48 | 140.04 | 33.44 |
| Rescue medication | 1,048.88 | 855.30 | 193.58 |
| Medication prescribed during hospital admission | 0.00 | 512.35 | (-)512.35 |
| Medication prescribed during re-visit | 240.00 | 320.00 | (-)80.00 |
| Other asthma-related medication | 560.35 | 430.53 | 129.82 |
| Tests | 4,000.00 | 4,000.00 | 0.00 |
| Total medical care costs | 6,423.38 | 6,788.92 | (-)365.54 |
| **Total direct medical costs paid for KCMH** | 13,757.39 | 15,219.09 | (-)1,461.70 |

(Continued to next page)

Table 4.6. (Continued): Total costs during the 3-day treatment period for the intention-to-treat patients in the MDI with spacer and DPI groups (according to the patient's perspective).

| Cost item | MDI with spacer (n = 40) | DPI (n = 40) | Difference* |
|---|---|---|---|
| (Continued from last page) | | | |
| **Direct medical costs paid for other providers** | | | |
| Hospital care costs | | | |
| Emergency room | 0.00 | 1,229.11 | (-)1,229.11 |
| Intensive care unit | 0.00 | 0.00 | 0.00 |
| Inpatient department | 1,770.41 | 0.00 | 1,770.41 |
| Outpatient department | 0.00 | 0.00 | 0.00 |
| Total hospital care costs | 1,770.41 | 1,229.11 | 541.30 |
| Medical care costs | | | |
| Medication | 9.10 | 0.00 | 9.10 |
| Chest x-ray | 0.00 | 126.43 | (-)126.43 |
| Total medical care costs | 9.10 | 126.43 | (-)117.33 |
| **Total direct medical costs paid for other providers** | 1,779.52 | 1,355.54 | 423.98 |
| **Direct non-medical costs** | N/A | N/A | N/A |
| **Total direct cost** | 15,536.91 | 16,574.63 | (-)1,037.72 |
| **Indirect costs** | | | |
| Costs of lost work days | 4,313.69 | 3,529.38 | 784.31 |
| **Total indirect costs** | 4,313.69 | 3,529.38 | 784.31 |
| **Total costs**** | 19,850.60 | 20,104.01 | (-)253.41 |

All cost data are presented in 2005 Baht; when necessary, the costs were adjusted to 2005 Baht using the medical and personal care item of CPI.
*Difference = MDI with spacer – DPI
**Total costs = Total direct costs + Total indirect costs
Abbreviations: CPI = consumer price index; DPI = dry powder inhaler; KCMH = King Chulalongkorn Memorial Hospital; MDI = metered dose inhaler; N/A = not available

### 4.2.4 Outliers

Outliers, i.e. patiens with markedly higher costs than those of the average patients, are a common problem in health economic analyses. The results were calculated both with and without any extreme outliers to see whether or not the outliers significantly affected the results.

There was one outlier with regard to the total direct medical costs in the DPI group. In the DPI group, the most costly patient incurred costs of Baht 6,288.14 and Baht 6,220.58 according to the provider's and patient's perspectives, respectively, and mainly because of the high cost of the inpatient department stay for 2 days in King Chulalongkorn Memorial Hospital (Baht 5,072.08 and Baht 3,540.83 calculated from the provider's and patient's perspectives, respectively). The total costs were derived from the sum of total indirect costs and total direct medical costs (equated with total direct costs because direct non-medical costs were not taken into account in this economic analysis), so this outlier affected both the provider's and patient's costs. As a result of this, the total direct medical costs (according to the provider's perspective) and the total costs (according to the patient's perspective) were higher in the DPI group than in the MDI with spacer group (Table 4.4 and 4.6, respectively). The study gave the same results for the means of total direct medical costs and total costs (Table 4.3. and 4.5, respectively).

When this patient was excluded, and recomputed the total direct medical costs and total costs for the DPI group, the costs were 47.12% and 30.94% lower, respectively. The mean and total direct medical costs calculated without this outlier for the 2 treatment groups were shown in Table 4.7 and 4.8, respectively. When the outlier belonged to the DPI group was excluded, the mean total direct medical costs for the DPI group was Baht 180.98 per patient compared with Baht 239.63 per patient for the MDI and spacer group, and there were not significant difference between the groups ($p = 0.081$). The same results were found when the analysis was conducted from the patient's perspective. The mean and total costs calculated without the outlier in the DPI group for the 2 treatment groups were shown in Table 4.9 and 4.10, respectively. The mean and total costs were higher in the MDI with spacer group, but did not reach statistically significant ($p = 0.480$). Accordingly, the mean total costs per patient was Baht 355.99 for the DPI group compared with Baht 496.27 for the MDI and spacer group. Thus, the outlier in the DPI group changed the results in non-significant way.

Table 4.7: Mean total direct medical costs per patient during the 3-day treatment period for the patients (excluding outlier) in the MDI with spacer and DPI groups (according to the provider's perspective).

| Cost item | MDI with spacer* (n = 40) | DPI* (n = 39)** | Mean Difference***(SE) | p-Value |
|---|---|---|---|---|
| **Direct medical costs** | | | | |
| Routine service costs | | | | |
| Emergency room | 0.00 (0.00) | 0.00 (0.00) | 0.00 (0.00) | 1.000 |
| Intensive care unit | 0.00 (0.00) | 0.00 (0.00) | 0.00 (0.00) | 1.000 |
| Inpatient department | 0.00 (0.00) | 0.00 (0.00) | 0.00 (0.00) | 1.000 |
| Outpatient department | 98.36 (237.12) | 50.44 (177.01) | 47.92 (47.00) | 0.310 |
| Total routine service costs | 98.36 (237.12) | 50.44 (177.01) | 47.92 (47.00) | 0.310 |
| Medical care costs | | | | |
| Study medication | 15.94 (2.62) | 11.14 (5.72) | 4.79 (1.01) | < 0.001**** |
| Oral corticosteroids | 3.61 (2.32) | 2.99 (2.34) | 0.62 (0.52) | 0.162 |
| Rescue medication | 21.83 (29.29) | 17.15 (24.12) | 4.68 (6.03) | 0.910 |
| Medication prescribed during hospital admission | 0.00 (0.00) | 0.00 (0.00) | 0.00 (0.00) | 1.000 |
| Medication prescribed during re-visit | 5.00 (17.77) | 6.83 (33.46) | (-)1.84 (6.01) | 0.693 |
| Other asthma-related medication | 11.66 (27.50) | 9.19 (16.98) | 2.47 (5.16) | 0.928 |
| Tests | 83.24 (0.00) | 83.24 (0.00) | 0.00 (0.00) | 1.000 |
| Total medical care costs | 141.27 (44.51) | 130.54 (46.77) | 10.73 (10.27) | 0.299 |
| **Total direct medical costs** | 239.63 (245.95) | 180.98 (200.87) | 58.65 (50.60) | 0.081 |

All cost data are presented in 2005 Baht; when necessary, the costs were adjusted to 2005 Baht using the medical and personal care item of CPI.
*Data are presented as mean value with SD in parentheses, unless otherwise stated.
**One patient was excluded because he was the most costly patient, the so-called "outlier", as a result of high costs for hospitalization.
***Mean difference = MDI with spacer – DPI
****Statistically significant difference ($p < 0.05$)
Abbreviations: CPI = consumer price index; DPI = dry powder inhaler; MDI = metered dose inhaler; SD = standard deviation; SE = standard error of difference

Table 4.8: Total direct medical costs during the 3-day treatment period for the patients (excluding outlier) in the MDI with spacer and DPI groups (according to the provider's perspective).

| Cost item | MDI with spacer (n = 40) | DPI (n = 39)* | Difference** |
|---|---|---|---|
| **Direct medical costs** | | | |
| Routine service costs | | | |
| Emergency room | 0.00 | 0.00 | 0.00 |
| Intensive care unit | 0.00 | 0.00 | 0.00 |
| Inpatient department | 0.00 | 0.00 | 0.00 |
| Outpatient department | 3,934.24 | 1,967.12 | 1,967.12 |
| Total routine service costs | 3,934.24 | 1,967.12 | 1,967.12 |
| Medical care costs | | | |
| Study medication | 637.44 | 434.57 | 202.88 |
| Oral corticosteroids | 144.42 | 116.58 | 27.84 |
| Rescue medication | 873.19 | 668.70 | 204.49 |
| Medication prescribed during hospital admission | 0.00 | 0.00 | 0.00 |
| Medication prescribed during re-visit | 199.80 | 266.40 | (-)66.60 |
| Other asthma-related medication | 466.49 | 358.42 | 108.07 |
| Tests | 3,329.60 | 3,246.36 | 83.24 |
| Total medical care costs | 5,650.94 | 5,091.02 | 559.92 |
| **Total direct medical costs** | 9,585.19 | 7,058.14 | 2,527.04 |

All cost data are presented in 2005 Baht; when necessary, the costs were adjusted to 2005 Baht using the medical and personal care item of CPI.
*One patient was excluded because he was the most costly patient, the so-called "outlier", as a result of high costs for hospitalization.
**Difference = MDI with spacer – DPI
Abbreviations: CPI = consumer price index; DPI = dry powder inhaler; MDI = metered dose inhaler

Table 4.9: Mean total costs per patient during the 3-day treatment period for the patients (excluding outlier) in the MDI with spacer and DPI groups (according to the patient's perspective).

| Cost item | MDI with spacer* (n = 40) | DPI* (n = 39)** | Mean Difference***(SE) | p-Value |
|---|---|---|---|---|
| **Direct medical costs paid for KCMH** | | | | |
| Hospital care costs | | | | |
| Emergency room | 0.00 (0.00) | 0.00 (0.00) | 0.00 (0.00) | 1.000 |
| Intensive care unit | 0.00 (0.00) | 0.00 (0.00) | 0.00 (0.00) | 1.000 |
| Inpatient department | 0.00 (0.00) | 0.00 (0.00) | 0.00 (0.00) | 1.000 |
| Outpatient department | 183.35 (442.02) | 94.03 (329.97) | 89.32 (87.62) | 0.310 |
| Total hospital care costs | 183.35 (442.02) | 94.03 (329.97) | 89.32 (87.62) | 0.310 |
| Medical care costs | | | | |
| Study medication | 10.02 (3.15) | 13.38 (6.87) | (-)3.36 (1.21) | < 0.001**** |
| Oral corticosteroids | 4.34 (2.79) | 3.59 (2.81) | 0.75 (0.63) | 0.162 |
| Rescue medication | 26.22 (35.19) | 20.60 (28.98) | 5.63 (7.24) | 0.910 |
| Medication prescribed during hospital admission | 0.00 (0.00) | 0.00 (0.00) | 0.00 (0.00) | 1.000 |
| Medication prescribed during re-visit | 6.00 (21.34) | 8.21 (40.19) | (-)2.21 (7.21) | 0.693 |
| Other asthma-related medication | 14.01 (33.03) | 11.04 (20.40) | 2.97 (6.20) | 0.928 |
| Tests | 100.00 (0.00) | 100.00 (0.00) | 0.00 (0.00) | 1.000 |
| Total medical care costs | 160.58 (53.46) | 156.82 (56.17) | 3.77 (12.34) | 0.761 |
| **Total direct medical costs paid for KCMH** | 343.93 (450.96) | 250.84 (356.84) | 93.09 (91.64) | 0.717 |

(Continued to next page)

Table 4.9 (Continued): Mean total costs per patient during the 3-day treatment period for the patients (excluding outlier) in the MDI with spacer and DPI groups (according to the patient's perspective).

| Cost item | MDI with spacer* (n = 40) | DPI* (n = 39)** | Mean Difference***(SE) | p-Value |
|---|---|---|---|---|
| (Continued from last page) | | | | |
| **Direct medical costs paid for other providers** | | | | |
| Hospital care costs | | | | |
| Emergency room | 0.00 (0.00) | 31.52 (196.82) | (-)31.52 (31.52) | 0.311 |
| Intensive care unit | 0.00 (0.00) | 0.00 (0.00) | 0.00 (0.00) | 1.000 |
| Inpatient department | 44.26 (279.93) | 0.00 (0.00) | 44.26 (44.26) | 0.323 |
| Outpatient department | 0.00 (0.00) | 0.00 (0.00) | 0.00 (0.00) | 1.000 |
| Total hospital care costs | 44.26 (279.93) | 31.52 (196.82) | 12.74 (54.57) | 1.000 |
| Medical care costs | | | | |
| Medication | 0.23 (1.03) | 0.00 (0.00) | 0.23 (0.16) | 0.160 |
| Chest x-ray | 0.00 (0.00) | 3.24 (20.25) | (-)3.24 (3.24) | 0.311 |
| Total medical care costs | 0.23 (1.03) | 3.24 (20.25) | (-)3.01 (3.20) | 0.594 |
| **Total direct medical costs paid for other providers** | 44.49 (280.80) | 34.76 (217.06) | 9.73 (56.57) | 0.574 |
| **Direct non-medical costs** | N/A | N/A | N/A | N/A |
| **Total direct cost** | 388.42 (610.88) | 285.60 (407.41) | 102.82 (117.13) | 0.860 |
| **Indirect costs** | | | | |
| Costs of lost work days | 107.84 (177.33) | 70.39 (218.00) | 37.45 (44.66) | 0.125 |
| **Total indirect costs** | 107.84 (177.33) | 70.39 (218.00) | 37.45 (44.66) | 0.125 |
| **Total costs*****| 496.27 (716.78) | 355.99 (553.55) | 140.28 (144.35) | 0.480 |

All cost data are presented in 2005 Baht; when necessary, the costs were adjusted to 2005 Baht using the medical and personal care item of CPI.
*Data are presented as mean value with SD in parentheses, unless otherwise stated.
**One patient was excluded because he was the most costly patient, the so-called "outlier", as a result of high costs for hospitalization.
***Mean difference = MDI with spacer – DPI ****Statistically significant difference ($p < 0.05$)
*****Total costs = Total direct costs + Total indirect costs
Abbreviations: CPI = consumer price index; DPI = dry powder inhaler; KCMH = King Chulalongkorn Memorial Hospital; MDI = metered dose inhaler; N/A = not available; SD = standard deviation; SE = standard error of difference

Table 4.10: Total costs during the 3-day treatment period for the patients (excluding outlier) in the MDI with spacer and DPI groups (according to the patient's perspective).

| Cost item | MDI with spacer (n = 40) | DPI (n = 39)* | Difference** |
|---|---|---|---|
| **Direct medical costs paid for KCMH** | | | |
| Hospital care costs | | | |
| Emergency room | 0.00 | 0.00 | 0.00 |
| Intensive care unit | 0.00 | 0.00 | 0.00 |
| Inpatient department | 0.00 | 0.00 | 0.00 |
| Outpatient department | 7,334.01 | 3,667.01 | 3,667.01 |
| Total hospital care costs | 7,334.01 | 3,667.01 | 3,667.01 |
| Medical care costs | | | |
| Study medication | 400.67 | 522.00 | (-)121.33 |
| Oral corticosteroids | 173.48 | 140.04 | 33.44 |
| Rescue medication | 1,048.88 | 803.24 | 245.64 |
| Medication prescribed during hospital admission | 0.00 | 0.00 | 0.00 |
| Medication prescribed during re-visit | 240.00 | 320.00 | (-)80.00 |
| Other asthma-related medication | 560.35 | 430.53 | 129.82 |
| Tests | 4,000.00 | 3,900.00 | 100.00 |
| Total medical care costs | 6,423.38 | 6,115.81 | 307.57 |
| **Total direct medical costs paid for KCMH** | 13,757.39 | 9,782.82 | 3,974.58 |

(Continued to next page)

Table 4.10. (Continued): Total costs during the 3-day treatment period for the patients (excluding outlier) in the MDI with spacer and DPI groups (according to the patient's perspective).

| Cost item | MDI with spacer (n = 40) | DPI (n = 39)* | Difference** |
|---|---|---|---|
| (Continued from last page) | | | |
| **Direct medical costs paid for other providers** | | | |
| Hospital care costs | | | |
| Emergency room | 0.00 | 1,229.11 | (-)1,229.11 |
| Intensive care unit | 0.00 | 0.00 | 0.00 |
| Inpatient department | 1,770.41 | 0.00 | 1,770.41 |
| Outpatient department | 0.00 | 0.00 | 0.00 |
| Total hospital care costs | 1,770.41 | 1,229.11 | 541.30 |
| Medical care costs | | | |
| Medication | 9.10 | 0.00 | 9.10 |
| Chest x-ray | 0.00 | 126.43 | (-)126.43 |
| Total medical care costs | 9.10 | 126.43 | (-)117.33 |
| **Total direct medical costs paid for other providers** | 1,779.52 | 1,355.54 | 423.98 |
| **Direct non-medical costs** | N/A | N/A | N/A |
| **Total direct cost** | 15,536.91 | 11,138.36 | 4,398.55 |
| **Indirect costs** | | | |
| Costs of lost work days | 4,313.69 | 2,745.08 | 1,568.62 |
| **Total indirect costs** | 4,313.69 | 2,745.08 | 1,568.62 |
| **Total costs*** ** | 19,850.60 | 13,883.43 | 5,967.17 |

All cost data are presented in 2005 Baht; when necessary, the costs were adjusted to 2005 Baht using the medical and personal care item of CPI.
*One patient was excluded because he was the most costly patient, the so-called "outlier", as a result of high costs for hospitalization.
**Difference = MDI with spacer – DPI
***Total costs = Total direct costs + Total indirect costs
Abbreviations: CPI = consumer price index; DPI = dry powder inhaler; KCMH = King Chulalongkorn Memorial Hospital; MDI = metered dose inhaler; N/A = not available

## 4.3 Clinical Outcomes

### 4.3.1 Clinical Outcomes within the Groups

The clinical outcomes within the MDI with spacer group were shown in Table 4.11, and in Table 4.12 for the DPI group. There was significant improvement in the clinical scores and in the number of successfully treated patients in both groups and at all assessment times ($p < 0.001$ for all outcomes). The Global Initiative for Asthma (GINA 2005) recommended the oxygen saturation assessment for monitoring the response to treatment in patients with asthma attacks. In each group, it was found that increases in oxygen saturation values compared with baseline within the groups were not statistically significant, except at 60 minutes after the first treatment in the DPI group ($p = 0.034$). However, these values indicated that there were improvement in the ventilation of patients in both groups. This was very important because hypercapnia (hypoventilation) develops more readily in young children than in adults and adolescents (GINA 2005), and supplementary oxygen is given if the patient is hypoxemic. There was not the use of supplementary oxygen in this study.

Table 4.11: Clinical outcomes at 0, 20, 40 and 60 minutes for the intention-to-treat patients in the MDI with spacer group.

| Outcome | Mean difference*(SD) | 95% CI | p-Value |
|---|---|---|---|
| Clinical scores (0-10) | | | |
| T=0 min. vs T=20 mins. | 1.68 (1.31) | 1.26 - 2.09 | < 0.001** |
| T=0 min. vs T=40 mins. | 2.40 (1.35) | 1.97 - 2.83 | < 0.001** |
| T=0 min. vs T=60 mins. | 2.55 (1.30) | 2.13 - 2.97 | < 0.001** |
| No.of successfully treated patients | | | |
| T=0 min. vs T=20 mins. | 24 (60.0%) | - | < 0.001** |
| T=0 min. vs T=40 mins. | 34 (85.0%) | - | < 0.001** |
| T=0 min. vs T=60 mins. | 36 (90.0%) | - | < 0.001** |
| $SaO_2$ (%) | | | |
| T=0 min. vs T=20 mins. | (-)0.25 (1.45) | (-)0.71 - 0.21 | 0.283 |
| T=0 min. vs T=40 mins. | (-)0.30 (1.42) | (-)0.75 - 0.15 | 0.181 |
| T=0 min. vs T=60 mins. | (-)0.40 (1.60) | (-)0.91 - 0.11 | 0.140 |

*Data are presented as mean difference with SD in parentheses, or as number of patients with % in parentheses.; Mean difference = mean value at $T_0$ - mean value at $T_n$

**Statistically significant difference ($p < 0.05$)

Abbreviations: CI = confidence interval; DPI = dry powder inhaler; MDI = metered dose inhaler; $SaO_2$ = oxygen saturation; SD = standard deviation; T = time

Table 4.12: Clinical outcomes at 0, 20, 40 and 60 minutes for the intention-to-treat patients in the DPI group.

| Outcome | Mean difference*(SD) | 95% CI | p-Value |
|---|---|---|---|
| Clinical scores (0-10) | | | |
| T=0 min. vs T=20 mins. | 1.53 (1.13) | 1.16 - 1.89 | < 0.001** |
| T=0 min. vs T=40 mins. | 1.95 (1.28) | 1.54 - 2.36 | < 0.001** |
| T=0 min. vs T=60 mins. | 2.15 (1.21) | 1.76 - 2.54 | < 0.001** |
| No.of successfully treated patients | | | |
| T=0 min. vs T=20 mins. | 26 (65.0%) | - | < 0.001** |
| T=0 min. vs T=40 mins. | 33 (82.5%) | - | < 0.001** |
| T=0 min. vs T=60 mins. | 37 (92.5%) | - | < 0.001** |
| $SaO_2$ (%) | | | |
| T=0 min. vs T=20 mins. | (-)0.40 (1.50) | (-)0.88 - 0.08 | 0.088 |
| T=0 min. vs T=40 mins. | (-)0.33 (1.79) | (-)0.90 - 0.25 | 0.349 |
| T=0 min. vs T=60 mins. | (-)0.58 (1.68) | (-)1.11 - (-)0.04 | 0.034** |

*Data are presented as mean difference with SD in parentheses, or as number of patients with % in parentheses.; Mean difference = mean value at $T_0$ - mean value at $T_n$

**Statistically significant difference ($p < 0.05$)

Abbreviations: CI = confidence interval; DPI = dry powder inhaler; MDI = metered dose inhaler; $SaO_2$ = oxygen saturation; SD = standard deviation; T = time

### 4.3.2 Clinical Outcomes between the Groups

There were not significant differences between the groups in the clinical scores, number of successfully treated patients, oxygen saturation, number of patients used rescue medications and number of patient admitted in the hospital (Table 4.13.). In comparison with the MDI and spacer group, the percentage of successfully treated patients were higher in the DPI group at 20 and 60 minutes, but there were not significant differences at all assessment times. The mean values of oxygen saturation in both groups were more than 95% at all assessment times, indicated the good response to the management of asthma attacks according to the Global Initiative for Asthma (GINA 2005), and there was not severe respiratory failure in the patients.

In term of rescue medication use, the patients in the MDI with spacer group had higher percentage of patients used rescue medications during the 3-day treatment period than in the DPI group, but did not reach statistical significant ($p = 0.516$). There was 1 patient (2.5%) belonged to the MDI with spacer group was hospitalized for 1 day in Police General Hospital, and 1 patient (2.5%) belonged to the DPI group was admitted for 2 days in King Chulalongkorn Memorial Hospital due to asthma re-exacerbations within 3 days after the treatment.

Table 4.13: Clinical outcomes at 0, 20, 40 and 60 minutes for the intention-to-treat patients in the MDI with spacer and DPI groups.

| Outcome | MDI with spacer* (n = 40) | DPI* (n = 40) | Mean Difference**(SE) | 95% CI | p-Value |
|---|---|---|---|---|---|
| Clinical scores (0-10) | | | | | |
| T = 0 min. | 3.90 (1.13) | 3.55 (1.24) | 0.35 (0.26) | (-)0.18 - 0.88 | 0.197 |
| T = 20 mins. | 2.23 (1.42) | 2.03 (1.51) | 0.20 (0.33) | (-)0.45 - 0.85 | 0.516 |
| T = 40 mins. | 1.50 (1.28) | 1.60 (1.30) | (-)0.10 (0.29) | (-)0.67 - 0.47 | 0.718 |
| T = 60 mins. | 1.35 (1.14) | 1.40 (1.19) | (-)0.05 (0.26) | (-)0.57 - 0.47 | 0.842 |
| No.of successfully treated patients | | | | | |
| T = 0 min. | 0 (0.0%) | 0 (0.0%) | - | - | - |
| T = 20 mins. | 24 (60.0%) | 26 (65.0%) | - | - | 0.817 |
| T = 40 mins. | 34 (85.0%) | 33 (82.5%) | - | - | 1.000 |
| T = 60 mins. | 36 (90.0%) | 37 (92.5%) | - | - | 1.000 |
| $SaO_2$ (%) | | | | | |
| T = 0 min. | 96.63 (1.53) | 96.65 (1.78) | (-)0.03 (0.37) | (-)0.76 - 0.71 | 0.671 |
| T = 20 mins. | 96.88 (2.02) | 97.05 (1.78) | (-)0.18 (0.43) | (-)1.02 - 0.67 | 0.911 |
| T = 40 mins. | 96.93 (1.87) | 96.98 (1.75) | (-)0.05 (0.40) | (-)0.86 - 0.76 | 0.996 |
| T = 60 mins. | 97.03 (1.87) | 97.23 (1.42) | (-)0.20 (0.37) | (-)0.94 - 0.54 | 0.837 |
| Rescue medication used | | | | | |
| No.of patients (yes/no) | 33/7 (82.5% / 17.5%) | 36/4 (90.0% / 10.0%) | - | - | 0.516 |
| Hospitalization | | | | | |
| No.of patients (yes/no) | 1/39 (2.5% / 97.5%) | 1/39 (2.5% / 97.5%) | - | - | 1.000 |

*Data are presented as mean difference with SD in parentheses, or as number of patients with % in parentheses, unless otherwise stated.
**Mean difference = MDI with spacer – DPI
Abbreviations: CI = confidence interval; DPI = dry powder inhaler; MDI = metered dose inhaler; $SaO_2$ = oxygen saturation; SD = standard deviation; SE = standard error of difference; T = time

### 4.3.3 Clinical Effectiveness

In term of clinical effectiveness, the number and percentage of successfully treated patients at 60 minutes were higher in the DPI group than in the MDI and spacer group (p = 1.000) (Table 4.14).

The effectiveness-time curves also showed the same results (Figure 4.1). With this approach, the effectiveness-time curve of the DPI group which nearly concided with the effectiveness-time curve of the MDI and spacer group reflected the effectiveness that were not different between the 2 treatment groups at all assessment times.

Table 4.14: Clinical effectiveness used for the economic analysis for the intention-to-treat patients in the MDI with spacer and DPI groups.

| Effectiveness | MDI with spacer (n = 40) | DPI (n = 40) | p-Value |
|---|---|---|---|
| No.of successfully treated patients (T=60 mins.) | 36 | 37 | 1.000 |
| % of successfully treated patients (T=60 mins.) | 90.00% | 92.50% | 1.000 |

Abbreviations: DPI = dry powder inhaler; MDI = metered dose inhaler; mins. = minutes; T = time

Figure 4.1: Effectiveness-time curves of the cumulative percentage of successfully treated patients for the MDI with spacer and DPI groups at 0, 20, 40 and 60 minutes.

### 4.3.4 Adverse Events

The adverse events results were summarized in Table 4.15, 4.16 and 4.17. The patients in both the MDI with spacer and DPI groups had a significant decrease in respiratory rate at all assessment times (Table 4.15 and 4.16, respectively). The Global Initiative for Asthma (GINA 2005) guided to normal rate of breathing in school-age children as < 30 breaths/minute, so the respiratory rates of patients in both groups were lied within the normal range at all assessment times as can be seen in Table 4.17, and there were not the clinical changes in breathing occurred during the study period.

Of parameters that might indicate adverse events due to beta2-agonist overexposure, the pulse rate change was measured. The results showed that there were not significant difference in this parameter between the two groups (Table 4.17.), however, the patients belonged to the MDI with spacer group had a significant increase in pulse rate at all assessment times compared with baseline (Table 4.15.). The increasing in pulse rate was also found in the DPI group, but it was not statistically significant except at 40 minutes (Table 4.16). The GINA (2005) guided to the limit of normal pulse rate in school-age children was < 110 beats/minute. Accordingly, the pulse rate of the patients belonged to the MDI with spacer group were lied out of the normal limit, and significantly increased at all assessment times compared with baseline. Although the increasing in pulse rate of the patients in the DPI group was also statistically significant at 40 minutes, the pulse rate were still lied within the normal limit at all assessment times.

The adverse events, i.e. tremor, palpitation and headache, were more frequent with the use of the MDI with spacer, however, there were not significant differences between the 2 treatment groups with respect to all parameters of adverse events (Table 4.17). Although some parameters, i.e. pulse rate and the incidence of palpitation, did not reach statistical significance between the 2 treatment groups, the study detected a strong trend for difference ($p = 0.070$ for pulse rate and $p = 0.055$ for the incidence of palpitation). The likely reason for this finding was that the study did not have enough power to show a difference due to small sample size.

Table 4.15: Adverse events at 0, 20, 40 and 60 minutes for the intention-to-treat patients in the MDI with spacer group.

| Parameter | Mean difference*(SD) | 95% CI | p-Value |
|---|---|---|---|
| RR (breaths/min.) | | | |
| T=0 min. vs T=20 mins. | 2.75 (5.65) | 0.94 - 4.56 | 0.002** |
| T=0 min. vs T=40 mins. | 3.50 (5.43) | 1.76 - 5.24 | < 0.001** |
| T=0 min. vs T=60 mins. | 4.73 (5.99) | 2.81 - 6.64 | < 0.001** |
| PR (beats/min.) | | | |
| T=0 min. vs T=20 mins. | (-)5.25 (12.54) | (-)9.26 - (-)1.24 | 0.014** |
| T=0 min. vs T=40 mins. | (-)6.05 (12.71) | (-)10.12 - (-)1.98 | 0.009** |
| T=0 min. vs T=60 mins. | (-)4.55 (11.72) | (-)8.30 - (-)0.80 | 0.033** |
| BP (mmHg) | | | |
| Systolic T=0 min. vs T=60 mins. | 1.93 (10.37) | (-)1.39 - 5.24 | 0.443 |
| Diastolic T=0 min. vs T=60 mins. | 2.18 (9.40) | (-)0.83 - 5.18 | 0.186 |
| Tremor | | | |
| No.of patients (yes/no) | 5/35 (12.5% / 87.5%) | - | 0.250 |
| Palpitation | | | |
| No.of patients (yes/no) | 5/35 (12.5% / 87.5%) | - | 0.375 |
| Headache | | | |
| No.of patients (yes/no) | 1/39 (2.5% / 97.5%) | - | 1.000 |

*Data are presented as mean difference with SD in parentheses, or as number of patients with % in parentheses.; Mean difference = mean value at $T_0$ - mean value at $T_n$

**Statistically significant difference ($p < 0.05$)

Abbreviations: BP = blood pressure; CI = confidence interval; MDI = metered dose inhaler; min. = minute; mmHg = millimeter mercury; PR = pulse rate; RR = respiratory rate; SD = standard deviation; T = time

Table 4.16: Adverse events at 0, 20, 40 and 60 minutes for the intention-to-treat patients in the DPI group.

| Parameter | Mean difference*(SD) | 95% CI | p-Value |
|---|---|---|---|
| RR (breaths/min.) | | | |
| T=0 min. vs T=20 mins. | 3.30 (4.51) | 1.86 - 4.74 | < 0.001** |
| T=0 min. vs T=40 mins. | 3.55 (4.40) | 2.14 - 4.96 | < 0.001** |
| T=0 min. vs T=60 mins. | 4.60 (5.08) | 2.97 - 6.23 | < 0.001** |
| PR (beats/min.) | | | |
| T=0 min. vs T=20 mins. | (-)3.60 (10.50) | (-)6.96 - 0.24 | 0.091 |
| T=0 min. vs T=40 mins. | (-)3.98 (10.08) | (-)7.20 - (-)0.75 | 0.022** |
| T=0 min. vs T=60 mins. | (-)2.70 (11.98) | (-)6.53 - 1.13 | 0.155 |
| BP (mmHg) | | | |
| Systolic T=0 min. vs T=60 mins. | (-)0.45 (6.60) | (-)2.56 - 1.66 | 0.559 |
| Diastolic T=0 min. vs T=60 mins. | 0.50 (8.57) | (-)2.24 - 3.24 | 0.366 |
| Tremor | | | |
| No.of patients (yes/no) | 2/38 (5.0% / 95.0%) | - | 1.000 |
| Palpitation | | | |
| No.of patients (yes/no) | 0/40 (0.0% / 100.0%) | - | N/A |
| Headache | | | |
| No.of patients (yes/no) | 0/40 (0.0% / 100.0%) | - | N/A |

*Data are presented as mean difference with SD in parentheses, or as number of patients with % in parentheses.; Mean difference = mean value at $T_0$ - mean value at $T_n$

**Statistically significant difference ($p < 0.05$)

Abbreviations: BP = blood pressure; CI = confidence interval; DPI = dry powder inhaler; N/A = not available; min. = minute; mmHg = millimeter mercury; PR = pulse rate; RR = respiratory rate; SD = standard deviation; T = time

Table 4.17: Adverse events at 0, 20, 40 and 60 minutes for the intention-to-treat patients in the MDI with spacer and DPI groups.

| Parameter | MDI with spacer* (n = 40) | DPI* (n = 40) | Mean difference**(SE) | 95% CI | p-Value |
|---|---|---|---|---|---|
| RR (breaths/min.) | | | | | |
| T = 0 min. | 29.75 (7.19) | 29.15 (6.85) | 0.60 (1.57) | (-)2.53 - 3.73 | 0.919 |
| T = 20 mins. | 27.00 (6.19) | 25.85 (5.10) | 1.15 (1.27) | (-)1.37 - 3.67 | 0.575 |
| T = 40 mins. | 26.25 (6.03) | 25.60 (5.01) | 0.65 (1.24) | (-)1.82 - 3.12 | 0.800 |
| T = 60 mins. | 25.03 (5.90) | 24.55 (4.43) | 0.48 (1.17) | (-)1.85 - 2.80 | 0.853 |
| PR (beats/min.) | | | | | |
| T = 0 min. | 110.28 (19.16) | 105.53 (19.05) | 4.75 (4.27) | (-)3.75 - 13.25 | 0.189 |
| T = 20 mins. | 115.53 (24.26) | 109.13 (18.01) | 6.40 (4.78) | (-)3.11 - 15.91 | 0.139 |
| T = 40 mins. | 116.33 (22.41) | 109.50 (16.02) | 6.83 (4.36) | (-)1.85 - 15.50 | 0.070 |
| T = 60 mins. | 114.83 (23.08) | 108.23 (17.49) | 6.60 (4.58) | (-)2.52 - 15.72 | 0.142 |
| BP (mmHg) | | | | | |
| Systolic T=0 min. | 106.83 (12.66) | 105.08 (10.99) | 1.75 (2.65) | (-)3.53 - 7.03 | 0.543 |
| T=60 mins. | 104.90 (8.87) | 105.53 (12.36) | (-)0.63 (2.41) | (-)5.41 - 4.16 | 0.594 |
| Diastolic T=0 min. | 67.65 (11.74) | 69.63 (8.38) | (-)1.98 (2.28) | (-)6.52 - 2.57 | 0.517 |
| T=60 mins. | 65.48 (9.23) | 69.13 (10.94) | (-)3.65 (2.26) | (-)8.15 - 0.85 | 0.191 |
| Tremor | | | | | |
| No.of patients (yes/no) | 5/35 (12.5% / 87.5%) | 2/38 (5.0% / 95.0%) | - | - | 0.432 |
| Palpitation | | | | | |
| No.of patients (yes/no) | 5/35 (12.5% / 87.5%) | 0/40 (0.0% / 100.0%) | - | - | 0.055 |
| Headache | | | | | |
| No.of patients (yes/no) | 1/39 (2.5% / 97.5%) | 0/40 (0.0% / 100.0%) | - | - | 1.000 |

*Data are presented as mean difference with SD in parentheses, or as number of patients with % in parentheses, unless otherwise stated.
**Mean difference = MDI with spacer – DPI
Abbreviations: BP = blood pressure; CI = confidence interval; DPI = dry powder inhaler; MDI = metered dose inhaler; min. = minute; mmHg = millimeter mercury; PR = pulse rate; RR = respiratory rate; SD = standard deviation; SE = standard error of difference; T = time

### 4.3.5 Re-exacerbations of Asthma Symptoms

The percentages of patients with re-exacerbations, defined as a worsening of the child's asthma symptoms in terms of cough, wheeze, dyspnea, absence from school and re-visit at hospital within 3 days, were higher in the MDI with spacer group than in the DPI group (Table 4.18). However, there were not significant differences between the 2 treatment groups with respect to all parameters of re-exacerbation parameters.

Table 4.18: Asthma re-exacerbations within 3 days after discharge for the intention-to-treat patients in the MDI with spacer and DPI groups.

| Parameter | MDI with spacer* (n = 40) | DPI* (n = 40) | Mean difference**(SE) | 95% CI | p-Value |
|---|---|---|---|---|---|
| Cough | | | | | |
| No.of patients (yes/no) | 27/13 (67.5% / 32.5%) | 30/10 (75.0% / 25.0%) | - | - | 0.621 |
| Wheeze | | | | | |
| No.of patients (yes/no) | 11/29 (27.5% / 72.5%) | 8/32 (20.0% / 80.0%) | - | - | 0.599 |
| Dyspnea | | | | | |
| No.of patients (yes/no) | 7/33 (17.5% / 82.5%) | 5/35 (12.5% / 87.5%) | - | - | 0.754 |
| Absence from school | | | | | |
| No.of patients (yes/no) | 11/29 (27.5% / 72.5%) | 6/34 (15.0% / 85.0%) | - | - | 0.274 |
| Mean no.of school days lost | 0.28 (0.45) | 0.23 (0.62) | 0.05 (0.12) | (-)0.19 - 0.29 | 0.228 |
| Re-visit at hospital | | | | | |
| No.of patients (yes/no) | 6/34 (15.0% / 85.0%) | 4/36 (10.0% / 90.0%) | - | - | 0.735 |
| Mean no.of re-visits | 0.15 (0.36) | 0.10 (0.30) | 0.05 (0.07) | (-)0.10 - 0.20 | 0.502 |

*Data are presented as mean difference with SD in parentheses, or as number of patients with % in parentheses, unless otherwise stated.
**Mean difference = MDI with spacer – DPI
Abbreviations: CI = confidence interval; DPI = dry powder inhaler; MDI = metered dose inhaler; SD = standard deviation; SE = standard error of difference

**4.4 Cost-Effectiveness Analysis**

The mean cost-effectiveness ratios and incremental cost-effectiveness ratios conducted from the provider's and patient's perspectives were shown in Table 4.19 and Table 4.20, respectively. From the provider's perspective, the mean costs per number and per percentage of successfully treated patients were lower for the MDI with spacer group than for the DPI group including the outlier, indicating that 1 case and 1% of successfully treated patients were achieved at lower mean costs than with the DPI. In addition, the ICERs also showed in favour of the MDI with spacer group. However, there was one outlier with regard to the provider's costs in the DPI group, the results were calculated both with and without the extreme outlier. On the other hand, the results of this study showed that the use of DPI was more cost-effective than the MDI with spacer when the outlier in the DPI group was excluded. Based on the effectiveness measure, the mean costs per 1 case of successfully treated patient was Baht 5.03 in the DPI group compared with Baht 6.66 in the MDI and spacer group. In addition, the mean costs per 1% of successfully treated patient for the DPI group compared with the MDI and spacer group were Baht 1.96 and Baht 2.66, respectively. Even though the results showed that the DPI was less costly and more efficacious than the MDI with spacer, the incremental analysis was performed for completeness and illustrative purposes. The ICER showed a cost saving for the DPI group relative to the MDI with spacer group, and indicated that by switching to the DPI from the MDI, the cost for each additional percentage of successfully treated patients would be reduced by Baht 25.42.

When the cost-effectiveness analysis was performed according to the patient's perspective, the study showed the same results derived from the provider's perspective. Whether including or excluding the outlier in the DPI group, the mean costs per number and per percentage of successfully treated patients were lower for the DPI group than for the MDI with spacer group (Table 4.20), indicating that 1 case and 1% of successfully treated patients were achieved at lower mean costs than with the MDI and spacer. The ICER also showed a cost saving for the DPI group excluding the outlier relative to the MDI with spacer group, and indicated that by switching to the DPI from the MDI with spacer, this resulted in a saving of Baht 60.79 for each additional percentage of successfully treated patients.

Table 4.19: Mean cost-effectiveness ratios and incremental cost-effectiveness ratios for the MDI with spacer and DPI groups (according to the provider's perspective).

| Parameter | MDI with spacer (n = 40) | DPI (including outlier) (n = 40) | DPI (excluding outlier) (n = 39)* |
|---|---|---|---|
| Cost | | | |
| Total provider costs | 9,585.19 | 13,346.28 | 7,058.14 |
| Mean total provider costs (per 1 patient) | 239.63 | 333.66 | 180.98 |
| Effectiveness | | | |
| No.of successfully treated patients (T=60 mins.) | 36 | 37 | 36 |
| % of successfully treated patients (T=60 mins.) | 90.00 | 92.50 | 92.31 |
| Cost-effectiveness ratio | | | |
| Per no.of successfully treated patients (baht per 1 case) | 6.66 | 9.02 | 5.03 |
| Per % of successfully treated patients (baht per 1%) | 2.66 | 3.61 | 1.96 |
| ICER | | | |
| Per no.of successfully treated patients (baht per additional case) | | 94.03 | N/A |
| Per % of successfully treated patients (baht per additional %) | | 37.61 | (-)25.42** |

All cost data are presented in 2005 Baht; when necessary, the costs were adjusted to 2005 Baht using the medical and personal care item of CPI.
*One patient was excluded because he was the most costly patient, the so-called "outlier", as a result of high costs for hospitalization.
**Negative value denoted that improvement in effectiveness were achieved at lower overall costs with DPI.
Abbreviations: CPI = consumer price index; DPI = dry powder inhaler; ICER = incremental cost-effectiveness ratio; MDI = metered dose inhaler; N/A = not available; T = time

Table 4.20: Mean cost-effectiveness ratios and incremental cost-effectiveness ratios for the MDI with spacer and DPI groups (according to the patient's perspective).

| Parameter | MDI with spacer (n = 40) | DPI (including outlier) (n = 40) | DPI (excluding outlier) (n = 39)* |
|---|---|---|---|
| Cost | | | |
| Total patient costs | 19,850.60 | 20,104.01 | 13,883.43 |
| Mean total patient costs (per 1 patient) | 496.27 | 502.60 | 355.99 |
| Effectiveness | | | |
| No.of successfully treated patients (T=60 mins.) | 36 | 37 | 36 |
| % of successfully treated patients (T=60 mins.) | 90.00 | 92.50 | 92.31 |
| Cost-effectiveness ratio | | | |
| Per no.of successfully treated patients (baht per 1 case) | 13.79 | 13.58 | 9.89 |
| Per % of successfully treated patients (baht per 1%) | 5.51 | 5.43 | 3.86 |
| ICER | | | |
| Per no.of successfully treated patients (baht per additional case) | | 6.34 | N/A |
| Per % of successfully treated patients (baht per additional %) | | 2.53 | (-)60.79** |

All cost data are presented in 2005 Baht; when necessary, the costs were adjusted to 2005 Baht using the medical and personal care item of CPI.
*One patient was excluded because he was the most costly patient, the so-called "outlier", as a result of high costs for hospitalization.
**Negative value denoted that improvement in effectiveness were achieved at lower overall costs with DPI.
Abbreviations: CPI = consumer price index; DPI = dry powder inhaler; ICER = incremental cost-effectiveness ratio; MDI = metered dose inhaler; N/A = not available; T = time

## 4.5 Regression Analysis

The results from ordinary least squares regressions presented with the logarithm of the total direct medical costs and the logarithm of the total costs as dependent variales were shown in Table 4.21. Ordinary least squares regression analyses were performed with the aim of identifying which variable had the greatest influence on the costs. The dependent variables were the logarithmically transformed total direct medical costs and the logarithmically transformed total costs according to the provider's and patient's perspectives.

The independent variables were "age", "duration of asthma", "severity of asthma at the first diagnosis", "gender", "treatment" and the interaction terms (i.e. the interactions between "treatment" and other variables). These independent variables were included to adjust for differences in baseline characteristics between the 2 treatment groups. This correction is important even when the differences between the 2 treatments are not statistically significant because small differences in multiple baseline characteristics can add up to substantial differences in expected outcome.

Models used in the regression analyses were log-lin models, where the dependent variable was logarithmic and the independent variables were linear. A logarithmic transformation was used for the dependent variables to reduce skewness and the influence of the most costly patient (i.e. the outlier). In this study, the regression models contained an admixture of quantitative and qualitative variables which typically found in most economic research.

Turning to the interpretations of the findings, each slope coefficient gave the proportional or percentage change in the costs for a given unit change in the value of the quantitative independent variable. The differential slope coefficient gave the value of the slope coefficient of independent variable for the patient using the DPI, indicating by how much the slope coefficient of independent variable in the DPI group differed from that of the MDI with spacer group, which was the base group. The coefficients attached to the various dummy variables were the differential intercept coefficients, showing by how much the proportional or percentage change in the costs of the variable that received a dummy value of 1 differed from that of the benchmark.

The intercept coefficients or constants in every models had high values and were statistically significant at 99% CI ($p < 0.01$), suggesting that there may be many factors that affected the costs but were not taken into account. As Table 4.21 showed, the differential intercept coefficients of "treatment" were statistically significant at 90% CI ($p < 0.10$) in the models with the logarithm of total direct medical costs as the dependent variable conducted from the provider's and patient's perspectives regardless of including or excluding the outlier (Model 1, 2, 3 and 4), but insignificant for the models with the logarithm of total costs (Model 5 and 6). In addition, when the outlier was excluded from the model which performed according to the provider's perspective, the differential intercept coefficient of "treatment" was also statistically significant at 95% CI ($p < 0.05$). Since the treatment with MDI and spacer was treated as the benchmark, for instance, the coefficient of -1.1992 attached to the "treatment" dummy variable in Model 2 means, holding all other factors constant, the direct

medical costs occurred by the patients using the DPI were smaller by about 120% (as compared with the patients using the MDI and spacer, the base category).

The interaction term was also considered. The differential slope coefficient of "treatment x age" was statistically significant at 90% CI ($p < 0.10$) in the model with the logarithm of total direct medical costs as the dependent variable conducted from the patient's perspective (Model 3). In this case, the slope coefficient of "age" was -0.0933 for the MDI with spacer group, but 0.0616 (-0.0933 + 0.1549) for the DPI group, suggesting that if the age of patient in the DPI group increases by 1 year, the total direct medical costs increased by about 6% (as compared with the patients in the MDI and spacer group, the base category).

A priori, the coefficients of "duration of asthma" and "severity of asthma at the first diagnosis" were expected to be positive, and the coefficients of "age" and "treatment" were expected to be negative. The results shown in Table 4.21 demonstrated that all independent variables had the expected signs, and the coefficients of "treatment" indicating the lower costs for patients using the DPI.

Table 4.21: Summary of the results from ordinary least squares regression analyses.

| Variable | Total direct medical cost (Provider's perspective) | | Total direct medical cost (Patient's perspective) | | Total cost (Patient's perspective) | |
|---|---|---|---|---|---|---|
| | Model 1 With outlier | Model 2 Without outlier | Model 3 With outlier | Model 4 Without outlier | Model 5 With outlier | Model 6 Without outlier |
| Constant | 5.895668 (0.507800)*** | 5.895668 (0.419414)*** | 6.193525 (0.599645)*** | 6.193525 (0.547296)*** | 6.447286 (0.667898)*** | 6.447286 (0.621266)*** |
| Age | -0.08089 (0.050250) | -0.080890 (0.041504)* | -0.093338 (0.059339) | -0.093338 (0.054158)* | -0.088512 (0.066093) | -0.088512 (0.061478) |
| Duration of asthma symptoms | 0.001604 (0.003353) | 0.001604 (0.002769) | 0.002489 (0.003959) | 0.002489 (0.003613) | 0.001577 (0.004410) | 0.001577 (0.004102) |
| Severity of asthma | 0.234454 (0.264358) | 0.234454 (0.218344) | 0.303469 (0.312172) | 0.303469 (0.284949) | 0.218153 (0.347704) | 0.218153 (0.323428) |
| Gender | -0.318953 (0.249340) | -0.318953 (0.205940) | -0.421168 (0.294437) | -0.421168 (0.268733) | -0.412079 (0.327951) | -0.412079 (0.305054) |
| Treatment | -1.327297 (0.686694)* | -1.199220 (0.567600)** | -1.472676 (0.810896)* | -1.360912 (0.740666)* | -1.338924 (0.903194) | -1.226027 (0.840771) |
| Treatment x Age | 0.109522 (0.073776) | 0.083895 (0.061095) | 0.154916 (0.087120)* | 0.132553 (0.079724) | 0.137609 (0.097037) | 0.115019 (0.090499) |
| Treatment x Duration of asthma symptoms | 0.000170 (0.005027) | -0.000550 (0.004154) | -0.003837 (0.005936) | -0.004465 (0.005421) | -0.002904 (0.006612) | -0.003538 (0.006153) |
| Treatment x Severity of asthma | -0.219705 (0.371309) | -0.005914 (0.308889) | -0.328153 (0.438467) | -0.141591 (0.403071) | -0.341965 (0.488374) | -0.153512 (0.457548) |
| Treatment x Gender | 0.456195 (0.371648) | 0.373910 (0.307288) | 0.615732 (0.438868) | 0.543928 (0.400983) | 0.457785 (0.488821) | 0.385253 (0.455177) |
| R-squared | 0.090797 | 0.139833 | 0.090480 | 0.104041 | 0.063639 | 0.676789 |
| Adjusted R-squared | -0.026100 | 0.027638 | -0.026458 | -0.012823 | -0.056750 | -0.043632 |
| Standard error of regression | 0.777330 | 0.642030 | 0.917924 | 0.83779 | 1.022405 | 0.951020 |
| Included observation | 80 | 79 | 80 | 79 | 80 | 79 |
| Data are presented as coefficient with standard error in parentheses, unless otherwise stated. | | | | | *p < 0.10; **p < 0.05; *** p < 0.01 | |

## 4.6 Sensitivity Analysis

The results of sensitivity analyses conducted from the provider's and patient's perspectives were shown in Table 4.22 and Table 4.23, respectively. The first sensitivity analysis was assessed using 2 scenarios for a change in the cost of the study drug. The first scenario assumed that the drug cost varied +/-30% in the cost per puff of the DPI, and in the cost per puff of the MDI for the second scenario. When the outlier in the DPI group was excluded, both cost-effectiveness ratios and ICERs (calculated from the provider's and patient's perspectives) remained in favour of the DPI after changing the study drug costs based on 2 scenarios as shown in Table 4.22 and 4.23.

Each cost variable had a large standard deviation, and mean calculations were very sensitive to extreme values, the median values were therefore complementary. The median of total provider costs and total patient costs were used instead of the mean values as part of the sensitivity analysis. The results demonstrated that both cost-effectiveness ratios and ICERs remained in favour of the DPI when the provider's and patient's perspectives were adopted, regardless of including or excluding the outlier in the DPI group as can be seen in Table 4.22 and 4.23, respectively. The ICERs had the negative signs, indicated that using the DPI in this group of patients not only improved outcomes, but also reduced the overall costs of asthma management.

In the last sensitivity analysis, the direct non-medical cost (i.e. transportation fee) was included in the cost calculation according to the patient's perspective. The analysis supposed that the patients went to the hospital with their parents by using the single-line bus, and the bus fare was Baht 6.00/trip in 2005. The hospital visits included in the calculation of direct non-medical costs were "unscheduled", and the transportation fee of each patient was calculated based on real situation occurred during the 3-day treatment period. The first scenario used the mean total costs in the cost-effectiveness analysis, and the cost-effectiveness ratios remained in favour of the DPI (Table 4.23). When the outlier belonged to the DPI group was excluded, the ICER showed that the DPI remained consistently cost-saving relative to the MDI with spacer treatment. The second scenario used the median of total costs in place of the mean values. As can be seen in Table 4.23, the sensitivity analysis performed on the cost-effectiveness ratios and the ICERs showed that the results continued to favour the DPI whether with or without the outlier in the DPI group.

The data obtained were robust to changes in underlying assumptions across a range of sensitivity analyses, as there was always a trend in favour of the DPI group, regardless of the assumption used.

Table 4.22: Sensitivity analysis results (according to the provider's perspective).

| Parameter | MDI with spacer (n = 40) | DPI (including outlier) (n = 40) | DPI (excluding outlier) (n = 39)* |
|---|---|---|---|
| **Assumption: Increasing in the cost/puff of DPI by 30%** | | | |
| Cost | | | |
| Total provider costs | 9,585.19 | 13,504.18 | 7,209.52 |
| Mean total provider costs (per 1 patient) | 239.63 | 337.60 | 184.86 |
| Effectiveness | | | |
| No.of successfully treated patients (T=60 mins.) | 36 | 37 | 36 |
| % of successfully treated patients (T=60 mins.) | 90.00 | 92.50 | 92.31 |
| Cost-effectiveness ratio | | | |
| Per no.of successfully treated patients (baht per 1 case) | 6.66 | 9.12 | 5.13 |
| Per % of successfully treated patients (baht per 1%) | 2.66 | 3.65 | 2.00 |
| ICER | | | |
| Per no.of successfully treated patients (baht per additional case) | | 97.97 | N/A |
| Per % of successfully treated patients (baht per additional %) | | 39.19 | (-)23.73** |
| **Assumption: Decreasing in the cost/puff of DPI by 30%** | | | |
| Cost | | | |
| Total provider costs | 9,585.19 | 13,188.39 | 6,906.77 |
| Mean total provider costs (per 1 patient) | 239.63 | 329.71 | 177.10 |
| Effectiveness | | | |
| No.of successfully treated patients (T=60 mins.) | 36 | 37 | 36 |
| % of successfully treated patients (T=60 mins.) | 90.00 | 92.50 | 92.31 |
| Cost-effectiveness ratio | | | |
| Per no.of successfully treated patients (baht per 1 case) | 6.66 | 8.91 | 4.92 |
| Per % of successfully treated patients (baht per 1%) | 2.66 | 3.56 | 1.92 |
| ICER | | | |
| Per no.of successfully treated patients (baht per additional case) | | 90.08 | N/A |
| Per % of successfully treated patients (baht per additional %) | | 36.03 | (-)27.10** |

(Continued to next page)

Table 4.22.(Continued): Sensitivity analysis results (according to the provider's perspective).

| Parameter | MDI with spacer (n = 40) | DPI (including outlier) (n = 40) | DPI (excluding outlier) (n = 39)* |
|---|---|---|---|
| **Assumption: Increasing in the cost/puff of MDI by 30%** | | | |
| Cost | | | |
| Total provider costs | 9,701.00 | 13,346.28 | 7,058.14 |
| Mean total provider costs (per 1 patient) | 242.52 | 333.66 | 180.98 |
| Effectiveness | | | |
| No.of successfully treated patients (T=60 mins.) | 36 | 37 | 36 |
| % of successfully treated patients (T=60 mins.) | 90.00 | 92.50 | 92.31 |
| Cost-effectiveness ratio | | | |
| Per no.of successfully treated patients (baht per 1 case) | 6.74 | 9.02 | 5.03 |
| Per % of successfully treated patients (baht per 1%) | 2.69 | 3.61 | 1.96 |
| ICER | | | |
| Per no.of successfully treated patients (baht per additional case) | | 91.13 | N/A |
| Per % of successfully treated patients (baht per additional %) | | 36.45 | (-)26.67** |
| **Assumption: Decreasing in the cost/puff of MDI by 30%** | | | |
| Cost | | | |
| Total provider costs | 9,701.00 | 13,346.28 | 7,058.14 |
| Mean total provider costs (per 1 patient) | 242.52 | 333.66 | 180.98 |
| Effectiveness | | | |
| No.of successfully treated patients (T=60 mins.) | 36 | 37 | 36 |
| % of successfully treated patients (T=60 mins.) | 90.00 | 92.50 | 92.31 |
| Cost-effectiveness ratio | | | |
| Per no.of successfully treated patients (baht per 1 case) | 6.58 | 9.02 | 5.03 |
| Per % of successfully treated patients (baht per 1%) | 2.63 | 3.61 | 1.96 |
| ICER | | | |
| Per no.of successfully treated patients (baht per additional case) | | 96.92 | N/A |
| Per % of successfully treated patients (baht per additional %) | | 38.77 | (-)24.16** |

(Continued to next page)

Table 4.22.(Continued): Sensitivity analysis results (according to the provider's perspective).

| Parameter | MDI with spacer (n = 40) | DPI (including outlier) (n = 40) | DPI (excluding outlier) (n = 39)* |
|---|---|---|---|
| **Assumption: Median of the total provider costs were used in place of the mean values.** | | | |
| Cost | | | |
| Total provider costs | 9,585.19 | 13,346.28 | 7,058.14 |
| Median total provider costs | 128.04 | 111.82 | 111.75 |
| Effectiveness | | | |
| No.of successfully treated patients (T=60 mins.) | 36 | 37 | 36 |
| % of successfully treated patients (T=60 mins.) | 90.00 | 92.50 | 92.31 |
| Cost-effectiveness ratio | | | |
| Per no.of successfully treated patients (baht per 1 case) | 3.56 | 3.02 | 3.10 |
| Per % of successfully treated patients (baht per 1%) | 1.42 | 1.21 | 1.21 |
| ICER | | | |
| Per no.of successfully treated patients (baht per additional case) | | (-)16.22** | N/A |
| Per % of successfully treated patients (baht per additional %) | | (-)6.49** | (-)7.06** |

*One patient was excluded because he was the most costly patient, the so-called "outlier", as a result of high costs for hospitalization.
**Negative value denoted that improvement in effectiveness were achieved at lower overall costs with DPI.
Abbreviations: DPI = dry powder inhaler; ICER = incremental cost-effectiveness ratio; MDI = metered dose inhaler; N/A = not available; T = time

Table 4.23: Sensitivity analysis results (according to the patient's perspective).

| Parameter | MDI with spacer (n = 40) | DPI (including outlier) (n = 40) | DPI (excluding outlier) (n = 39)* |
|---|---|---|---|
| **Assumption: Increasing in the cost/puff of DPI by 30%** | | | |
| Cost | | | |
| Total patient costs | 19,850.60 | 20,293.68 | 14,065.26 |
| Mean total patient costs (per 1 patient) | 496.27 | 507.34 | 360.65 |
| Effectiveness | | | |
| No.of successfully treated patients (T=60 mins.) | 36 | 37 | 36 |
| % of successfully treated patients (T=60 mins.) | 90.00 | 92.50 | 92.31 |
| Cost-effectiveness ratio | | | |
| Per no.of successfully treated patients (baht per 1 case) | 13.79 | 13.71 | 10.02 |
| Per % of successfully treated patients (baht per 1%) | 5.51 | 5.48 | 3.91 |
| ICER | | | |
| Per no.of successfully treated patients (baht per additional case) | | 11.08 | N/A |
| Per % of successfully treated patients (baht per additional %) | | 4.43 | (-)58.77 |
| **Assumption: Decreasing in the cost/puff of DPI by 30%** | | | |
| Cost | | | |
| Total patient costs | 19,850.60 | 19,914.35 | 13,701.60 |
| Mean total patient costs (per 1 patient) | 496.27 | 497.86 | 351.32 |
| Effectiveness | | | |
| No.of successfully treated patients (T=60 mins.) | 36 | 37 | 36 |
| % of successfully treated patients (T=60 mins.) | 90.00 | 92.50 | 92.31 |
| Cost-effectiveness ratio | | | |
| Per no.of successfully treated patients (baht per 1 case) | 13.79 | 13.46 | 9.76 |
| Per % of successfully treated patients (baht per 1%) | 5.51 | 5.38 | 3.81 |
| ICER | | | |
| Per no.of successfully treated patients (baht per additional case) | | 1.59 | N/A |
| Per % of successfully treated patients (baht per additional %) | | 0.64 | (-)62.81** |

(Continued to next page)

Table 4.23.(Continued): Sensitivity analysis results (according to the patient's perspective).

| Parameter | MDI with spacer (n = 40) | DPI (including outlier) (n = 40) | DPI (excluding outlier) (n = 39)* |
|---|---|---|---|
| **Assumption: Increasing in the cost/puff of MDI by 30%** | | | |
| Cost | | | |
| Total patient costs | 19,991.40 | 20,104.01 | 13,883.43 |
| Mean total patient costs (per 1 patient) | 499.78 | 502.60 | 355.99 |
| Effectiveness | | | |
| No.of successfully treated patients (T=60 mins.) | 36 | 37 | 36 |
| % of successfully treated patients (T=60 mins.) | 90.00 | 92.50 | 92.31 |
| Cost-effectiveness ratio | | | |
| Per no.of successfully treated patients (baht per 1 case) | 13.88 | 13.58 | 9.89 |
| Per % of successfully treated patients (baht per 1%) | 5.55 | 5.43 | 3.86 |
| ICER | | | |
| Per no.of successfully treated patients (baht per additional case) | | 2.82 | N/A |
| Per % of successfully treated patients (baht per additional %) | | 1.13 | (-)62.31 |
| **Assumption: Decreasing in the cost/puff of MDI by 30%** | | | |
| Cost | | | |
| Total patient costs | 19,991.40 | 20,104.01 | 13,883.43 |
| Mean total patient costs (per 1 patient) | 499.78 | 502.60 | 355.99 |
| Effectiveness | | | |
| No.of successfully treated patients (T=60 mins.) | 36 | 37 | 36 |
| % of successfully treated patients (T=60 mins.) | 90.00 | 92.50 | 92.31 |
| Cost-effectiveness ratio | | | |
| Per no.of successfully treated patients (baht per 1 case) | 13.88 | 13.58 | 9.89 |
| Per % of successfully treated patients (baht per 1%) | 5.55 | 5.43 | 3.86 |
| ICER | | | |
| Per no.of successfully treated patients (baht per additional case) | | 9.86 | N/A |
| Per % of successfully treated patients (baht per additional %) | | 3.94 | (-)59.26 |

(Continued to next page)

Table 4.23.(Continued): Sensitivity analysis results (according to the patient's perspective).

| Parameter | MDI with spacer (n = 40) | DPI (including outlier) (n = 40) | DPI (excluding outlier) (n = 39)* |
|---|---|---|---|
| **Assumption: Median of the total patient costs were used in place of the mean values.** | | | |
| Cost | | | |
| Total patient costs | 19,850.60 | 20,104.01 | 13,883.43 |
| Median total patient costs | 192.95 | 145.23 | 144.59 |
| Effectiveness | | | |
| No.of successfully treated patients (T=60 mins.) | 36 | 37 | 36 |
| % of successfully treated patients (T=60 mins.) | 90.00 | 92.50 | 92.31 |
| Cost-effectiveness ratio | | | |
| Per no.of successfully treated patients (baht per 1 case) | 5.36 | 3.93 | 4.02 |
| Per % of successfully treated patients (baht per 1%) | 2.14 | 1.57 | 1.57 |
| ICER | | | |
| Per no.of successfully treated patients (baht per additional case) | | (-)47.72** | N/A |
| Per % of successfully treated patients (baht per additional %) | | (-)19.09** | (-)20.95** |
| **Assumption: Including the direct non-medical costs and using mean values** | | | |
| Cost | | | |
| Total patient costs | 20,012.60 | 20,236.01 | 13,979.43 |
| Mean total patient costs (per 1 patient) | 500.32 | 505.90 | 358.45 |
| Effectiveness | | | |
| No.of successfully treated patients (T=60 mins.) | 36 | 37 | 36 |
| % of successfully treated patients (T=60 mins.) | 90.00 | 92.50 | 92.31 |
| Cost-effectiveness ratio | | | |
| Per no.of successfully treated patients (baht per 1 case) | 13.90 | 13.67 | 9.96 |
| Per % of successfully treated patients (baht per 1%) | 5.56 | 5.47 | 3.88 |
| ICER | | | |
| Per no.of successfully treated patients (baht per additional case) | | 5.59 | N/A |
| Per % of successfully treated patients (baht per additional %) | | 2.23 | (-)61.48** |

(Continued to next page)

Table 4.23.(Continued): Sensitivity analysis results (according to the patient's perspective).

| Parameter | MDI with spacer (n = 40) | DPI (including outlier) (n = 40) | DPI (excluding outlier) (n = 39)* |
|---|---|---|---|
| **Assumption: Including the direct non-medical costs and using median values** | | | |
| Cost | | | |
| Total patient costs | 20,012.60 | 20,236.01 | 13,979.43 |
| Median total patient costs | 192.95 | 145.23 | 144.59 |
| Effectiveness | | | |
| No.of successfully treated patients (T=60 mins.) | 36 | 37 | 36 |
| % of successfully treated patients (T=60 mins.) | 90.00 | 92.50 | 92.31 |
| Cost-effectiveness ratio | | | |
| Per no.of successfully treated patients (baht per 1 case) | 5.36 | 3.93 | 4.02 |
| Per % of successfully treated patients (baht per 1%) | 2.14 | 1.57 | 1.57 |
| ICER | | | |
| Per no.of successfully treated patients (baht per additional case) | | (-)47.72** | N/A |
| Per % of successfully treated patients (baht per additional %) | | (-)19.09** | (-)20.95** |

*One patient was excluded because he was the most costly patient, the so-called "outlier", as a result of high costs for hospitalization.
**Negative value denoted that improvement in effectiveness were achieved at lower overall costs with DPI.
Abbreviations: DPI = dry powder inhaler; ICER = incremental cost-effectiveness ratio; MDI = metered dose inhaler; N/A = not available; T = time

# CHAPTER V

# DISCUSSIONS AND CONCLUSIONS

The inhalation route is widely used for the treatment of asthma because this delivers the drug directly to the site of action in the airways in concentrations that are likely to be effective, while systemic side effects are minimized or even avoided. The most commonly used inhaler is the pressurized metered dose inhaler (pMDI), which has been in clinical use for more than 40 years. One common problem with pMDIs is that they require a good inhalation technique in order to obtain optimal efficacy of the administered dose. Also they contain propellants and lubricants that may cause bronchoconstriction in some patients. The use of a spacer device can eliminate the need for coordination between actuation and inhalation, however, this addition makes the inhalation system more bulky and more expensive, and decrease portability. Additionally, the dose of the drug deposited in the lungs by MDIs varied more and was lower than deposited by the multidose dry powder inhalers (DPIs) (Borgstrom and Newman 1993 quoted in Liljas, Stahl and Pauwels 1997; Thorsson, Edsbacker and Conradsson 1994 quoted in Liljas, Stahl and Pauwels 1997). Treatment effectiveness therefore varied between different inhalation devices. Moreover, it is influenced by patients' preferences for a particular inhalation device, which in turn may affect their compliance. These factors may affect health care utilization. Furthermore, in Thailand, all CFC-containing MDIs have been phased out since December, 2005. Although alternative propellants have been developed, CFC-free pMDIs have been slow to appear on the market. The transition from the CFC-containing MDIs to CFC-free inhalers, i.e. either DPIs or non-CFC MDIs, will take place over a period of a few years in Thailand.

As new and frequently more expensive drugs (e.g. DPIs) are developed, there is a need to assess both their effectiveness in reducing or controlling asthma symptoms, and determine their long-term cost-effectiveness. This study represented the health economic analysis of asthma treatment given via different inhalation devices. The purpose of this study was to analyse and compare the cost-effectiveness of the DPI with the MDI and spacer for delivering inhaled short-acting beta2-agonist in the management of mild to moderate acute exacerbations of childhood asthma.

## 5.1 Discussions

### 5.1.1 Baseline Characteristics

As can be seen in Table 4.1, this study showed that there were not statistically significant differences in demographics and clinical characteristics between the MDI with spacer and DPI groups at baseline, so the randomization was successful.

### 5.1.2 Resource Utilization

Calculation of the costs of asthma management were based on resources consumed by patients in the intention-to-treat population during the study period. The following resource data were collected and included in the cost analysis, e.g. hospital contacts, physician contacts, the cost of spacer (included in the MDI with spacer group only, and not included in the DPI group) and medications (study drugs, rescue medications, concurrent prescription medications related to the treatment of asthma, asthma exacerbations or treatment of adverse events). All visits included in the cost analysis were “unscheduled”. During this study period, there were 2 hospital admissions, 1 emergency department visit and 10 unscheduled outpatient department visits as a result of the children’s asthma (Table 4.2).

An unexpected finding in this study was the low rate of non-drug resource use (i.e. hospital and physician contacts), showing that severe exacerbations or the worsening of asthma symptoms after treatment were infrequent in this patient population. Liljas, Stahl and Pauwels (1997) conducted an open randomized parallel-group study in children treated with inhaled corticosteroids and/or inhaled beta2-agonists delivered via the MDI and via the DPI, and they found that the non-drug resource use was higher than in this study. Some possible explanations for this finding were that the study performed by Liljas, Stahl and Pauwels was conducted in larger population for longer duration, and the effective asthma control was established with the interventions used in this study. To detect whether there was any real differencd between the groups in hospitalization and length of stay, the longer duration of the study and larger number of patients would be useful.

The number of days absent from school or work was lower in the DPI group relative to the MDI with spacer group (9 days vs 11 days). The monetary values for days off work (productivity costs) can also be estimated, and was shown in Table 4.5 and 4.6. The saving in productivity costs in the DPI group resulted from the reduction in the number of days absent from school or work, however, there were not significant difference between the 2 treatment groups.

### 5.1.3 Cost Issues

The economic analysis was conducted primarily from the provider’s perspective and secondarily from the patient’s perspective. Cost estimates were derived for both direct medical costs and indirect costs. This study focused on direct medical costs and indirect costs due to absence from work by parents or caretakers. Direct non-medical costs and intangible costs were not taken into account because data were lacking. Intangible costs to the patients and families, such as worry and inconvenience, or the costs associated with mortality (reasonably assumed to be negligible), were not considered in this analysis.

The direct medical costs were assessed using the point of view of the provider. The cost incurred by the provider was the real cost of delivering the services to the patients at King Chulalongkorn Memorial Hospital, thus the total provider costs of delivering each intervention to asthmatic patints was the sum of total routine service costs and total medical care costs. The mean and total direct medical costs occurred during the

study period were higher in the DPI group than in the MDI with spacer group (Table 5.1), mainly due to the higher routine service costs, in particular with hospitalization cost. The difference was not statistically significant. Costs are usually very unevenly distributed among patients (Molken, Doorslaer and Vliet 1994 quoted in Liljas, Stahl and Pauwels 1997) and outliers, i.e. patients with markely higher costs than those of the average patients, are a common problem in health economic analyses (Liljas, Stahl and Pauwels 1997). The results of this economic analysis showed that there was an uneven distribution of costs, and the direct medical costs for the DPI group was heavily influenced by one patient with high costs, the so-called "outlier", while none of outlier in the MDI with spacer group. In the DPI group, the most costly patient incurred costs of Baht 6,288.14 according to the provider's perspective, mainly due to the high cost for hospitalization (Baht 5,072.08). When the investigator recomputed the total direct medical costs without this outlier, the total direct medical costs were 47.12% lower in the DPI group, and the mean total direct medical costs per patient was lower in the DPI group than in the MDI with spacer group, although it was not statistically significant (Table 5.1). The total costs (according to the patient's perspective) were calculated from the sum of total indirect costs and total direct medical costs, so the total costs were also influenced by this outlier, and resulted in the higher mean and total costs in the DPI group (Table 5.2). When the outlier belonged to the DPI group was excluded, the total costs were 30.94% lower in the DPI group, and the mean total costs for the DPI group was Baht 355.99 per patient compared with Baht 496.27 per patient for the MDI and spacer group (Table 5.2). Thus, the outlier in the DPI group changed the results in non-significant way.

When the medical care costs were considered separately, the mean of study medication cost calculated from the provider's perspective was significantly lower in the DPI group than in the MDI with spacer group. By contrast, the mean of study medication cost was significantly higher in the DPI group when adopt the patient's perspective. This difference was explained mainly by including or excluding the cost of spacer. When the cost of study medication for each intervention was calculated according to the provider's perspective, the study medication cost for the MDI with spacer group consisted of the fixed cost of a spacer for each patient and variable cost of study drug depended on the number of doses used. On the other hand, the cost of spacer was not taken into account when the patient's perspective was adopted, because the patients did not be charged by the provider for this cost. This exclusion resulted in a significant reduction of study medication cost in the MDI with spacer group. The average number of doses of study drug (salbutamol) per patient were lower in the DPI group than in the MDI with spacer group. Accordingly, the average number of doses of study drug used in the DPI group was 9 puffs per patient compared with 14 puffs in the MDI and spacer group. There may be several reasons that explain why the doses of study drug used in the MDI with spacer group was higher than in the DPI group. One possible explanation for this finding was that in this study, the spacer had to be primed with 5 puffs of study drug before use in order to prevent the electrostatic charge. This charge attracts the aerosol particles to the surface of the spacer, and can significantly reduce the dose available from inhalation. Some health care professionals recommend that the spacers should be primed for up to 20 doses to reduce static, which was both inconvenient, and wasted drug (Orion Pharma 2001; Peters *et al*. 2002; Khilnani and Banga 2004). Several published studies showed that a nominal dose given via the DPI was more effective than the same nominal dose given via the MDI (Agertoft and Pedersen 1993 quoted in Liljas, Stahl

and Pauwels 1997; Brambilla *et al*. 1994 quoted in Liljas, Stahl and Pauwels 1997; Selroos *et al*. 1994 quoted in Liljas, Stahl and Pauwels 1997). Differences in lung deposition of inhaled drug between the DPI and the MDI were also documented. The dose of the drug deposited in the lungs by the MDI varied more, and was lower than that deposited by the multidose DPI. Nana *et al*. (1998) found that salbutamol inhaled via the DPI was as effective as via the MDI with spacer, but at half dose. In that study, a total of 4 mg was given by multiple actuations via the MDI according to the guidelines on management of acute asthma. This corresponded to half the dose given via the DPI (2 mg). The difference in effect between the DPI and the MDI was very small and was not statistically significant. Another study showed that the lung deposition after the DPI inhalation was twice the lung deposition after the MDI inhalation. This relationship was also reflected in the efficacy measured as $FEV_1$ (Borgstrom *et al*. 1996 quoted in Nana *et al*. 1998). Newhouse *et al*. (2003) conducted a randomized, double-blind, double-dummy placebo-controlled seven-way crossover study in order to compare bronchoprotection from methacholine challenge of the DPI with the MDI. They found that the potency ratio of 1.29 suggested a slightly improved lung deposition of salbutamol from the DPI compared with the MDI. Borgstrom *et al*. (1996 quoted in Liljas, Stahl and Pauwels 1997) calculated that the DPI/MDI dose potency ratio was 2/1 for lung deposition and clinical efficacy, i.e. only a half dose given via the DPI achieved the same efficacy as a full dose given via the MDI. Thus, although the acquisition cost was higher in the DPI group, the additional cost of DPI was partly offset by reductions in costs resulting from the lower doses of study drug and lower utilization of oral corticosteroids, rescue medication and other asthma-related medication.

In this study, the routine service costs incurred by the provider (Table 5.1) were higher than the hospital care costs charged to the patient (Table 5.2), that means the provider had to bear this burden. From the cost analysis of patient services at King Chulalongkorn Memorial Hospital conducted by Kamolratanakul, Sriratanaban and Ngamkaitphaisan (2001), the highest routine service unit cost was incurred by the pediatric patient (about Baht 5,767.25 per one day) compared with other groups of patients, and the pediatric department had the highest capital costs in the hospital. Accordingly, the hospital should be mindful of the total costs occurred as well as clinical aspects of the treatment, not just acquisition costs of drugs. For example, the introduction of more expensive drugs (e.g. the DPIs) may lead to better management of asthma symptoms and reduced total costs on health services.

Indirect costs were estimated as costs of lost productivity for parents or caretakers due to asthma-related school absence days. The number of days missed from school or work was lower in the DPI group. The reduction in days absent from school or work had an intrinsic value in itself in reduced disruption to patients' and families' lives. The hospitalization was disruptive, and may also be distressing or frightening for patients and their families. Time lost from work or education may impair future career prospects. The adverse impact of asthma, especially poorly controlled asthma, on the patients' lives. The results were found by Janson and Reed (2000 quoted in Jonsson *et al*. 2004) in a population-base survey conducted in the USA, shown that 22% of patients with poorly controlled asthma felt that their diseases interfered with their career plans, and 44% felt that this interfered with their social lives. In this study, the indirect costs were lower in the DPI group than in the MDI with spacer group (Table 5.2). The saving in productivity costs (about Baht 19.61 and Baht 37.45 when

including and excluding the outlier, respectively) in the DPI group was resulted from the reduction in the number of days missed from school. However, when the indirect costs were included in the cost analysis (taking the patient's perspective), there was not statistically significant difference in total costs between the 2 treatment groups.

Table 5.1: Summary of the direct medical costs during the 3-day treatment period (according to the provider's perspective).

| **Cost item** | **MDI with spacer (n = 40)** | **DPI (including outlier) (n = 40)** | **DPI (excluding outlier) (n = 39)** |
|---|---|---|---|
| Direct medical cost | 9,585.19 (239.63) | 13,346.28 (333.66) | 7,058.14 (180.98) |
| RSC | 3,934.24 (98.36) | 7,694.91 (192.37) | 1,967.12 (50.44) |
| MCC | 5,650.94 (141.27) | 5,651.38 (141.28) | 5,091.02 (130.54) |

Data are presented as total costs with mean value in parentheses.
Abbreviations: DPI = dry powder inhaler; MCC = medical care costs; MDI = metered dose inhaler; RSC = routine service costs

Table 5.2: Summary of the total costs during the 3-day treatment period (according to the patient's perspective).

| Cost item | MDI with spacer (n = 40) | DPI (including outlier) (n = 40) | DPI (excluding outlier) (n = 39) |
|---|---|---|---|
| **Direct medical costs paid for KCMH** | 13,757.39 (343.93) | 15,219.09 (380.48) | 9,782.82 (250.84) |
| Hospital care costs | 7,334.01 (183.35) | 8,430.17 (210.75) | 3,667.01 (94.03) |
| Medical care costs | 6,423.38 (160.58) | 6,788.92 (169.72) | 6,115.81 (156.82) |
| **Direct medical costs paid for other providers** | 1,779.52 (44.49) | 1,355.54 (33.89) | 1,355.54 (34.76) |
| Hospital care costs | 1,770.41 (44.26) | 1,229.11 (30.73) | 1,229.11 (31.52) |
| Medical care costs | 9.10 (0.23) | 126.43 (3.16) | 126.43 (3.24) |
| **Direct costs** | 15,536.91 (388.42) | 16,574.63 (414.37) | 11,138.36 (285.60) |
| **Indirect costs** | 4,313.69 (107.84) | 3,529.38 (88.23) | 2,745.08 (70.39) |
| **Total costs** | 19,850.60 (496.27) | 20.104.01 (502.60) | 13,883.43 (355.99) |

Data are presented as total costs with mean value in parentheses.
Abbreviations: DPI = dry powder inhaler; KCMH = King Chulalongkorn Memorial Hospital; MDI = metered dose inhaler

### 5.1.4 Clinical Effectiveness

Cost-effectiveness analyses are difficult to perform without a standardized effectiveness parameter. In asthma, a standard outcome measure has not been identified that could be used universally in the evaluations. Although there is debate over the choice of endpoints for measuring effectiveness in economic analyses in asthma, the effectiveness used in this study has been used in other published studies (Steinmetz *et al*. 1998; Volmer *et al*. 1999; Stempel *et al*. 2000; Bisgaard *et al*. 2001), and likely cover the goals of asthma management. The number and percentage of successfully treated patients at 60 minutes, defined as those with clinical scores reduce $\geq$ 50% from baseline or clinical scores $\leq$ 3, were the effectiveness used in the cost-effectiveness analysis. The Modified Wood's Clinical Score (consisted of the assessment of cyanosis, inspiratory breath sound, accessory muscle used, wheezing and cerebral function) was chosen to measure the improvement in asthma symptoms and response to inhaled salbutamol. There were not significant differences in effectiveness between the 2 treatment groups, although there was a trend in favour of the DPI. The difference was not statistically significant, however, this was perhaps unsurprising as the study did not have enough power to show a difference due to small sample size, and these results were also similar to the previous studies (Ahlstrom, Svenonius and Svensson 1989 quoted in Drblik *et al*. 2003; Fuglsang and Pedersen 1989 quoted in Drblik *et al*. 2003; Hultquist *et al*. 1989 quoted in Drblik *et al*. 2003; Laberge *et al*. 1994 quoted in Drblik *et al*. 2003; Drblik *et al*. 2003).

### 5.1.5 Adverse Events

The outcome measures included an assessment of adverse events were performed in this study (Table 4.15 – 4.17). There were not serious adverse events related to the study medication were observed, and both interventions were generally well tolerated. The overall incidence of adverse events in terms of tremor, palpitation, hypotension and headache was very low, and the most common event (incidence 8.75%) being tremor. Extrapulmonary sympathetic effects such as tremor, palpitation and headache were found in this study to be more frequent in patients receiving salbutamol delivered via the MDI and spacer compared with via the DPI (Table 4.17).

### 5.1.6 Cost-Effectiveness Analysis

For the cost-effectiveness analysis conducted according to the provider's perspective, the mean costs per number and per percentage of successfully treated patients were lower in the MDI with spacer group than in the DPI group including the outlier (Table 5.3). On the other hand, the mean costs per number and per percentage of successfully treated patients were lower for the DPI group when the outlier in this group was excluded, indicating that 1 case and 1% of successfully treated patients were achieved at lower mean costs than with the MDI and spacer (Table 5.3). When the patient's perspective was adopted, the use of DPI was more cost-effective than the MDI with spacer whether with or without the outlier in the DPI group (Table 5.3).

An incremental analysis is necessary when a treatment is less costly and less effective, or more costly and more effective than a comparator (Stempel *et al*. 2000; Bisgaard *et al.* 2001). Even though the results showed that the total costs was lower, and the effectiveness was higher for one of the interventions (the so-called "dominant"), the

incremental analysis was still performed in this study for completeness and illustrative purposes. Incremental cost-effectiveness ratios (ICERs) were meaningful to health-care decision makers as this information allowed them to estimate the costs of switching from the MDI with spacer to the DPI. However, to date, little information is available describing an acceptable ICER threshold for asthma therapy (Stanford, Edwards and Rickard 2000). Molken *et al*. (1995 quoted in Stanford, Edwards and Rickard 2000) found that the acceptable ICER for asthma therapy was approximately $US 5/day (1989 prices).

In this study, the ICERs were calculated to determine the additional health-care costs that must be paid to achieve additional successfully treated patients with the DPI relative to the MDI with spacer. When the outlier belonged to the DPI group was excluded, the ICERs were negative indicating that using the DPI in this group of patients not only improved outcomes, but also reduced asthma management costs (Table 5.3.). The incremental cost-effectiveness analysis showed a cost saving for the DPI relative to the MDI with spacer, and indicated that by switching to the DPI from the MDI with spacer, the costs for each additional percentage of successfully treated patients would be reduced by Baht 25.42 and Baht 60.79 according to the provider's and patient's perspectives, respectively.

Table 5.3: Summary of mean cost-effectiveness ratios and incremental cost-effectiveness ratios for the MDI with spacer and DPI groups (according to the provider's and patient's perspectives).

| Parameter | MDI with spacer (n = 40) | DPI (including outlier) (n = 40) | DPI (excluding outlier) (n = 39) |
|---|---|---|---|
| **Provider's perspective** | | | |
| Cost-effectiveness ratio | | | |
| Per no.of successfully treated patients (baht per 1 case) | 6.66 | 9.02 | 5.03 |
| Per % of successfully treated patients (baht per 1%) | 2.66 | 3.61 | 1.96 |
| ICER | | | |
| Per no.of successfully treated patients (baht per additional case) | | 94.03 | N/A |
| Per % of successfully treated patients (baht per additional %) | | 37.61 | (-)25.42** |
| **Patient's perspective** | | | |
| Cost-effectiveness ratio | | | |
| Per no.of successfully treated patients (baht per 1 case) | 13.79 | 13.58 | 9.89 |
| Per % of successfully treated patients (baht per 1%) | 5.51 | 5.43 | 3.86 |
| ICER | | | |
| Per no.of successfully treated patients (baht per additional case) | | 6.34 | N/A |
| Per % of successfully treated patients (baht per additional %) | | 2.53 | (-)60.79** |

**Negative value denoted that improvement in effectiveness were achieved at lower overall costs with DPI.
Abbreviations: DPI = dry powder inhaler; ICER = incremental cost-effectiveness ratio; MDI = metered dose inhaler; N/A = not available

### 5.1.7 Regression Analysis

Ordinary least squares regression analyses were performed with the aim of identifying which variable had the greatest influence on the costs. A logarithmic transformation was used for the dependent variables to reduce the skewness and influence of the most costly patient (i.e. the outlier). It should be noted that the extreme cost outliers were often found in many published studies on asthma therapy (Liljas, Stahl and Pauwels 1997; Sullivan *et al*. 2003). The independent variables were "age", "duration of asthma", "severity of asthma", "gender", "treatment" and the interaction terms. The results from the regression analyses were provided in Table 4.21. The intercept coefficients or constants in every models had high value and were statistically significant at 99% CI ($p < 0.01$), suggesting that there may be many factors that affected the costs but were not taken into account. In addition, quite a few variables were statistically significant ("age" and "treatment"), suggesting that there may be other factors should be included in the models. This finding was supported by recently published studies that included both socioeconomic and demographic variables (e.g. income of patient's family, family size, educational status of patient and family, residence, age, gender, severity of illness, smoking status, other diseases) showed the better results than this study (Liljas. Stahl and Pauwels 1997; Molken, Doorslaer and Till 1998; Ozminkowski *et al*. 2000; Sullivan *et al*. 2001). The socioeconomic data were not included in this study because data were lacking due to this economic analysis was a retrospective analysis based on clinical data. However, the demographic data included in this study were in accordance with other studies performed previously.

The explanatory power of these models (express as $R^2$) were 6% to 14%. This might seem a rather low value, but low $R^2$ values were typically found in cross-sectional data (Newhouse *et al*. 1989 quoted in Liljas. Stahl and Pauwels 1997; Vliet 1992 quoted in Liljas. Stahl and Pauwels 1997). The coefficients of "treatment" were statistically significant at 90% CI ($p < 0.10$) in the models with the logarithm of total direct medical costs as the dependent variable conducted from the provider's and patient's perspectives regardless of including or excluding the outlier (Model 1, 2, 3 and 4 provided in Table 4.21), but insignificant for the models with the logarithm of total costs (Model 5 and 6 provided in Table 4.21). In addition, when the outlier was excluded from the model which performed according to the provider's perspective, the differential intercept coefficient of "treatment" was also statistically significant at 95% CI ($p < 0.05$). In addition, the coefficients of "treatment" had negative sign, indicating the lower costs for the patients treated with the DPI.

The costs were assessed by regression analyses in order to keep the background variables constant so as to isolate the treatment group effect. This was an important additional analysis, especially if the randomization process happened to be unsuccessful from a health economic perspective.

### 5.1.8 Sensitivity Analysis

The sensitivity of the results was examined by changing in various assumptions, i.e. changing the cost per puff of the study drugs by 30%, using the medians of costs in place of the mean vlues and including the direct non-medical costs (i.e. transportation fee) in the patient's cost calculation. The sensitivity analyses performed on the cost-

effectiveness ratios and the ICERs demonstrated that the data obtained were robust to changes in underlying assumptions across a range of sensitivity analyses, as there was always a trend in favour of the DPI group, regardless of the assumption used.

## 5.2 Recommendations

There were a number of limitations to this study that need to be considered. Firstly, this study was conducted by choosing King Chulalongkorn Memorial Hospital as the model for the economic evaluation. However, different hospitals may have different health care systems, different treatment patterns and culture differences in health care use, and these may cause different patterns of resource utilization. Secondly, cost of provider was calculated from secondary data of cost analysis at King Chulalongkorn Memorial Hospital, however, cost may cannot be generalized from one hospital to another because difference in the cost of health care interventions and medications vary between hospitals, especially in different levels of hospitals. Thirdly, the cost for a day absent from school was estimated by using the human capital approach. This approach, however, would bias against individuals who were unemployed, children below school age, housewives/husbands and retired individuals, which was one of the drawbacks of the human capital approach. Fourthly, the clinical study was conducted during March 1, 2005 to December 31, 2005, as this time period, the seasons (rainy season and/or winter) and adverse weather conditions, such as cool temperatures and high humidity have been associated with asthma exacerbations, and may be related to the increased number of asthma exacerbations and the decreased response to treatment. Fifthly, this study based on the 3-day which was short duration, therefore, it was not possible to assess the long term cost-effectiveness of the study drugs. In addition, this short duration may underestimate the true costs because hospitalization was a rare but expensive consequence of poorly controlled asthma. The length of the study also made it difficult and impractical to consider indirect costs, which should ideally be incorporated into economic analysis. Finally, this cost-effectiveness analysis was a retrospective analysis based on clinical data conducted in 8 centers which enrolled 432 patients. However, a total of 80 asthmatic patients who came to King Chulalongkorn Memorial Hospital were taken into account because this study chose only King Chulalongkorn Memorial Hospital as the model for economic evaluation. The differences between 2 treatment groups for some parameters, such as cost items, clinical outcomes and adverse events, were not statistically significant as maybe this study did not have enough power to show a difference due to small sample size, so further large-scale studies should be carried out.

However, despite these limitations, this study provided further evidence of the economic value of inhaled short-acting beta2-agonist delivered via different inhallation devices, i.e. the DPI compared with the MDI and spacer. Further large-scale and long-term studies would be beneficial to further validate the findingd of this study and economic studies in this age group. Pharmacoeconomic analysis of treatment for a chronic disease such as asthma should ideally involve as long an evaluation period as possible, and further studies of larger scale and longer duration would be useful to help establish the longer term cost and effectiveness benefits of these 2 asthma treatments.

The clinical and economic analyses should be interpreted within the context of the parameters of the trial and analysis. These conclusions were drawn from an economic

evaluation performed alongside a well-designed randomized controlled open-label clinical trial. Both physicians and patients knew which treatment was being used. The disadvantages of unblinded trials is that they do not allow the investigators to determine the extent to which the effects and costs directly results from the treatment or from confounding factors. The lack of blinding may introduce bias that can affect the results, especially with small sample sizes. However, economic evaluations attempt to estimate the economic impact of treatments in regular clinical practice. Unblinded trials reflect the real world. In this world, costs not only result from the needs of patients, but also from the preferences and actions of the patients and physicians. Thus, it can be argued that trials with concurrent economic analysis should be unblinded. In addition, this idea was also supported by other published studies (Molken, Doorslaer and Till 1998; Malone and Luskin 2003).

## 5.3 Conclusions

The rising cost of asthma care, however, is at odds with moves to tighten health care budgets. Asthma has been the target of intense activity in the areas of clinical practice guidelines, disease management, drug formulary design and other efforts that are at least in part aimed at reducing medical expenditures and increasing quality for asthma care. This study represented the health economic analysis of asthma treatment given via different inhalation devices. The purpose of this study was to analyse and compare the cost-effectiveness of the DPI with the MDI and spacer for delivering inhaled short-acting beta2-agonist in the management of mild to moderate acute exacerbations of childhood asthma.

The effectiveness of the treatment, measured as the number and percentage of successfully treated patients at 60 minutes defined as those with the Modified Wood's Clinical Score reduce $\geq$ 50% from baseline or clinical scores $\leq$ 3, was found a trend in favour of the DPI, although did not reach statistical significance compared with the MDI and spacer group.

The economic analysis was conducted primarily from the provider's perspective and secondarily from the patient's perspective. This study focused on direct medicl costs and indirect costs due to absence from work by parents or caretakers. Costs were unevenly distributed within the groups, that was relatively few asthmatic patients contributed to most of the total costs. There was one outlier with regard to the direct medical costs in the DPI group. The most costly patient, mainly as a result of high costs for hospitalization, had the great influence on the costs calculated from both provider's and patient's perspectives.

Although the acquisition cost of the DPI was higher than the MDI, this additional cost was partly offset by reductions in other costs resulting from lower utilization of healthcare resources. When the outlier belonged to the DPI group was excluded, the mean of total provider costs was lower in the DPI group than in the MDI with spacer group (Baht 180.98 for the DPI group, and Baht 239.63 for the MDI with spacer group). The same results were found when the analysis was conducted from the patient's perspective. The mean of total patient costs was also lower in the DPI group than in the MDI with spacer group (Baht 355.99 for the DPI group, and Baht 496.27 for the MDI with spacer group). However, the differences in the provider's costs and the patient's costs between the 2 treatment groups were not statistically significant at

95% CI ($p < 0.05$). Accordingly, when the outlier belonged to the DPI group was excluded, the results from the cost-effectiveness analysis showed in favour of the DPI. This indicated that using the DPI in this group of patients not only improved outcomes, but also reduced asthma management costs according to the provider's and patient's perspectives. These results were robust over a wide range of assumptions as demonstrated by the sensitivity analyses, and complemented the results of the primary clinical analysis which demonstrated the good efficacy of the DPI.

The results of this study suggested that in children aged 5 to 18 years with acute exacerbations of asthma, inhaled short-acting beta2-agonists administered via the DPI was a well-tolerated and cost-effective management strategy, from the perspective of the provider and the patient. Thus, the DPI was an effective alternative to the MDI and spacer in the management of mild to moderate acute exacerbations of childhood asthma.

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# APPENDICES

**Appendix A**

## Cost-effectiveness analysis of DPI and MDI with spacer in acute exacerbations of childhood asthma: A case study of King Chulalongkorn Memorial Hospital

### Identification data

Center No ☐ Enrollment code E ☐☐☐

Patient Initial ☐☐☐ Age (years) ☐☐

Date ☐☐ - ☐☐ - ☐☐☐☐ Date of birth ☐☐ - ☐☐ - ☐☐☐☐

D D - M M - Y Y Y Y D D - M M - Y Y Y Y

### Inclusion criteria

| | | Yes | No |
|---|---|---|---|
| 1. | Age 5-18 year | ☐ | ☐ |
| 2. | Modified Wood's Asthma Score ≤ 7 | ☐ | ☐ |
| 3. | Informed consent | ☐ | ☐ |
| 4. | Turbuhaler tester passed (only Easyhaler® group) | ☐ | ☐ |

### Exclusion criteria

| | | Yes | No |
|---|---|---|---|
| 1. | History of admit PICU or ET intubation | ☐ | ☐ |
| 2. | Repeated exacerbation within 7 days | ☐ | ☐ |
| 3. | History of chronic diseases i.e. heart, liver, kidney / BPD / salbutamol allergy / brittle asthma | ☐ | ☐ |

**The patient fulfils all inclusion / none of exclusion criteria.** ☐ ☐

### Demographic characteristics

Sex ☐ M ☐ F Weight (kgs) ☐☐☐

Race ☐ Thai ☐ Others..... Height (cms) ☐☐☐

Year diagnosed asthma ☐☐☐☐ Duration of asthma symptoms (mths) ☐☐☐

Severity of asthma ☐ Intermittent ☐ Mild persistent

☐ Moderate persistent ☐ Severe persistent

Current Treatment ☐ ICS.....Dose.....mcg/day

☐ ICS + .....

Exacerbation within 12 months..... time(s)

Hospitalization during 12 months.....time(s)

Short acting $\beta_2$ agonist used ..... time(s)/month

## Salbutamol administration

| Route | Dose number | Time of administration |
|---|---|---|
| ☐ MDI with Volumatic | ☐ 1 | ☐☐ : ☐☐ |
| ☐ Easyhaler | ☐ 2 | ☐☐ : ☐☐ |
| ☐ Nebulizer | ☐ 3 | ☐☐ : ☐☐ |
| | | HH : MM (24-hour) |

## Results

| Time (min) | 0 | 20 | 40 | 60 |
|---|---|---|---|---|
| Modified Wood's Asthma Score | ☐ | ☐ | ☐ | ☐ |
| $O_2$ saturation (%) | ☐☐☐ | ☐☐☐ | ☐☐☐ | ☐☐☐ |
| RR (breath/min) (Timed for 60 sec) | ☐☐ | ☐☐ | ☐☐ | ☐☐ |
| PR (beat/min) (Timed for 60 sec) | ☐☐☐ | ☐☐☐ | ☐☐☐ | ☐☐☐ |
| BP (Ps-Pd) (mmHg) | ☐☐☐-☐☐☐ | | | ☐☐☐-☐☐☐ |

## Adverse reactions

| | 0 min | | 20 min | | 40 min | | 60 min | |
|---|---|---|---|---|---|---|---|---|
| | Yes | No | Yes | No | Yes | No | Yes | No |
| Tremor | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |
| Palpitation | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |
| Others | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |

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**Consequences**

| | Yes | No | |
|---|---|---|---|
| Prednisolone used | ☐ | ☐ | ..... |
| Rescue medication | ☐ | ☐ | ..... |
| Admission | ☐ | ☐ | ..... |
| Other medications | ☐ | ☐ | ..... |

Record by.....Signature.....Date ☐☐ - ☐☐ - ☐☐☐☐
D D - M M - Y Y Y Y

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**Follow up on day 3** ☐ Visit ☐ By phone

| **Symptoms** | Yes | No | |
|---|---|---|---|
| Cough | ☐ | ☐ | ..... |
| Wheeze | ☐ | ☐ | ..... |
| Dyspnea | ☐ | ☐ | ..... |
| Missed school | ☐ | ☐ | ..... |
| Re-visit within 3 days | ☐ | ☐ | ..... |

Record by.....Signature.....Date ☐☐ - ☐☐ - ☐☐☐☐
D D - M M - Y Y Y Y

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## Reference

**Table 1** Modified Wood's Clinical Scoring System

| Clinical | 0 | 1 | 2 |
|---|---|---|---|
| Cyanosis | No | In room air | In $FiO_2$ 40% |
| Inspiratory Breath Sounds | Normal | Unequal | Decreased or Absent |
| Accessory Muscle Used | No | Moderate (subcostal retraction) | Maximal (suprasternal + subcostal retraction and/or flaring ala nasi) |
| Wheezing | No | Moderate (expiratory wheezing) | Marked (inspiratory + expiratory wheezing) |
| Cerebral Function | Normal | Depressed or Agitated | Coma |

**Table 2**

| Severity | Daytime Symptoms | Nighttime Symptoms | PEFR |
|---|---|---|---|
| Intermittent | < 1 time a week | $\underline{\leq}$ 2 times a month | $\underline{\geq}$ 80% predictive value variability < 20% |
| Mild Persistent | > 1 time a week but < 1 time a day Attack may affect activity | > 2 times a month | $\underline{\geq}$ 80% predictive value variability 20-30% |
| Moderate Persistent | Daily Attack affect activity | > 1 time a week | 60-80% predictive value variability > 30% |
| Severe Persistent | Continuous Limited physical activity | Frequent | $\underline{\leq}$ 60% predictive value variability > 30% |

**Appendix B**

# BIOGRAPHY

**Name** Miss Kannika Numuang

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**E-mail address** kannika@kk.co.th

**Current Position** Head of Scientific Support Department

**Education**

| | |
|---|---|
| 1997 – 2002 | Bachelor of Pharmacy, Mahidol University |

**Working Experience**

| | |
|---|---|
| 2005 – Present | Head of Scientific Support Department |
| 2004 – Present | Clinical Research Assistant |
| 2003 – Present | Business Development Assistant |
| 2003 – Present | Product Trainer and Scientific Support |
| 2002 – 2003 | Quality Assurance |